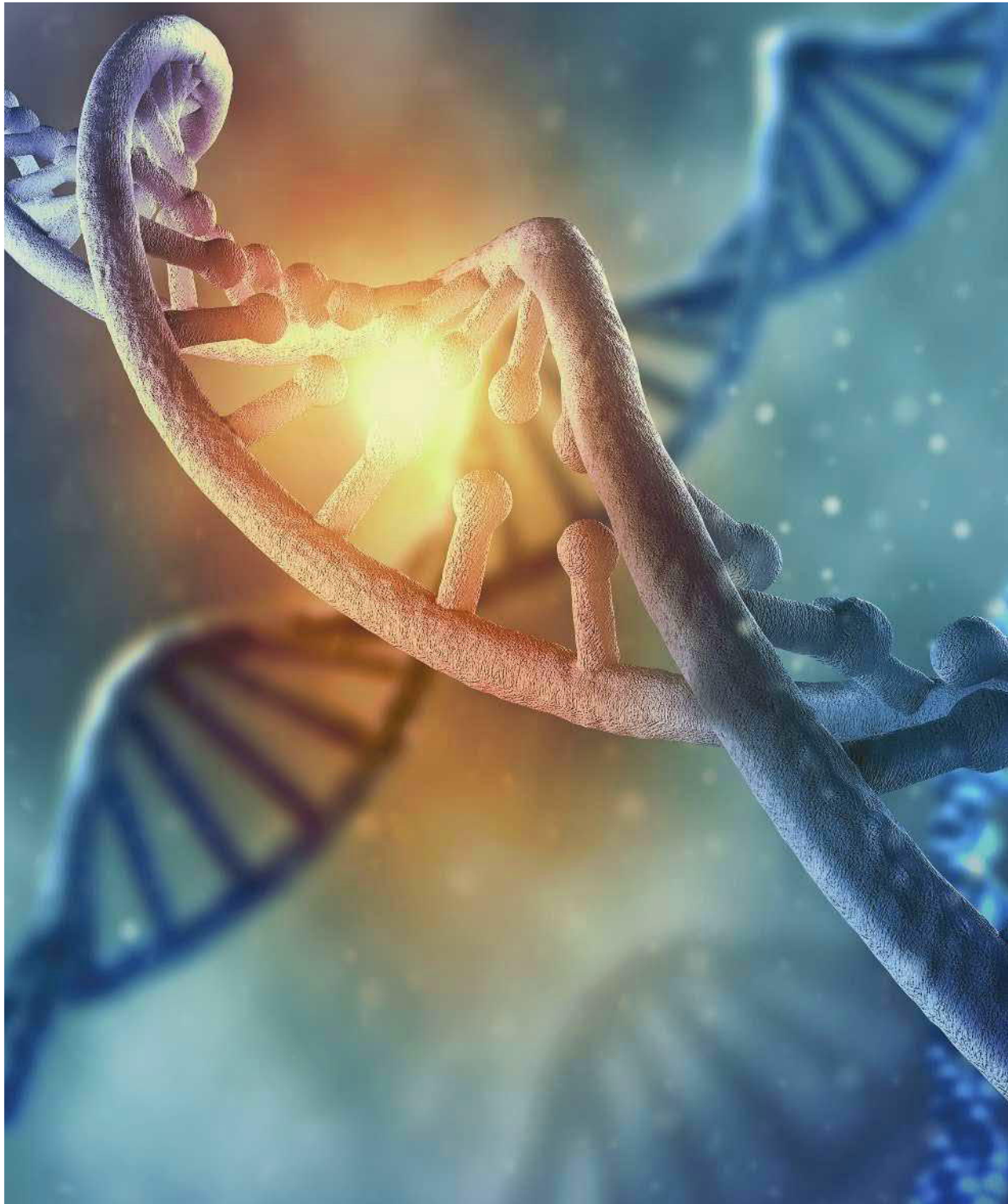


The GALE ENCYCLOPEDIA *of* **GENETIC DISORDERS**

VOLUME 3

P–Z, Organizations, Glossary, General Index

FIFTH EDITION



The GALE ENCYCLOPEDIA *of*
GENETIC DISORDERS

FIFTH EDITION

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The GALE ENCycloPEDIA *of*
GENETIC DISORDERS

FIFTH EDITION

VOLUME

1

A–F

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Organizations	1983
Glossary	2007
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PLEASE READ—IMPORTANT INFORMATION

The *Gale Encyclopedia of Genetic Disorders*, Fifth Edition is a health reference product designed to inform and educate readers about diseases and disorders with genetic origins, and about the treatments and therapies designed to deal with them. Gale believes the product to be comprehensive, but not necessarily definitive. It is intended to supplement, not replace, consultation with a physician or other health-care practitioners. While Gale has made substantial efforts to provide information that is accurate, comprehensive, and up-to-date, Gale makes no representations or warranties of any kind,

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FOREWORD

We are at the dawn of a Golden Age of genetic and genomic science and medicine. Once the stuff of science fiction, sequencing the entire human genome is now a relatively routine, though nonetheless remarkable, procedure. Genetic research has opened a veritable treasure chest—and in some instances, a Pandora’s box—of new scientific and medical insights.

It’s long been known that heredity affects health. Genetics—the study of single genes and their effects on the body and mind—explains how and why certain traits such as hair color and blood type run in families. Genomics—the study of more than single genes—considers the functions and interactions of all the genes in the genome. Epigenetics studies heritable characteristics that influence gene expression through mechanisms other than alterations of a DNA sequence. Epigenetics decodes how environmental factors influence the expression and function of genes, contributing to health or illness.

At the outset of the Human Genome Project in 1993, scientists speculated that human cells likely contained upwards of 100,000 unique, protein-encoding genes. However, by the conclusion of the project only about 22,300 genes were identified. Why so great a discrepancy? The English language uses only 26 distinct letters, but their combinations give rise to roughly 170,000 words (not to mention an additional 47,000 now considered obsolete). Similarly, the human genome, with only about one-fifth as many genes as originally thought, combines their functions into multigene genomic systems.

Understanding the interconnectedness of genomic systems promises far greater insight and clinical scope than genetics for the diagnosis and treatment of disease. Medical genomics draws on our ever-expanding knowledge of the entire genome and deepens our understanding of commonly occurring diseases such as breast and colorectal cancer, Parkinson’s disease, and Alzheimer’s disease. Genomics also plays a role in diseases once believed to be caused entirely by infectious pathogens (disease-causing agents), such as the human immunodeficiency virus (HIV) and tuberculosis. Rather than simple

cause-and-effect relationships, these frequently occurring disorders are now understood to result from interactions between multiple genes and environmental factors. Genetic variations frequently play a protective or a causative role in the expression of diseases.

A common approach in medicine has been to divide diseases into three broad categories: diseases that are primarily genetic in origin; those primarily attributable to environmental causes; and those arising from the interplay between genetics and the environment. With our advancing understanding of genomics and epigenetics, the previously clear distinctions between these categories are shrinking. It’s becoming apparent that the way genes interact with one another, with the environment, and with the biological conditions in which they operate is a better way to understand the subtleties, and sometimes the patient-specific characteristics, of disease.

This encyclopedia considers some of the disorders believed to be predominantly genetic in origin and others that are the result of genes interacting with environmental factors.

Another way to characterize genetic disorders is by their pattern of inheritance, as single gene, multifactorial, chromosomal, or mitochondrial. Single-gene disorders (also known as Mendelian or monogenic disorders) are caused by mutations in the DNA sequence of just one gene. Because genes control the synthesis of proteins, a mutated gene may produce a protein that is unable to carry out its intended function, resulting in a disorder. The dysfunctional version of the gene that causes the disorder is referred to as a mutant or as a disease allele (an allele is a gene variation, most of which do not cause disease). There are more than 10,000 known single-gene disorders including cystic fibrosis, sickle-cell anemia, and Huntington’s disease.

Multifactorial or polygenic disorders result from a complex combination of environmental factors and mutations in multiple genes. For example, many genes that influence susceptibility to breast cancer have been identified, rendering a patient’s risk more difficult to

analyze and address than single-gene or chromosomal disorders. Some of the most common chronic diseases that are multifactorial in origin include heart disease, Alzheimer's disease, arthritis, diabetes, and cancer.

Chromosomal disorders are produced by abnormalities in chromosome structure, missing or extra copies of chromosomes, or errors such as translocations (the repositioning of a DNA sequence from one chromosome to another). Down syndrome is a chromosomal disorder in which an individual has an extra, third copy of chromosome 21. (This tripling is why Down syndrome is also known as trisomy 21.)

Mitochondrial disorders result from mutations in the non-chromosomal DNA of mitochondria, organelles involved in aerobic cellular energy production. Compared with the other patterns of inheritance, mitochondrial disorders occur infrequently.

Although many diseases, disorders, and conditions are termed “genetic,” classifying a disease as genetic simply means that there is an identified genetic component to its origin or its expression. Many medical geneticists contend that most diseases cannot be classified as either strictly genetic or environmental. The expression of a genetic disease can sometimes be altered, even to the point of complete suppression, by environmental factors. Similarly, diseases due to infectious pathogens may not be expressed because of a genetic predisposition for a protective immune response. Each disorder, in each individual, exists along a continuum spanning a range of genetic and environmental causes.

Today, in the third decade of the 21st century, the possibility of preventing and changing genetic legacies appears within reach of modern medical science. Genomic medicine predicts the risk of disease in the individual, whether highly probable, as in the case of some of the well-established single-gene disorders, or as an increased susceptibility likely to be influenced by environmental factors. The great promise of genomic medicine is to make preventive measures more powerful and treatment more specific to the individual, enabling investigation and treatments that are custom-tailored to an individual's genetic susceptibilities, or to the characteristics of the specific disease or disorder. Genomic analyses can personalize medicine, accurately predicting which individuals will respond to certain therapies or survive certain infections and it can inform development of new treatments.

Among the many exciting advances in clinical genetics and genomics are the increased use of polygenic risk scoring to identify individuals at risk for heart disease, cancer, and other chronic conditions. Liquid biopsies, which detect DNA that has escaped from cells, offer a less invasive way to detect cancers and monitor

the effectiveness of treatment. CRISPR/Cas9 (an acronym that stands for “Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-Associated Protein 9”) technologies can be used to edit genomes. Efforts are currently underway to use them to address single-gene disorders. After early setbacks, gene therapy has now proven to be a successful approach to treatment for hemophilia and spinal muscular atrophy.

Today, molecular technologies that rapidly identify viral pathogens are in use worldwide. For example, pathogen genomics were used to track the Ebola virus epidemic in West Africa between 2014 and 2015. More recently, genomic sequencing decoded the genes of SARS-CoV-2, the virus that causes COVID-19, enabling scientists to detect and monitor the spread of genetic variants. The mRNA (messenger RNA) technology used to create lifesaving COVID-19 vaccines encodes information that teaches the body to synthesize harmless antigens that mimic vulnerable portions of the actual virus, thereby stimulating the body's production of virus-neutralizing antibodies. This technology is being applied to develop vaccines and treatments for a wide range of pathogens, from HIV, Zika, malaria, and tuberculosis to influenza and cancer—in less time and at lower costs than traditional methods.

The widespread availability and direct-to-consumer marketing of genetic and genomic tests that do not require a prescription or referral from a physician present new opportunities, but also pose new challenges. Personal genomic tests may be used by people seeking to learn more about their ancestry and their health (specifically their carrier status, disease risk, and response to drugs). Proponents of such testing maintain that people who learn more about their genetic risks will take steps to improve their health and well-being. Skeptics worry about the stress that such knowledge can create and how the results of testing may be used.

Advances in genetics and genomics research and treatment raise a host of ethical, legal, and social questions and considerations. For example, is it appropriate to perform tests for conditions for which no treatment exists? How should we interpret and act on test results, such as an individual's increased susceptibility to a disease that is associated with several genes and environmental triggers? How do we ensure just and fair access to genomic science and treatments, especially for those with fewer resources? How do we resolve concern about the use of genome-editing technologies for heritable genetic changes? How do we understand and communicate the influence of genomics on concepts of race and ethnicity? How do we respect intensely personal cultural and religious differences of opinion about the use of genomic data to inform medical decision making?

This encyclopedia aims to inform and educate readers about the origins of genetic disorders and the promise and progress made to detect and treat them. We also hope that it will inspire discussion and debate about

wise and judicious use genetic and genomic research and technologies.

Barbara Wexler, MPH

INTRODUCTION

The Gale Encyclopedia of Genetic Disorders is a unique and invaluable source for information regarding diseases and conditions of a genetic origin. This collection of 575 entries provides in-depth coverage of disorders ranging from exceedingly rare to very well-known. In addition, several non-disorder entries have been included to facilitate understanding of common genetic concepts and practices such as chromosomes, genetic counseling, and genetic testing. Also included are two entries new to the fifth edition that discuss issues of race: “Race and genetics” debunks the idea that race is a genetic or biological characteristic, and “HeLa cells” discusses the contribution of Henrietta Lacks to genetic research and the ways in which medical ethics have evolved.

This encyclopedia avoids medical jargon and uses language that laypersons can understand, while still providing thorough coverage of each disorder in a manner medical professionals will find beneficial as well. *The Gale Encyclopedia of Genetic Disorders* fills a gap between basic consumer health resources, such as single-volume family medical guides, and highly technical professional materials.

Each entry discussing a particular disorder follows a standardized format that provides information at a glance. The rubrics used include:

- Definition
- Description
- Genetic profile
- Demographics
- Signs and symptoms
- Diagnosis
- Treatment and management
- Prognosis
- Resources
- Key terms

INCLUSION CRITERIA

A preliminary list of diseases and disorders was compiled from a wide variety of sources, including professional medical guides and textbooks, as well as consumer guides and encyclopedias. The advisory board, made up of medical and genetic experts, evaluated the topics and made suggestions for inclusion. Final selection of topics to include was made by the advisory board in conjunction with Gale, Part of Cengage Group editors.

ABOUT THE CONTRIBUTORS

The essays were compiled by experienced medical writers including genetic counselors, physicians, and other health-care professionals. The advisors reviewed the completed essays to insure they are appropriate, up-to-date, and medically accurate.

HOW TO USE THIS BOOK

The Gale Encyclopedia of Genetic Disorders has been designed with ready reference in mind.

- Straight **alphabetical arrangement** of topics allows users to locate information quickly.
- **See also terms** at the end of an entry direct the reader to related articles.
- A list of **key terms** are provided where appropriate to define unfamiliar terms or concepts. Additional terms may be found in the **glossary** at the back of volume 3.
- The **resources** section directs readers to additional sources of medical information on a topic.
- Many entries contain “**Questions to Ask Your Doctor**” sidebars, which provide patients or caregivers with pertinent questions for their medical professionals.

- Valuable **contact information** for organizations and support groups is included with most entries. The appendix contains an extensive list of **organizations** arranged in alphabetical order.
- A comprehensive **general index** guides readers to all topics and persons mentioned in the text.

GRAPHICS

The Gale Encyclopedia of Genetic Disorders contains more than 350 full-color illustrations, including photographs and pedigree charts. A complete symbol guide for the pedigree charts can be found in the appendix.

ALPHABETICAL LIST OF ENTRIES

A

18p deletion syndrome
18q deletion syndrome
22q11.2 deletion syndrome
22q13 deletion syndrome
3-M syndrome
3-Methylglutaconic aciduria type 2
3D organoid biosystems
46,XX testicular disorder of sex development
Aarskog syndrome
Abetalipoproteinemia
Absence of vas deferens
Accutane embryopathy
Aceruloplasminemia
Achondrogenesis
Achondroplasia
ACHOO syndrome
Acrocallosal syndrome (ACLS), Schinzel type; Joubert syndrome; and related disorders
Acromegaly
Adams-Oliver syndrome
Adaptive immunity
Adelaide-type craniosynostosis
Adenylosuccinate lyase deficiency
Adrenoleukodystrophy
Agenesis of the corpus callosum
Aicardi syndrome
ALA dehydratase deficiency
Alagille syndrome
Albinism
Alcoholism
Alexander disease
Alkaptonuria
Alpha thalassemia
Alpha-1 antitrypsin deficiency
Alpha-thalassemia X-linked intellectual disability syndrome
Alport syndrome
Alström syndrome
Alzheimer's disease
Ambiguous genitalia
Amelia
Amelogenesis imperfecta
Amniocentesis
Amyloidosis
Amyotrophic lateral sclerosis
Androgen insensitivity syndrome
Anencephaly
Angelman syndrome
Ankylosing spondylitis
Apert syndrome
Arginase deficiency
Arnold-Chiari malformation
Arthrogryposis multiplex congenita
Arthropathy-camptodactyly syndrome
Asperger syndrome
Asplenia
Asthma
Astrocytoma
Ataxia-Telangiectasia
Attention deficit hyperactivity disorder
Atypical Singleton-Merten syndrome
Autism spectrum disorders
Autologous germline mitochondrial transfer
Autosomal dominant multiple pterygium syndrome
AUTS2 syndrome

B

Bardet-Biedl syndrome
Base editing
Beare-Stevenson cutis gyrata syndrome
Beckwith-Wiedemann syndrome
Beta thalassemia
Bicuspid aortic valve
Biotinidase deficiency
Bipolar disorder
Birt-Hogg-Dubé syndrome
Bloom syndrome
Blue rubber bleb nevus syndrome
Brachydactyly
Branchiootorenal (BOR) syndrome
Breast cancer
Bruton agammaglobulinemia

C

Campomelic dysplasia
Camurati-Engelmann disease
Canavan disease
Cancer
Cancer genetics
Cardiofaciocutaneous syndrome
Carnitine palmitoyltransferase deficiency
Carpenter syndrome
Caudal dysplasia
CECR1 gene-recurrent fevers and strokes in children
Celiac disease
Cell-free DNA test
Cenani-Lenz syndrome

Central core disease
Cerebral autosomal dominant
arteriopathy with subcortical
infarcts and leukoencephalopathy
(CADASIL)
Cerebral palsy
Channelopathies
Charcot-Marie-Tooth disease
CHARGE syndrome
Chediak-Higashi syndrome
Chondrodysplasia punctata
Chondrosarcoma
CHOPS syndrome
Chorionic villus sampling
Choroideremia
Chromosomal abnormalities
Chromosome
Cleft lip and palate
Cleidocranial dysplasia
Clubfoot
Cockayne syndrome
CODAS syndrome
Coffin-Lowry syndrome
Coffin-Siris syndrome
Cohen syndrome
Cole-Carpenter syndrome
Colitis
Collagenopathy, types II and XI
Coloboma
Color blindness
Combined pituitary hormone
deficiency
Computational genomics
Cone-rod dystrophy
Congenital adrenal hyperplasia
Congenital contractural
arachnodactyly
Congenital heart disease
Congenital hypothyroid syndrome
Congenital microcoria
Conjoined twins
Connectome genetics
Corneal dystrophy
Cornelia de Lange syndrome
Costello syndrome
Cowden syndrome
Crane-Heise syndrome
Craniofacial microsomia
Craniosynostosis

Creutzfeldt-Jakob disease
Cri du chat syndrome
Crispr/Cas
Crohn's disease
Crouzon syndrome
Crouzonodermoskeletal syndrome
Cystic Fibrosis
Cystinosis
Cystinuria

D

Dandy-Walker malformation
De novo
Dementia, hereditary forms
Dent disease
Dentatorubral-pallidoluysian atrophy
Depression
Diabetes
Diamond-Blackfan anemia
Diastrophic dysplasia
Direct-to-consumer genetic testing
Disorders of sex development (DSD)
DNA (deoxyribonucleic acid)
DNA methylation
Donohue syndrome
Down syndrome
Duane syndrome
Dubowitz syndrome
Duchenne and Becker muscular
dystrophy
Dyschondrosteosis
Dysplasia
Dystonia

E

Ectodermal dysplasia
Ectrodactyly-ectodermal dysplasia-
clefting syndrome
Edwards syndrome
Ehlers-Danlos syndrome
Ellis-van Creveld syndrome
Emery-Dreifuss muscular dystrophy
Encephalocele
Epidermolysis bullosa
Epigenetic inheritance
Epigenome

Epilepsy
Erythropoietic porphyria
Erythropoietic protoporphyria
Essential hypertension
Essential tremor
Ex vivo lentiviral gene therapies
Exome sequencing
Expanded carrier screening (ECS)

F

Fabry disease
Facioscapulohumeral muscular
dystrophy
Factor V Leiden thrombophilia
Familial adenomatous polyposis
Familial dysautonomia
Familial idiopathic basal ganglia
calcification
Familial lipoprotein lipase
deficiency
Familial Mediterranean fever
Fanconi anemia
Fanconi-Bickel syndrome
Feingold syndrome
Fetal alcohol spectrum disorders
FG syndrome
Fibroblast growth factor receptor-
related conditions
First-trimester pregnancy screening
Fluorescent in situ hybridization
Focal dermal hypoplasia
Fragile X syndrome
Fraser syndrome
Freeman-Sheldon syndrome
Friedreich ataxia
Frontonasal dysplasia
Frontotemporal dementia
Fryns syndrome

G

Galactosemia
Galactosialidosis
Gamete donor anonymity
Gastric cancer
Gastroschisis
Gaucher disease

Gene
Gene editing
Gene fusion
Gene mutations
Gene panel testing
Gene pool
Gene regulatory networks
Gene therapy
Genetic anthropology
Genetic counseling
Genetic disorders
Genetic gain
Genetic Information Nondiscrimination Act (GINA)
Genetic mapping
Genetic testing
Genetics and congenital anomalies
Genome
Genome sequencing
Genome- and epigenome-wide association studies
Genomic medicine
Genotype and phenotype
Genotype tissue expression project (GTEx)
Germline genome editing
Germline mosaicism
Giant congenital melanocytic nevus
Glanzmann thrombasthenia
Glaucoma
Glycine encephalopathy
Glycogen storage diseases
GM1-gangliosidosis
Greig cephalopolysyndactyly
Griscelli syndrome

H

Haim-Munk syndrome
Hair loss syndromes
Hallermann-Streiff syndrome
Hand-foot-genital syndrome
Harlequin ichthyosis
HeLa cells
Hemihypertrophy (Hemihyperplasia)
Hemochromatosis

Hemolytic-uremic syndrome
Hemophilia
Hepatocellular carcinoma
Herceptin
Hereditary angioneurotic edema
Hereditary colorectal cancer
Hereditary coproporphyrria
Hereditary desmoid disease
Hereditary hearing loss and deafness
Hereditary hemorrhagic telangiectasia
Hereditary hypertrophic cardiomyopathy
Hereditary multiple osteochondromas
Hereditary neuropathy with liability to pressure palsies
Hereditary pancreatitis
Hereditary spastic paraplegia
Hereditary spherocytosis
Hermansky-Pudlak syndrome
Hirschsprung disease
Holoprosencephaly
Holt-Oram syndrome
Homocystinuria
Human Genome Project
Huntington's disease
Hutchinson-Gilford progeria syndrome
Hydrocephalus
Hydrolethrus syndrome 1 (HLS1)
Hydrops fetalis
Hyperlipoproteinemia
Hyperoxaluria
Hyperphenylalaninemia
Hypochondrogenesis
Hypochondroplasia
Hypophosphatasia
Hypophosphatemia
Hypospadias and epispadias

I

Ichthyosis
Imprinting
Incontinentia pigmenti
Infertility

Inheritance
Inherited arrhythmia

J

Jackson-Weiss syndrome
Jacobsen syndrome
Jervell and Lange-Nielsen syndrome
Joubert syndrome

K

Kabuki syndrome
Kallmann syndrome
Karyomapping
Karyotype
Keppen-Lubinsky syndrome
Klinefelter syndrome
Klippel-Feil syndrome
Klippel-Trenaunay-Weber syndrome
Kniest dysplasia
Krabbe disease

L

L1 syndrome
Langer-Saldino achondrogenesis
Larsen syndrome
Laterality sequence
Leber congenital amaurosis
Leber hereditary optic atrophy
Leigh Syndrome
Lesch-Nyhan syndrome
Leukodystrophy
Li-Fraumeni syndrome
Limb-girdle muscular dystrophy
Liquid biopsy
Lissencephaly
Long QT syndrome
Lowe oculocerebrorenal syndrome
Lupus
Lynch syndrome

M

Macular degeneration—age-related
Major histocompatibility complex

Male infertility
 Malignant hyperthermia
 Mannosidosis
 Marfan syndrome
 Marshall syndrome
 Marshall-Smith syndrome
 MCAD deficiency
 McCune-Albright syndrome
 McKusick-Kaufman syndrome
 Meckel's diverticulum
 Meckel-Gruber syndrome
 Melanoma
 Menkes syndrome
 Metaphyseal dysplasia
 Methemoglobinemia, beta-globin type
 Methylenetetrahydrofolate reductase variant (MTHFR gene variant)
 Methylmalonic acidemia
 Micro syndrome
 Microbiome
 Microcephaly
 Microcephaly and hypomyelination
 Microcephaly with spastic diplegia
 Microdeletion and microdeletion syndromes
 Microphthalmia with linear skin defects
 Miller-Dieker syndrome
 Mitochondrial disease
 Mitochondrial replacement therapy (MRT)
 Moebius syndrome
 Monosomy 1p36 syndrome
 Mowat-Wilson syndrome
 Moyamoya
 mRNA vaccine technology
 Mucopolidosis
 Mucopolysaccharidoses
 Muir-Torre syndrome
 Multifactorial inheritance
 Multiple endocrine neoplasia
 Multiple epiphyseal dysplasia
 Multiple lentigines syndrome
 Multiple sclerosis
 Multiplex ligation-dependent probe amplification

Muscular dystrophy
 Mutations (on-target and off-target)
 Myasthenia gravis
 MYH9-related disorders
 Myopia
 Myotonia congenita
 Myotonic dystrophy
 Myotubular myopathy

N

Nail-patella syndrome
 Nance-Insley syndrome
 Narcolepsy
 Nephrogenic diabetes insipidus
 Neu-Laxova syndrome
 Neural tube defects
 Neurofibromatosis
 Neuronal ceroid lipofuscinoses
 Nevoid basal cell carcinoma
 Next-generation sequencing
NGLY1 deficiency
 Niemann-Pick disease
 Nijmegen breakage syndrome
 Noninvasive prenatal screening
 Noonan syndrome
 Norrie disease
 Nucleic acid therapies

O

Obesity
 Oculodentodigital syndrome
 Oligohydramnios sequence
 Omphalocele
 Oncogene
 Opitz syndrome
 Oral-facial-digital syndrome
 Organic acidemias
 Ornithine transcarbamylase deficiency
 Osteoarthritis
 Osteogenesis imperfecta
 Osteoporosis
 Osteosarcoma
 Otopalatodigital syndrome
 Ovarian cancer

P

Pallister-Hall syndrome
 Pallister-Killian syndrome
 Pancreatic beta cell agenesis
 Pancreatic cancer
 Panic disorder
 Pantothenate kinase-associated neurodegeneration
 Parkes Weber syndrome
 Parkinson's disease
 Paroxysmal nocturnal hemoglobinuria
 Patent ductus arteriosus
 Pedigree analysis
 Pelizaeus-Merzbacher disease
 Pendred syndrome
 Pervasive developmental disorders
 Peutz-Jeghers syndrome
 Pfeiffer syndrome
 Pharmacogenetics
 Pharmacogenomics
 Phenylketonuria (PKU)
 Pierre-Robin sequence
 Poland anomaly
 Polycystic kidney disease
 Polycystic ovary syndrome
 Polydactyly
 Polygenic risk scoring
 Pompe disease
 Pontocerebellar hypoplasia (PCH)
 Porphyrias
 Prader-Willi syndrome
 Preimplantation genetic diagnosis
 Prenatal ultrasound
 Primary ciliary dyskinesia
 Primary familial brain calcification
 Primordial dwarfism
 Prion diseases
 Propionic acidemia
 Prostate cancer
 Protein C deficiency
 Protein S deficiency
 Proteus syndrome
 PRPS1 gene mutation—progressive hearing loss
 Prune-belly syndrome
 Pseudo-Gaucher disease
 Pseudoachondroplasia

Pseudoxanthoma elasticum
PTSD (post-traumatic stress disorder)
Pulmonary arterial hypertension
Pyloric stenosis
Pyruvate carboxylase deficiency
Pyruvate dehydrogenase complex deficiency
Pyruvate kinase deficiency

R

Race and genetics
Raynaud's disease
Recurrence risk counseling
Refsum disease
Renal agenesis
Renal failure due to hypertension
Renal-hepatic ciliopathy
Renpenning syndrome
Retinitis pigmentosa
Retinoblastoma
Rett syndrome
Rheumatoid arthritis
Rhizomelic chondrodysplasia punctata
Rhodopsin
Rieger syndrome
RNA (ribonucleic acid)
Roberts SC phocomelia
Robinow syndrome
Rothmund-Thomson syndrome
Rubinstein-Taybi syndrome
Russell-Silver syndrome

S

Saethre-Chotzen syndrome
Schinzel-Giedion syndrome
Schizophrenia
Schwartz-Jampel syndrome
Scleroderma
Sclerosing bone dysplasias
Scoliosis
Seckel syndrome
Selfish gene theory
Septo-optic dysplasia
Severe combined immunodeficiency

Short-rib thoracic dysplasia with or without polydactyly
Shprintzen-Goldberg craniosynostosis syndrome
Sialidosis
Sickle cell disease
Simpson-Golabi-Behmel syndrome
Single genome sequencing
Sirenomelia
Sjögren-Larsson syndrome
Skeletal dysplasia
Smith-Fineman-Myers syndrome
Smith-Lemli-Opitz syndrome
Smith-Magenis syndrome
Sotos syndrome
SPARCA1 spectrin-associated autosomal recessive cerebellar ataxia type 1
Spastic cerebral palsy
Spina bifida
Spinal and bulbar muscular atrophy
Spinal muscular atrophy
Spindle transfer technique
Spinocerebellar ataxia
Spinocerebellar ataxia 3
Spondyloepiphyseal dysplasia
Spondyloepiphyseal dysplasia congenita
SRY (sex-determining region Y)
Stargardt disease
Stem cells
Steroid-resistant nephrotic syndrome type 2/Galloway-Mowat syndrome
Stickler syndrome
Sturge-Weber syndrome
Super Enhancers (SE)
SWI/SNF-related autism syndrome

T

Tangier disease
TAR syndrome
Tay-Sachs disease
Teratogen
Thalidomide embryopathy
Thanatophoric dysplasia

Thoracic aortic aneurysms
Thyroid hormone resistance syndrome
Tourette syndrome
Treacher Collins syndrome
Trichorhinophalangeal syndrome
Triosephosphate isomerase deficiency
Triple X syndrome
Triploidy
Trismus-pseudocamptodactyly syndrome
Trisomy 13
Trisomy 8 mosaicism syndrome
Tuberous sclerosis complex
Turner syndrome
Twin reversed arterial perfusion (TRAP) sequence

U

Urea cycle disorders
Urogenital adysplasia syndrome
Usher syndrome

V

Van der Woude syndrome
VATER association
Viral variant
Von Hippel-Lindau syndrome
von Willebrand disease

W

Waardenburg syndrome
Walker-Warburg syndrome
Weaver syndrome
Weissenbacher-Zweymuller syndrome
Werner syndrome
Whole-exome and whole-genome sequencing
Williams syndrome
Wilson disease
Wiskott-Aldrich syndrome
Wolf-Hirschhorn syndrome
Wolman disease

X-Z

X-linked intellectual disability
 X-linked severe combined
 immunodeficiency
 X-linked sideroblastic anemia

Xeroderma pigmentosum
 XMEN
 XXXX Syndrome
 XXXXX syndrome
 XYY syndrome
 YY syndrome

Zebrafish studies
 Zellweger spectrum
 Zimmermann-Laband
 syndrome
 Zinner syndrome
 Zygote

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SYMBOL GUIDE FOR PEDIGREE CHARTS

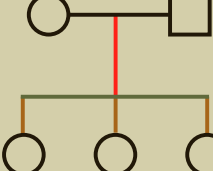
Pedigree charts are visual tools for documenting biological relationships in families and the presence of disorders. Using these charts, medical professionals such as geneticists and genetic counselors can analyze the genetic risk in a family for a particular trait or condition by tracking which individuals have the disorder and determining how it is inherited.

A standard set of symbols has been established for use in creating pedigree charts. Those found within the

body of several entries in the encyclopedia follow the symbol guide explained on the next page.

The exact style and amount of information presented on the chart varies for each family and depends on the trait or condition under investigation. Typically, only data that is directly related to the disorder being analyzed will be included. For more information, see the “Pedigree analysis” entry in the third volume.

Symbol Guide for Pedigree Charts

	Male		Miscarriage
	Female		Pregnancy terminated due to affected condition
	Affected male		Elective termination of pregnancy
	Affected female		Female with no children by choice
	Carrier male		Female with no children due to medical infertility
	Carrier female		Identical twin females
	Deceased male		Fraternal twin females
	Deceased female		Consanguineous relationship
	Male adopted into a family		Relationship no longer exists
	Female adopted into a family		Unknown family history
	Gender not specified		d.79y Died at 79 years
	Pregnancy		dx.41y Diagnosed at 41 years
	Four males		Relationship line Line of descent Sibship line Individual line
	Three females		



18p deletion syndrome

Definition

18p deletion syndrome involves a range of signs and symptoms resulting from a deletion of all or part of the short arm (p) of chromosome 18. These signs and symptoms vary greatly, depending on the extent of the deletion. However, they often include a short stature, distinctive facial features, and mild-to-moderate intellectual impairment. 18p deletion syndrome is also called partial monosomy of chromosome 18 or simply 18p.

Description

The 23 pairs of human chromosomes—one member of each pair from the mother and one from the father—carry the genes that confer the information for making all of the proteins in the body. A small constriction called the centromere divides each chromosome into a long arm (q) and a short arm (p). 18p deletion syndrome is caused by a missing piece from the short arm of one of the two members of the chromosome 18 pair. In comparison, 18q deletion syndrome is caused by a missing piece from the long arm of chromosome 18. The term “De Grouchy syndrome” can refer to either 18p or 18q deletion syndromes. The term “partial monosomy of chromosome 18p” indicates that the deleted genes are present only on the intact chromosome 18.

An 18p deletion may include all or only part of the short arm of chromosome 18, with signs and symptoms of the syndrome dependent on the specific genes that are missing. Like most other chromosome abnormalities, 18p increases the risk of birth defects, developmental delays, and learning disabilities, although specific problems vary greatly depending on the size of the deletion.

Genetic profile

Although the cause of 18p deletions is not known, in 85% of reported cases, the parents’ chromosomes are normal. Thus, the syndrome has usually not been inherited

from a parent with an 18p deletion. Rather, the deletion has arisen spontaneously, presumably during formation of the parental egg or sperm cell. This is called a *de novo* or spontaneous deletion. For this reason, parents of a child with 18p deletion syndrome are usually not at increased risk of having another child with the condition. In a small number of cases, the mother has been found to have an 18p deletion (as of 2015, there had been no reports of 18p fathers). In the case of an 18p parent, each of that parent’s offspring has a 50% risk of inheriting 18p deletion syndrome. Sometimes a parent of a child with 18p deletion syndrome is found to have a common chromosome abnormality known as a balanced translocation, in which genetic material has been exchanged between chromosomes. Because there is no significant gain or loss of genes, the translocation does not cause any symptoms in the parent. However, formation of the parent’s egg or sperm cells may be affected. In such cases, the likelihood of having another child with a chromosome 18 abnormality is greatly increased. It is also possible for 18p deletions to occur during fetal development, in which case only some cells in the body have the deletion. This is called mosaic 18p deletion syndrome.

In most people with 18p deletion syndrome, the 18p is the only chromosome abnormality. However, sometimes the deletion results from a more complex chromosome rearrangement, such as an unbalanced translocation. Such a rearrangement may cause not only 18p but also the duplication of another piece of a chromosome. The symptoms of such a rearrangement are difficult to predict, since the affected individual may have characteristics of a chromosome duplication as well as a deletion.

Chromosome 18 contains about 2.5% of the total DNA of a cell. The short (p) arm is estimated to have about 100 genes, whereas the long (q) arm contains 300–500 genes. Thus far, all reported cases of 18p are missing the chromosome tip (distal portion). Studies have suggested that many people with 18p deletion syndrome—but by no means all—have a chromosome 18 that broke off at a “hot-spot” near the centromere known as 18p11.1. Researchers

are trying to correlate the breakpoints in 18p and the lost genes with symptoms. For example:

- Patients with a deletion that leaves intact the chromosome region 18p11.1–18p11.21 have normal intelligence or only very minor learning difficulties compared to patients with deletions in this region.
- Holoprosencephaly (HPE), a malformation of the forebrain that also affects facial features, has been mapped to the most distal portion of 18p (the tip) in at least some patients.
- A round face appears to also be due to deletion of a distal region.
- Growth retardation and seizures appear to correlate with loss of the distal half of 18p.
- Drooping of the upper eyelid (ptosis) and a short neck have been mapped to loss of the proximal (closest to the centromere) half of 18p.
- Dystonia (abnormal muscle tone or contraction), which affects a few patients with 18p deletion syndrome, has been mapped to a region that includes the *DYT7* gene.

Demographics

18p deletion syndrome is very rare, affecting about 1 in 50,000 births. Since the first report of the syndrome by Jean de Grouchy and his research team in 1963, more than 150 case studies have been published. Approximately 60% of reported cases are female, and the actual ratio of affected females to males may be higher.

Signs and symptoms

Symptoms and their severity vary greatly. Many traits associated with 18p deletion syndrome are relatively non-specific and are affected by multiple genes on multiple chromosomes, contributing to symptom variability. There have even been reports of people with 18p with few or no symptoms who were not diagnosed until they had severely affected children. Many symptoms of 18p deletion syndrome are similar to those of 18q deletion syndrome. About 80% of 18p deletion syndrome patients have vision problems, especially strabismus (imbalanced eye muscles). Other common symptoms include:

- short stature, sometimes due to growth hormone deficiency
- a round face
- large ears
- ptosis
- mild-to-moderate intellectual impairment, although IQ scores vary from normal to severely impaired
- developmental delays
- speech delay and communication difficulties
- sinking in of the sternum in the chest (pectus excavatum or funnel chest)

- curvature of the spine
- hypotonia (low muscle tone)
- frequent ear infections in infants and children
- foot abnormalities

Serious brain and spinal cord abnormalities affect 10% to 15% of patients. About 10% of patients have brain malformations associated with HPE, in which the brain fails to completely divide into hemispheres. This leads to cleft lip, cleft palate, a flat nasal bridge, and closely spaced eyes. Between 10% and 25% of patients have heart defects. Other reported symptoms include:

- pituitary hormone deficiencies
- thyroid problems
- a small head (microcephaly)
- wide-set eyes (hypertelorism)
- an extra skin fold at the inner corner of the eye (epicanthal fold)
- short, webbed neck
- small jaw
- palate abnormalities
- dental abnormalities
- enlarged tonsils
- a broad trunk
- minor genital abnormalities, especially in males
- hand abnormalities
- hair abnormalities
- breathing problems including asthma
- digestive problems, especially chronic constipation
- juvenile arthritis
- deficiency in immunoglobulin A (IgA) antibodies, which can increase susceptibility to infection
- behavior problems, including aggressive behaviors and temper tantrums
- social and emotional problems
- hyperactivity and attention deficit
- sleep problems
- autism spectrum disorder
- seizures in a small number of children

Diagnosis

Examination

The most common characteristics of 18p deletion syndrome are non-specific and may not be obvious at birth. Even characteristic facial features may not become apparent until about age three. A complete neurological exam is used to detect and evaluate neurologic deficits.

KEY TERMS

18p—A deletion from the short arm of chromosome 18.

18q—A deletion from the long arm of chromosome 18.

Autism spectrum disorder—A variable developmental disorder that includes an impaired ability to communicate and form normal social relationships.

Centromere—A constricted region of a chromosome that is involved in cell division and is used to define the long arm (q) and short arm (p) of the chromosome.

Chromosomes—Linear structures of genetic material in the cell nucleus, consisting of DNA and proteins; human cells have 23 pairs of chromosomes, with one member of each pair contributed by each parent.

Cleft lip—Tissue of the upper lip that does not fuse during prenatal development.

Cleft palate—Abnormal development of the roof of the mouth that leaves an opening.

De Grouchy syndrome—Deletions in chromosome 18, originally identified in the 1960s by the French geneticist Jean de Grouchy.

Fluorescent in situ hybridization (FISH)—A technique used to visualize chromosome abnormalities.

Holoprosencephaly; HPE—An extremely variable developmental defect in the formation of the brain and face. The forebrain does not grow forward or divide completely into hemispheres.

Karyotype—The visual characteristics of the chromosomes of a cell.

Microcephaly—A small head.

Monosomy—The presence of only one chromosome of a pair. 18p is a partial monosomy, since it is the absence of a portion of one chromosome.

Preimplantation genetic diagnosis (PGD)—In vitro fertilization followed by genetic analysis of the resulting embryos to ensure that only healthy embryos are implanted in the mother's uterus.

Ptosis—A drooping upper eyelid.

Translocation—Transfer of part of a chromosome to another position, especially on a different chromosome. A balanced translocation does not result in the loss or duplication of any genetic material. However, an unbalanced translocation does involve loss or gain of genetic material.

Tests

Karyotyping visualizes the chromosomes in cells and can detect chromosome abnormalities such as rearrangements and deletions. Cytogenetic fluorescent in situ hybridization (FISH) can supply detailed information about the deleted chromosome region. A microarray called an array-CGH determines the exact DNA base pairs that are deleted. The parents' chromosomes are analyzed to determine whether the 18p was inherited or spontaneous.

Procedures

Various procedures are performed depending on the patient's suspected abnormalities. Procedures include magnetic resonance imaging (MRI) of the brain and spinal cord or an echocardiogram to detect heart defects. An electroencephalogram (EEG) may be performed if there is a risk of seizures.

Treatment and management

Traditional

Treatment and management depend on the specific symptoms. Surgeries can correct some abnormalities. Plastic surgery can correct craniofacial abnormalities,

specifically ptosis, cleft lip, or palate. Some children require special supportive footwear or braces for orthopedic problems. Regular screening is important for detecting vision, hearing, thyroid, and other problems. Extra dental care is very important. Physical, occupational, and speech therapies, special-needs education, and supportive care can alleviate other symptoms of 18p deletion syndrome.

Drugs

Drug therapy also depends on the symptoms. Children may be treated with growth hormone to prevent short stature. Anti-seizure medications can reduce or eliminate seizures.

Prognosis

The prognosis for 18p deletion syndrome depends on the specific symptoms and their severity. Severe congenital effects may cause death before or shortly after birth. However, early death is the exception. In the absence of serious brain abnormalities, such as severe HPE, most people with 18p deletion syndrome have normal life-spans. Many people with 18p have only mild or moderate learning difficulties and can live active and independent or semi-independent lives.

QUESTIONS TO ASK YOUR DOCTOR

- What information will genetic tests provide about my child's syndrome?
- Did my child inherit 18p deletion syndrome from me or my partner?
- What are the chances that I will have another child with 18p deletion syndrome?
- What medical treatments and developmental supports will my child require?
- What is my child's prognosis?

Prevention

Sometimes 18p is detected prenatally by chorionic villus sampling or amniocentesis, and craniofacial abnormalities may be visible on prenatal ultrasounds. In most cases, 18p is not inherited from an affected parent and is caused by a spontaneous, unpredictable chromosome deletion. However, parents of a child with 18p deletion syndrome will be tested to see if either has an 18p deletion or chromosomal rearrangement that resulted in their child's syndrome. If so, they are at high risk of having another child with the deletion and may choose to have prenatal or preimplantation genetic diagnosis (PGD). PGD requires in vitro fertilization, embryo biopsies to obtain chromosome karyotypes, and subsequent implantation into the mother's uterus of one or more embryos with normal chromosomes.

Resources

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- Isik, Esra, et al. "Evaluation of Six Patients with Chromosome 18 Structural Anomalies and Novel Findings." *The Journal of Pediatric Research*, vol. 7, no. 4, 2020, p. 267+.
- Sheth, Harsh, et al. "Mosaic chromosome 18 anomaly delineated in a child with dysmorphism using a three-pronged cytogenetic techniques approach: a case report." *BMC Medical Genomics*, vol. 13, no. 1, 2020.
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"Chromosome 18." MedlinePlus Genetics. August 18, 2020. <https://medlineplus.gov/genetics/chromosome/18/#conditions> (accessed May 14, 2021).

ORGANIZATIONS

- Chromosome 18 Clinical Research Center. Department of Pediatrics, University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78229, (210) 567-7000, <https://wp.uthscsa.edu/chrome-18/>
- Chromosome 18 Registry & Research Society, 7155 Oakridge Drive, San Antonio, TX 78229, (210) 657-4968, office@chromosome18.org, <http://www.chromosome18.org>
- Unique—Rare Chromosome Disorder Support Group, The Stables, Station Rd. W., Oxted, UK RH8 9EE, +44(0)1883 723356, info@rarechromo.org, <http://www.rarechromo.org>

Margaret Alic, PhD

18q deletion syndrome

Definition

18q deletion syndrome includes the signs and symptoms caused by deletions of the long arm (q) of chromosome 18. The extent of the 18q deletion varies, affecting as many as 500 genes. Therefore, symptoms and severity also vary greatly, but may include mental disability or developmental delays, facial and limb abnormalities, hearing problems, and short stature, among others. 18q deletion syndrome is known by a variety of names including chromosome 18q-syndrome, monosomy 18q, De Grouchy syndrome, or simply 18q.

Description

Chromosomes are the structures that contain genes. A gene is made up of DNA and produces a protein. Chromosomes are thus structures that organize DNA in particular combinations for particular purposes. The 23 pairs of human chromosomes—one member of each pair is contributed by each parent—are numbered from one to 22 and then X and Y for the sex chromosomes. Observing the physical structure of a chromosome, one sees a small constriction, called the centromere, which divides each chromosome into a long arm (q) and a short arm (p). 18q deletion syndrome is caused by a missing piece of the long arm of one of the two members of the chromosome 18 pair. Most 18q deletions occur near the end of the long arm and are called distal 18q. Deletions near the centromere—known as proximal 18q—are very rare, with only a couple dozen cases described since proximal 18q was first identified in 1974. Because 18q deletions affect varying numbers of genes, symptoms of the

syndrome vary from mild to severe. For instance, some patients have intellectual disability (an IQ score below 70–75) and developmental delays, whereas others may have only very mild intellectual deficiencies or even normal intelligence and development. Many patients have distinctive facial features, such as a wide nose and mouth or a cleft palate.

Genetic profile

The cause of an 18q deletion is unknown. It typically occurs spontaneously, during formation of the egg or sperm in a parent or very early in embryonic development. Thus, most patients do not have a family history of the syndrome. It is not passed down from one generation to the next and is not likely to occur in siblings. In rare cases, however, a child may inherit the 18q deletion from a mildly affected parent or from a parent carrying a chromosomal rearrangement that does not involve the loss or gain of genetic material and produces no symptoms. If the 18q deletion occurs during fetal development, the affected individual may have a mixture of cells with and without the deletion. In most cases, the 18q deletion is the only chromosome abnormality. However, in some cases, the deletion is the result of a more complex rearrangement of chromosome 18. This, in turn, results in less predictable signs and symptoms.

Chromosomes are divided into “bands.” Distal 18q deletions usually start at bands 21 to 23 and extend to include the tip of the long chromosome arm. Proximal deletions usually involve chromosome segments between the centromere and band 21.1, leaving the tip of the chromosome intact.

Demographics

18q deletion syndrome is very rare, occurring in only about 1 in 40,000 births. Nevertheless, it is the second most common abnormality of chromosome 18 after trisomy 18 (an extra chromosome 18).

Signs and symptoms

Symptoms

Depending on which genes are missing, symptoms of a distal 18q deletion may include:

- short stature, possibly resulting from a growth hormone deficiency
- leukodystrophy—degeneration of white matter in the brain and spinal cord—which may be caused by the loss of a gene called myelin basic protein. This protein is important for the production of myelin that covers, protects, and insulates nerve fibers
- developmental delays

KEY TERMS

Aural atresia—The absence of the external ear canal.

Autism spectrum disorder—A variable developmental disorder that includes an impaired ability to communicate and form normal social relationships.

Centromere—A constricted region of chromosomes that is involved in cell division and is used to define the long arm (q) and short arm (p) of a chromosome.

Cleft lip—Tissue of the upper lip that does not fuse during prenatal development.

Cleft palate—Abnormal development of the roof of the mouth that leaves an opening.

De Grouchy syndrome—Deletions in chromosome 18, originally identified in the 1960s by the French geneticist Jean de Grouchy.

Distal 18q—A deletion of the end of the long arm of chromosome 18, including the tip.

Fluorescent in situ hybridization (FISH)—A technique that is used to visualize chromosome abnormalities.

Genital hypoplasia—Underdeveloped genitals.

Intellectual disability—A lack of normal mental development, usually defined as an IQ score below 70–75.

Leukodystrophy—Loss of myelin (white matter) in the brain, spinal cord, or peripheral nervous system.

Microcephaly—A small head.

Midfacial hypoplasia—Subnormal growth of the central face.

Myelin—The white, fatty, covering of nerve fibers.

Proximal 18q—A deletion within the long arm of chromosome 18, near the centromere.

- cognitive impairment including intellectual deficits
- autism spectrum disorder
- head and facial abnormalities, which can include an unusually small head (microcephaly), large protruding ears, widely spaced and deep-set eyes, a wide and downturned mouth, cleft lip and/or palate, and mid-facial hypoplasia.
- eye movement disorders or other vision problems
- skin problems
- limb, hand, and foot deformities, such as clubfoot or shortened thumbs

- hearing loss and aural atresia—absence of an external ear canal—often accompanied by malformation of the ear
- ear and sinus infections
- underdeveloped genitals (genital hypoplasia), especially in males
- heart defects or heart disease
- poor muscle tone, sometimes accompanied by mild obesity, poor reflexes, or tremor
- gastrointestinal problems such as reflux or hernias
- thyroid problems
- low levels of immunoglobulin A (IgA) antibodies, causing susceptibility to infection
- seizures
- behavioral problems, such as aggressiveness, tantrums, and/or hyperactivity

Proximal 18q deletions present different symptoms than distal 18q deletions. Proximal 18q deletions affect brain development and function. Children may have developmental delays, some degree of cognitive impairment, and speech problems. Patients with proximal 18q frequently have poor muscle tone. Seizures are much more common than with distal 18q deletions, affecting about half of patients with proximal 18q deletion syndrome. Heart defects are rare and problems with the genitourinary tract are less common in patients with proximal 18q deletion syndrome. Patients may have foot abnormalities. Although patients may have small stature, this does not appear to due to growth hormone deficiency. Vision problems are common with patients with proximal 18q deletion syndrome. However, hearing loss is less common than with distal 18q.

Diagnosis

Examination

Distinctive facial features—which may be evident only on close examination—as well as other physical abnormalities and developmental delay may help with a preliminary diagnosis. However, a confirmed diagnosis of 18q deletion syndrome requires a genetic test.

Tests

18q deletion syndrome is diagnosed by examining the chromosomes in cells using fluorescent in situ hybridization (FISH).

Procedures

Magnetic resonance imaging (MRI) is used to determine the extent of myelin deficiency in the central nervous system.

QUESTIONS TO ASK YOUR DOCTOR

- My baby has been diagnosed with 18q deletion syndrome; what types of developmental delays can I expect?
- What types of screenings should my child have and how often?
- At what age can my child safely be given growth hormones and how effective are they?
- Does my child require surgery for hearing loss?
- Are there any alternative treatments?
- Will my child always require seizure medication?

Treatment and management

Traditional

Although 18q deletion syndrome cannot be cured, many of the symptoms are treatable. For example, aural atresia can be relieved by surgery, called canalplasty, that creates a normal-sized ear canal. Plastic surgery can correct cleft lip or palate, midfacial hypoplasia, and other craniofacial abnormalities. Regular screening is important for detecting vision, hearing, and other problems. Extra dental care is very important. Physical therapy, special-needs education, and supportive care can alleviate other symptoms of the condition.

Drugs

Drug therapy depends on the symptoms. Children with distal 18q are often treated with growth hormone to prevent short stature. Anti-seizure medications can reduce or eliminate seizures.

Prognosis

Prognosis varies depending on the specific symptoms and their severity. Some characteristics of 18q, such as growth hormone deficiency, can be effectively treated. However, other symptoms, such as developmental delay or intellectual disability, may be lifelong. Most children with 18q who are in good health and have no major birth defects live into adulthood. The majority of patients with distal 18q die at a young age. The distal deletions include the transcription factor 4 (*TCF4*) gene, which leads to more complex medical and developmental problems, including breathing problems.

Prevention

Since 18q deletion syndrome is not usually inherited from an affected parent, there is no prevention. Although genetic testing for 18q can be performed on the amniotic fluid early in pregnancy, there is usually no reason to suspect the syndrome unless one parent is known to carry a chromosome 18 deletion or other chromosomal abnormality. In most cases, the risk that a couple will have a second child with 18q deletion syndrome is very low. However, if one parent has an 18q deletion, there is a 50% chance that each of his or her children will have the deletion.

Resources

PERIODICALS

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ORGANIZATIONS

- Arc of the United States, 1825 K Street NW, Suite 1200, Washington, DC 20006, (202) 534-3700, (800) 433-5255, (202) 534-3731, <https://thearc.org/about-us/contact-us/>, <https://www.thearc.org>
- Children's Craniofacial Association, 13140 Coit Road, Suite 517, Dallas, TX 75240, (800)535-3643, contactCCA@ccakids.com, <https://ccakids.org>
- Chromosome 18 Clinical Research Center. Department of Pediatrics, University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78229, (210) 567-7000, <https://wp.uthscsa.edu/chrome-18/>
- Chromosome 18 Registry & Research Society, 7155 Oakridge Drive, San Antonio, TX 78229, (210) 657-4968, office@chromosome18.org, <http://www.chromosome18.org>
- Unique—Rare Chromosome Disorder Support Group, The Stables, Station Rd. W., Oxted, UK RH8 9EE, +44(0)1883 723356, info@rarechromo.org, <http://www.rarechromo.org>

United Leukodystrophy Foundation, 224 North Second Street, Suite 2, Dekalb, IL 60115, (815) 748-3211, (800) 728-5483, (815)748-0844, office@ulf.org, <http://ulf.org>

Leslie A Mertz, PHD
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22q11.2 deletion syndrome

Definition

22q11.2 deletion syndrome is a relatively common genetic disorder characterized by congenital heart defects, palate abnormalities, distinct facial features, immune problems, learning disabilities, and other abnormalities. This syndrome is caused by a deletion of chromosomal material from the long arm of chromosome 22 (22q) that leads to a wide spectrum of effects.

Description

22q11.2 deletion syndrome is also known as velocardiofacial syndrome, DiGeorge syndrome, Sphrintzen syndrome, conotruncal anomaly face syndrome, and the CATCH-22 syndrome. Because of the wide variability in the features of this syndrome, medical professionals originally thought that 22q11.2 deletion syndrome was more than one syndrome, and it was separately described by a number of physicians—Dr. DiGeorge, Dr. Sphrintzen, and others. Dr. DiGeorge described the more severe end of 22q11.2 deletion syndrome (infants with congenital heart defects, unusual facial features, and immune system abnormalities). The term velocardiofacial (VCF) syndrome was used for the milder end of 22q11.2 deletion syndrome. These individuals usually had palate anomalies, distinct facial features, and learning disabilities.

22q11.2 deletion syndrome is an extremely variable syndrome. The main features are congenital heart defects, distinctive facial features, and palate (roof of the mouth) problems. Other problems include immune system abnormalities, thyroid problems, kidney abnormalities and learning difficulties including mild developmental delay. Very rarely do individuals have all of the problems associated with this syndrome. Most individuals with 22q11.2 deletion syndrome have only a few of the associated features. Some individuals with 22q11 deletion syndrome are very mildly affected, and others are more severely affected. The reason for the wide variability in this syndrome is not known.

Genetic profile

22q11.2 deletion syndrome is a genetic disorder caused by a deletion of chromosomal material from the

KEY TERMS

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Conotruncal heart abnormality—Congenital heart defects particularly involving the ventricular (lower chambers) outflow tracts of the heart includes subarterial ventricular septal defect, pulmonic valve atresia and stenosis, tetralogy of Fallot and truncus arteriosus.

Velo—Derived from the Latin word *velum*, meaning palate and back of the throat.

long arm of chromosome 22. A series of genes are located in this region. Individuals with 22q11.2 deletion syndrome may have some or all of these genes deleted. This syndrome is sometimes called a microdeletion syndrome or a contiguous gene syndrome. Contiguous refers to the fact that these genes are arranged next to each other. The size of the deletion can be large or small, which may explain why some individuals with 22q11.2 deletion syndrome are more severely affected than others. The exact genes responsible for this syndrome are not known.

22q11.2 deletion syndrome is an autosomal dominant disorder. Genes always come in pairs and in an autosomal dominant disorder only one gene needs to be missing or altered for an individual to have the disorder. About 10%–15% of the time, deletion of the long arm of chromosome 22 that causes this syndrome is inherited from a parent. If a parent has 22q11.2 deletion syndrome, then there is a 50% chance they will pass the deletion on to each of their children who will also be affected with 22q11 syndrome. For reasons that are not understood, it is possible for a parent with mild features of 22q11.2 deletion syndrome to have a child with severe features of the syndrome.

Although 22q11.2 deletion syndrome is an autosomal dominant disorder, over 85%–90% of individuals with this disorder are the only individuals in their family with this disorder. When this is the case, the chromosome deletion that causes 22q11.2 deletion syndrome is called *de novo*. A *de novo* deletion is one that occurs for the first time in the affected individual. The causes of *de novo* chromosome deletions are not known. Parents of a child with 22q11.2 deletion syndrome due to a *de novo* deletion are very unlikely to have a second child with 22q11.2 deletion syndrome.

Demographics

22q11.2 deletion syndrome is one of the most common chromosomal deletion syndromes. It is estimated that approximately 1 in 2,000 to 1 in 6,000 individuals has a deletion of chromosome 22q11. Approximately 130,000 individuals in the United States have 22q11.2 deletion syndrome. Because of the extreme variability of this syndrome, it is possible that individuals with milder features are under diagnosed and the exact incidence of this disorder is not known. As more physicians become familiar with this syndrome, it is likely that more individuals will be correctly diagnosed.

Individuals with 22q11.2 deletion syndrome are diagnosed based upon physical findings. Of infants born with congenital heart defects, 5% will be found to have a deletion of chromosome 22q11. Of infants with a cleft palate, approximately 5%–8% of them will be found to have a 22q11 deletion.

Signs and symptoms

22q11.2 deletion syndrome is a multisystem disorder. It is also sometimes referred to as velocardiofacial syndrome. This name reflects the organ systems that are most commonly affected in 22q11.2 deletion syndrome. “Velo” is from the Latin word *velum*, which means “palate” and back of the throat, “cardio” refers to the heart, and “facial” refers to the distinctive facial features of individuals with 22q11.2 deletion syndrome. While it may seem unusual that these three separate areas are affected, a possible explanation lies in the early development of the embryo. Very early in development, the cells that will become the heart, face and thyroid lie next to each other in a region called the neural crest. As the embryo continues to develop, these cells migrate or move to become organs (the heart, face, and palate). It is believed that the deletion of chromosomal material from chromosome 22q causes a problem in the migration of these cells leading to the variability of features or problems seen in 22q11.2 deletion syndrome.

In addition to the heart, palate, and face, many other organ systems can also be affected including the kidneys, the immune system, the brain, the throat, the skeletal system, the skin, the genitourinary system and the endocrine (hormone) system. It is not possible to cover every possible feature of 22q11.2 deletion syndrome, but the following is an overview of the most common features.

The characteristic facial features seen in individuals with 22q11.2 deletion syndrome include a long face with narrow palpebral fissures (the opening for the eyes), a prominent nasal bridge (the arch of the nose between the eyes), a slightly bulbous nasal tip, a long nose, small ears with thick helical folds, and a small jaw. None of these

features individually is abnormal, but the combination of features is characteristically seen in individuals with 22q11.2 deletion syndrome. These features may not be present or as easily noticeable in African-American individuals with 22q11.2 deletion syndrome.

Approximately 70% of individuals with 22q11.2 deletion syndrome have palate abnormalities. These may include complete cleft palate (an opening of the bones and skin of the roof of the mouth) or a submucous cleft palate (an opening of only the bones of the roof of the mouth covered by skin). Other individuals with 22q11.2 deletion syndrome have more subtle palate and throat abnormalities including velopharyngeal insufficiency, which is a problem in the coordination between the tongue, palate, and throat muscles. All of these problems can lead to feeding problems in infancy and speech problems such as hypernasal speech.

Cardiac or congenital heart defects are one of the more serious symptoms of 22q11.2 deletion syndrome and affect about 75% of individuals. There is a wide range of cardiac abnormalities seen in 22q11.2 deletion syndrome. Some are minor and may require no treatment, some are correctable by surgery, and others are invariably fatal. The most common heart defects seen in individuals with 22q11.2 deletion syndrome are truncus arteriosus, interrupted aortic arch, tetralogy of Fallot, ventricular septal defects (VSDs), pulmonary stenosis and patent ductus arteriosus. Many of these heart defects are known as conotruncal heart defects. Conotruncal refers to the type of embryonic cells that were involved in the development of these regions of the heart.

Immune problems are another of the serious problems associated with this syndrome. Because of the underdevelopment of the thymus gland, individuals with 22q11.2 deletion syndrome can have reduced amounts of the cells necessary to fight infections—T cells. Because of this reduction in T cells, individuals with 22q11.2 deletion syndrome are more prone to getting infections and less able to fight them off. The degree of immune deficiency can be variable with some individuals having life-threatening infections and others having much milder problems.

Growth problems may be seen in children with 22q11.2 deletion syndrome. Infants with 22q11.2 deletion syndrome are often diagnosed as having failure to thrive. This may result from feeding problems due to their palate abnormalities but they can also have gastroesophageal reflux and vomiting problems. It also appears that individuals with 22q11.2 deletion syndrome have generalized growth problems. Most adult individuals with 22q11.2 deletion syndrome have short stature.

Individuals with 22q11.2 deletion syndrome can also have specific learning disabilities and possibly mild developmental delay. The learning disabilities are specific. Most individuals with learning disabilities have a discrepancy between their performance IQ score (higher) and their verbal IQ score (lower) that indicates a nonverbal learning disability. Simple IQ testing may not reveal this learning disability and it is important to evaluate the components of IQ scores separately. Individuals with 22q11.2 deletion syndrome seem to do better at verbal learning and do well in subjects such as reading. They have more trouble with abstract concepts such as math.

Individuals with 22q11.2 deletion syndrome are also at risk to develop psychological problems and mental illness. 22q11.2 deletion syndrome has been associated with higher rates of bipolar affective disorder, manic-depressive illness, and schizoaffective disorder when compared to individuals who do not have 22q11.2 deletion syndrome. Other mood disorders, such as depression, also occur at a higher incidence in individuals with 22q11.2 deletion syndrome. Most of these disorders appear during adolescence or adulthood. Some individuals with 22q11.2 deletion syndrome are mildly mentally retarded. Others have learning disabilities and some are diagnosed as having attention deficit hyperactivity disorder.

Endocrine problems are also commonly seen. The endocrine system is the hormone producing system of the body and is composed of glands such as the thyroid and parathyroid. Individuals with 22q11.2 deletion syndrome may either be missing one or more of these glands or have underactive glands. An underactive thyroid is called hypothyroidism and an underactive parathyroid is called hypoparathyroidism. Because the parathyroids help to regulate the level of calcium in the body, individuals with 22q11.2 deletion syndrome also have problems with their calcium levels. Low levels of calcium can lead to seizures.

Individuals with 22q11.2 deletion syndrome may also have kidney problems such as a cystic kidney, missing (aplastic) kidney, or malformed kidney. They can have limb differences such as extra fingers or ribs, or problems with the vertebrae in the back that might lead to scoliosis.

Diagnosis

The diagnosis of 22q11.2 deletion syndrome is usually made by a physician familiar with the syndrome and based upon a physical examination of the individual and a review of the patient's medical history. It is often made in infants after a heart problem is diagnosed. In children without significant heart problems, the possibility of a diagnosis may first be raised by preschool teachers or by other medical professionals such as plastic surgeons and speech therapists. These medical professionals may be

QUESTIONS TO ASK YOUR DOCTOR

- Please explain the meaning of the term “22q11 syndrome.”
- What is the pattern of inheritance of 22q11 syndrome?
- What are the symptoms associated with 22q11 syndrome in children?
- Are there organizations that provide support for parents who have children with 22q11 syndrome?

seeing the child for one of the features of 22q11.2 deletion syndrome and may be the first ones to become suspicious about the diagnosis. In rare cases, the diagnosis is made in a parent after they have had an affected child.

While a diagnosis can be made based upon physical examination and medical history, the diagnosis is now confirmed by a DNA test.

Sometimes the 22q11 deletion is large enough that it can be seen during a karyotype analysis. A karyotype is a microscopic analysis of an individual's chromosomes. However, many 22q11 deletions are too small to be seen by microscopic examination, and another specific technique called fluorescent in situ hybridization testing, or FISH testing, can determine whether genetic material is missing. A FISH test will be positive (detect a deletion) in over 95% of individuals with 22q11.2 deletion syndrome. A negative FISH test for 22q11.2 deletion syndrome means that no genetic material is missing from the critical region on chromosome 22. Research testing on these individuals usually reveals that up to 5% of individuals with 22q11.2 deletion syndrome will have a smaller deletion that is not picked up by the routine FISH test.

Prenatal testing (testing during pregnancy) for 22q11.2 deletion syndrome is possible using the FISH test on DNA sample obtained by chorionic villus sampling (CVS) or by amniocentesis. Chorionic villus sampling is a prenatal test that is usually done at 10–12 weeks of pregnancy and involves removing a small amount of tissue from the placenta. Amniocentesis is a prenatal test that is usually performed at 16–18 weeks of pregnancy and involves removing a small amount of the amniotic fluid that surrounds the fetus. DNA is obtained from these samples and tested to see if the deletion responsible for 22q11.2 deletion syndrome is present. While prenatal testing is possible, it is not routinely performed. Typically, the test is done only if there is a family

history of 22q11.2 deletion syndrome or if a congenital heart defect has been seen on a sonogram (ultrasound).

A sonogram uses sound waves to provide an image of a fetus. During the second trimester of pregnancy, it becomes possible to evaluate the fetal heart. If a heart defect is detected, DNA testing may be offered to the parents (along with other tests) to determine the cause of the heart defect. Unfortunately, congenital heart defects are common and there are many other syndromes that also cause congenital heart defects.

Treatment and management

Because of the incredible variability seen in 22q11.2 deletion syndrome, there is no one plan of treatment for all affected individuals. The treatment and management of an individual with 22q11.2 deletion syndrome depends on his or her age and symptoms. Because 22q11.2 deletion syndrome is a multisystem disorder, it is important to have multiple evaluations. Individuals with 22q11.2 deletion syndrome may see geneticists, plastic surgeons, immunologists, cardiologists, rheumatologists, endocrinologists, ophthalmologists, neurosurgeons, pediatricians, audiologists, and specialists in feeding, speech, and child development.

It is important that all individuals with 22q11.2 deletion syndrome have a cardiac evaluation by a cardiologist. An evaluation may include special tests such as a chest x-ray, electrocardiogram, and echocardiogram (ultrasound of the heart). Some cardiac defects do not require treatment, and others may require surgery.

Because of the wide variety of cleft palate and velopharyngeal problems, all individuals with 22q11.2 deletion syndrome should be evaluated by a cleft palate team. Cleft palate teams may include a plastic surgeon, ENT (ear, nose, and throat) specialist, genetic counselor and other staff. Because of the effect of cleft palate abnormalities on speech, all children with deletion 22q11 should have a speech evaluation and speech therapy if necessary. A referral to a feeding specialist may also be helpful if there is a cleft problem or other medical problem that interferes with feeding.

Because of the possibility and serious nature of immune problems, individuals with 22q11.2 deletion syndrome should have an immune evaluation. This can be done by an immunologist and usually requires blood tests to check immune function.

Individuals with 22q11.2 deletion syndrome should also have an endocrinology examination to check the function of their thyroid, parathyroid, and pituitary glands. They may also see an endocrinologist if they are having growth problems.

Neurologists can help with issues such as seizures and other neurology problems. Psychiatrists can help with psychiatric illness and problems arising from having a chronic illness.

Individuals with 22q11.2 deletion syndrome should be seen by a geneticist to confirm the diagnosis and to discuss issues such as the inheritance of 22q11.2 deletion syndrome, the recurrence risks and the availability of pre-natal diagnosis. Geneticists can also help arrange the necessary medical consults.

Prognosis

The prognosis for individuals with 22q11.2 deletion syndrome is highly dependent on the medical complications of the specific individual. Because this is such a variable syndrome, it is impossible to give one prognosis. The cardiac defects associated with 22q11.2 deletion syndrome are a major variable in determining prognosis. Those with serious heart defects have a guarded prognosis. Individuals with 22q11.2 deletion syndrome with minor or treatable cardiac defects have a good prognosis. Good medical care and treatment of problems allows most individuals with 22q11.2 deletion syndrome to have a normal lifespan.

While the physical features and medical complications of 22q11.2 deletion syndrome can affect prognosis, the degree of intellectual and psychological disability can also have an effect. Those individuals with normal IQ and no mental illness have a good prognosis. Those with learning disabilities can benefit from specific educational interventions. Individuals with developmental delay need more help but can do well in sheltered environments. Individuals with mental illness may or may not do well. Some individuals benefit from psychiatric counseling and medication.

The range of abilities among individuals with 22q11.2 deletion syndrome is very wide, and the ultimate functioning of an individual is dependent on his or her abilities.

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ORGANIZATIONS

"22q and You" Center, The Children's Hospital of Philadelphia, 3401 Civic Center Boulevard, Philadelphia, PA 19104, (215) 590-23800, (800) 879-2467, genetics@email.chop.edu, <http://www.chop.edu/centers-programs/22q-and-you-center>

Chromosome 22 Central, 7108 Partinwood Drive, Fuquay-Varina, NC 27526, (919) 567-8167, <http://www.c22c.org>

Cleft Lip and Palate Foundation of Smiles, 2044 Michael Avenue SW, Wyoming, MI 49509 (616) 329-1335, <http://www.cleftsmile.org>

FACES: The National Craniofacial Association, 600 N. Holtzclaw Avenue, Chattanooga, TN 37404, (423) 266-1632, (800) 332-2373, faces@faces-cranio.org, <http://www.faces-cranio.org>

International 22q11.2 Deletion Syndrome Foundation, Inc., P.O. Box 532, Matawan, NJ 07747, (877) 739-1849, info@22q.org, <http://www.22q.org>

Kathleen Fergus, MS, CGC

22q13 deletion syndrome

Definition

The 22q13 deletion syndrome is a microdeletion syndrome. It results from missing a small segment of genetic material on the end of the long arm (q) of chromosome 22. The condition was first described in the literature in the 1980s. Individuals with the condition have a variety of features. The most common features are developmental delay, delayed or absent speech, and weak muscles (also known as hypotonia or low muscle tone).

Description

Phelan-McDermid syndrome, also known as 22q12 deletion syndrome, is named after the doctors known for their research on this syndrome. In the past, the condition had been referred to by both names, but Phelan-McDermid syndrome is now the preferred name.

Phelan-McDermid syndrome results from a chromosome difference. People typically have 23 pairs of chromosomes. The first 22 chromosomes are called autosomes and are numbered one to 22. The last pair are the sex chromosomes, identified as X and Y. Each chromosome has a long part (q) and a short part (p). Packed in the chromosomes are genes, which are important because they determine how a person grows, develops, and functions. They also determine physical features of an individual, such as eye color and the shape of a person's face. When a person's genes are missing or not working properly, the result can be health problems, learning difficulties, and/or physical differences.

Individuals with 22q13 deletion syndrome are missing part of a chromosome. The syndrome's name provides the location of the missing part. It is on the long arm of chromosome 22 at the very end (location q13). Since the 22q13 region contains genes, people missing this region do not have all the proper instructions for development. As a result, they have similar learning difficulties, physical differences, and behavior problems.

Genetic profile

The 22q13 deletion syndrome is caused by an absence of genetic material on chromosome 22. There are several different ways for an individual to have a deletion of 22q13. Approximately 80% of individuals with Phelan-McDermid syndrome have either a terminal deletion of 22q13 or an interstitial deletion of 22q13. A terminal deletion of 22q13 occurs when the entire short arm of chromosome 22 after the regions of 22q13 is missing. An interstitial deletion of 22q13 occurs when a small area within the 22q13 region is deleted but the rest of the long arm is still present. Approximately 20% of people with Phelan-McDermid syndrome have deletions of 22q13 due to a chromosome rearrangement such as an unbalanced chromosome translocation or other type of chromosome rearrangement. A very small number of people have Phelan-McDermid syndrome due to a disruption or mutation within the *SHANK3* gene.

Three genes have been identified as involved in causing the features of Phelan-McDermid syndrome—*SHANK3*, *ACR*, and *RABL2B*. The *SHANK3* gene is the critical gene for the diagnosis of Phelan-McDermid

KEY TERMS

Microdeletion syndrome—A syndrome caused by the deletion of a very small amount of chromosomal material.

Prenatal diagnosis—The use of a medical test to determine if an unborn baby has the genetic condition.

syndrome. Virtually all individuals with Phelan-McDermid syndrome have a deletion of this gene, or other genetic change within the *SHANK3* gene, that disrupts the function of this gene. The *SHANK3* gene codes for the SHANK3 protein, which is found in the brain, heart, kidney and other organs. The SHANK3 protein's most important role is in the brain. Researchers believe an absence of the SHANK3 protein causes the neurological features of intellectual disability and speech delay. In addition, mutations in the *SHANK3* have been seen in individuals with autism.

When a person is diagnosed with 22q13 deletion syndrome, it is usually the first time it has been seen in the family. For most parents, the chance of having a second child with the condition is low. In some families, however, an increased risk exists for having a second child with the syndrome. In these families, a parent usually has a balanced translocation, which means that parent has the correct amount of chromosome material, but the material is rearranged. The rearrangement usually does not cause problems in the parent. However, when the parent has a child, the child may receive extra or missing pieces of chromosome material.

If a parent has a balanced translocation involving the 22q13 region, he or she may be at risk of having multiple children with the syndrome. Therefore, parents of a child with 22q13 deletion syndrome should consider genetic testing for balanced translocations. Parents who are found to carry a translocation may decide to pursue prenatal diagnosis for future pregnancies. If an individual with 22q13 deletion syndrome had children, he or she would have a 50% chance of having a child with the condition and a 50% chance of having a child without the condition. As of the past few years, there were no known cases of an individual with the condition having children.

Demographics

The 22q13 deletion syndrome affects males, females, and all ethnicities. It is not known how many people have

22q13 deletion syndrome. The syndrome is considered rare, and researchers believe it is often underdiagnosed.

Signs and symptoms

Individuals with 22q13 deletion syndrome have a variety of symptoms. In addition, the severity of each feature ranges from mild to severe. Therefore, two people with the syndrome may have very different characteristics. The characteristics most commonly seen are developmental delay, low muscle tone, speech difficulties (lack of speech or absence of speech), and advanced growth. Many individuals also have behavior differences, including autistic-like behavior and/or excessive chewing.

In addition, some children learn a specific skill and lose it. The medical term for the loss of a skill is regression. When children with the condition lose a skill, it is usually in the area of speech. Other characteristics that are not as common in the syndrome but have been reported include drooping eyelids, large head, webbing between the second and third toes, large hands, lack of sweat, seizures, flaky toenails, and differently shaped ears, skull, and/or forehead.

Diagnosis

The diagnosis is made by determining the 22q13 chromosome region is missing. Sometimes the deletion of chromosome 22 can be seen by a routine chromosome analysis. Often, however, the deletion is difficult to see and other molecular genetic testing methodologies are used. While only one type of testing used to be the standard for diagnosis, new genetic testing methods are now preferred. The molecular genetic tests that are used to diagnose Phelan-McDermid syndrome include genomic microarray technologies, such as array-based comparative genomic hybridization (aCGH) or chromosomal microarray analysis (CMA) and targeted deletion analysis, such as fluorescence in situ hybridization (FISH) or multiplex ligation-dependent probe amplification (MLPA). The genomic microarray technologies look for copy number variants (CNVs), and can detect the 22q13.3 deletion. The targeted deletion analysis tests detect missing (deleted) or extra (duplicated) chromosome segments.

Recently, several suggestions regarding testing for the condition have been presented in the literature. One suggestion was that physicians should consider testing babies with an unknown cause of weak muscles at birth. Physicians should also test individuals with severe speech delay and autistic-like behavior or people with developmental delay, absent or delayed speech, and physical differences.

Treatment and management

Treatment for 22q13 varies depending on the presenting symptoms and physical differences. Individuals may see a variety of specialists, including geneticists, psychologists, and neurologists. Most people with the syndrome receive speech, occupational, and/or physical therapy. Each type of therapy helps with specific features of the syndrome. For example, speech therapy can help improve communication; occupational therapy can assist in developing life skills; physical therapy can help strengthen muscles.

Support groups and resources are available for individuals with 22q13 deletion syndrome and their families. Information can be obtained through the Phelan-McDermid Deletion Syndrome Foundation.

Prognosis

In general, most individuals with 22q13 deletion syndrome need help and supervision all of their lives. However, the specific prognosis varies with each person depending on his or her specific characteristics. For example, an individual with mild intellectual deficits and a few physical differences would be expected to have a better prognosis than a person with severe intellectual disability, no speech, and behavior problems. Also, some individuals will have regression or loss of a specific skill, especially in the area of speech. It is not possible to determine which people will lose skills.

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ORGANIZATIONS

Chromosome 22 Central, 7108 Partinwood Drive, Fuquay-Varina, NC Canada 27526, info@c22c.org, <http://www.c22c.org>

Phelan-McDermid Syndrome Foundation, 8 Sorrento Drive, Osprey, FL 34229, (941) 485-8000, <http://www.pmsf.org>

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3D organoid biosystems

Definition

A 3D organoid biosystem is a three-dimensional (3D) group of cells grown outside of the body that mimics a human organ (organoid). Organoids are grown from cells derived from human stem cells or tissue from biopsy samples. Stem cells are undifferentiated cells from an adult or embryo that can develop into any cell of the body and can make copies of themselves indefinitely. They are used in research, drug discovery, vaccine development, and medical treatment and may one day be used for organ transplants.

Description

The word “organoid” means “organ-like.” Organoids have some of the functions of a real organ, but they are as small as the size of a pea. For example, a brain organoid has nerve cells (neurons) that can communicate with each other. A brain organoid also has different regions that are similar to those of the brain. Although organoids can currently be created that resemble some aspects of organs, they are not equivalent to a fully functioning organ. For example, intestine organoids have a structure that is similar to the lining of the intestine, but they are not as complex as the intestinal tract.

Organoids have three main characteristics:

1. They are 3D mini-organs made up of several types of cells.
2. They have the complexity and organization of an organ.
3. They have some of the functionality of an organ.

The limitations of using organoids are:

KEY TERMS

Biopsy—The examination of a piece of tissue taken from the body. It is often done when there is a tumor or other abnormality.

Cell—Building blocks that provide structure to the body and perform all of the functions of the body. Cells contain genetic information and can copy themselves. There are many different types of cells in the body.

Embryonic stem cells—Cells that are derived from the early human embryo that can transform into any different type of cell and can make copies of themselves indefinitely.

Induced pluripotent stem cells—Adult cells that are reprogrammed so that they can develop into all types of cells of the body and can make copies of themselves indefinitely.

Organ—An organ is a group of cells that form a structure that has a specific function. For example, the heart, stomach, or brain.

Stem cells—Cells that can transform into any different type of cell and can make copies of themselves indefinitely.

Tissue—Living material that is made up of cells that have a common function. The four types of tissue are connective, epithelial (skin), muscle, and nervous tissue.

- They do not contain all of the types of cells found in a real organ, so they do not completely represent an organ.
- It can be hard for researchers to recreate a specific disease in an organoid.
- They do not have all of the functionality of an organ.
- They can take years to develop.

Organoid Uses

Human organoids are currently used in research to develop drugs and study disease, body functions, and development. For example, they have been used to study things like intestinal function, infectious and genetic diseases. In the future, they may be used to create organs that can be used in transplants.

Researchers can study genetic diseases by growing organoids from cells that have gene mutations. This can help them see how different mutations cause certain genetic conditions. For example, researchers used intestinal organoids to discover a gene mutation that prevents the intestines from developing properly. They found that

they were unable to create healthy intestinal organoids when they used tissue from six patients with an intestinal disorder, and they discovered that the six patients had a mutation in the same gene that was involved in the development of the intestines.

Organoid research can also be used to study how microbes like viruses and bacteria infect human cells. For example, researchers have used lung organoids the size of a lentil to study the impact of COVID-19 on the lungs. They also have used organoids to discover how SARS-CoV-2, the virus that causes COVID-19, can infect different types of organoids. This work allowed them to demonstrate how COVID-19 attacks multiple organs and not just the lungs.

Organoids are used in the development of medications. They allow researchers to see how well an organ responds to a drug candidate and whether the drug is toxic. Organoids make drug discovery easier, because they allow researchers to study many different types of drugs at the same time and to test on human organs earlier rather than testing them solely on animals. In the future, organoids made from a patient's stem cells could allow for the development of personalized medicine, customized for each individual patient.

Organoid Development

To make organoids, researchers take stem cells or cells from tissue and add them to a medium in which they can grow, like a protein material. They then provide them with an environment that will promote growth by adding specific nutrients and chemicals. Often, these components must be added in a particular order and way. The growing conditions also help the stem cells multiply and develop into the different cells that are part of the organ that is being mimicked. The cells need to organize themselves in the structures found in the organ. For example, the cells in kidney organoids organize themselves into small tubes (tubules) like those in real kidneys. It is difficult to create organoids, and it can take many years to figure out the proper growing conditions. Once the growing conditions have been worked out and provided to the cells, the cells can develop into organoids on their own.

3D printing of Organoids

3D printing promises to help speed the development process, reduce the costs, and increase the size of organoids. It also may be possible to 3D-print organs for transplantation. Eventually, it could be possible to take cells from a patient and use them to create the tissue or organ that they need, which could eliminate the risk of rejection found by using donor organs and could decrease the difficulty and cost of finding a suitable donor.

Organoids can be created by special 3D printers that use ink made of live cells or biological materials that can provide support to the cells. The printer converts a computer model into a printed shape. Harvard University professor Jennifer Lewis is researching using 3D printing to create heart organoids. She used a 3D printer to create sections of heart tissue and then added stem cells, which were stimulated to form heart cells. Eventually, all of the cells fused together and began to beat together like a heart. Researchers hope to be able to 3D print the entire heart for use in transplants.

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Lisa M. Andres, MS, CGC

3-M syndrome

Definition

3-M syndrome is a rare autosomal recessive disorder characterized by dysmorphic features such as short stature (dwarfism), skeletal abnormalities, and growth retardation without abnormal cognitive function. It was named for the researchers who first identified it (Miller, McKusick, and Malvaux). This syndrome may also be referred to as 3-MSBN, dolichospondylic dysplasia, or Le Merrer syndrome.

Description

3-M syndrome is an intrauterine growth malformation syndrome caused by mutation of a gene coding for proteins largely associated with the checks and balances of other proteins. Individuals with the syndrome display a slow growth rate and symptoms limited mostly to the skeletal system. The types of mutations seen throughout 3-M syndrome research include, but are not limited to, substitutions of one amino acid for another sometime during the coding process (DNA replication, transcription, or translation) of the cullin 7 protein. Other mutations of the gene result in a cullin 7 protein that is abnormally short and nonfunctional.

Genetic profile

Gene mutations in 3-M syndrome occur in the CUL7, OBSL1, or CCDC8 genes. The CUL7 gene has a cytogenic location 6p21.1, meaning that it is located on the short arm of chromosome 6 at position 21.1. It has a molecular location on chromosome 6 from base pairs 43,037,616 to 43,053,949. CUL7, also known as cullin 7 for the protein it codes for, appears to be the major gene responsible for causing 3-M syndrome. It is seen in roughly 77% of cases, while OBSL1 mutations account for roughly 16% and CCDC8 mutations account for roughly 7%. Research has identified at least 25 mutations in the CUL7 gene in individuals previously diagnosed with 3-M syndrome.

In addition to the 25 recorded mutations that have an outcome of 3-M syndrome, one other variant has also been discovered. This variant, found within a small population of individuals in the Yakut region of Siberia, has recently been categorized as a heterozygous autosomal recessive mutation. The mutation has been mapped out to show that the CUL7 gene in this group genetically causes the substitution of a stop codon for one glutamine. The result of this exchange is an early stop of the coding of the rest of the gene, leading to incorrect coding for—and ultimately incorrect functioning of—the protein. Due to its heterogeneous nature, the Yakut variant of 3-M syndrome results in more severe physiological abnormalities. Other case studies around the world have revealed a homozygous deletion in exon 18, which causes a frameshift mutation of the CUL7 gene and leads to the disorder.

The CUL7 gene plays a role in the ubiquitin-proteasome system, which breaks down and disposes of unwanted or malformed proteins. This system also plays a role in the regulation of the levels of proteins involved in the timing of cell division and growth. CUL7 specifically codes for the protein cullin 7, which helps to assemble the E3 ubiquitin ligase complex. Cullin 7 works

KEY TERMS

Aneurysm—An abnormal blood-filled bulge in a blood vessel, and especially an artery, resulting from weakening (as from disease) of the vessel wall.

Asphyxia—The state of not being able to breathe.

Cognitive—Of, relating to, or involving conscious mental activities (such as thinking, understanding, learning, and remembering).

Cytogenic—Pertaining to the production of cells.

Dwarfism—The condition of stunted growth.

Dysmorphic—An anatomical malformation.

Growth Hormone—A vertebrate polypeptide hormone that is secreted by the anterior lobe of the pituitary gland and regulates growth.

Heterozygous mutation—A mutation in which both copies of a gene are mutated.

Intrauterine—Of, situated in, used in, or occurring within the uterus.

Ubiquitin-proteasome system—A multicomponent system that identifies and degrades unwanted proteins in the cytoplasm of all cells. It is involved in cell growth and differentiation, DNA replication and repair, apoptosis, and stress and immune responses.

within the complex alongside other proteins to tag and then dispose of unwanted proteins. When the gene is coded incorrectly, such as in the case of 3-M syndrome, the body cannot manage proteins correctly, which results in the malformation of the human body as a whole. Research, however, is lacking studies that outline the relationship between cullin 7 and the signs and symptoms of the disorder, specifically the connection between the protein and the skeletal system. Despite the lack of research in this area, however, it is known that these gene abnormalities only appear in 3-M syndrome.

Demographics

Although 3-M syndrome's prevalence is unknown, it is estimated that approximately 100 individuals have been diagnosed since the first case in 1975, found by Miller. Laws of Mendelian genetics and the literature have shown that each sibling of an individual with 3-M syndrome has a 25% chance of having the genetic mutation, a 50% chance of being a carrier, and a 25% chance of neither. Along with developing most of the identified physical and radiological characteristics of 3-M

syndrome, people with this form of the genetic disorder have a high prevalence of respiratory problems leading to death in infancy. This is more highly associated with the Yakut short stature syndrome variant seen in Siberia.

Signs and symptoms

Individuals with 3-M syndrome show signs of growth retardation in-utero, although they typically have a full or almost full gestation period. This slow growth rate occurs after birth as well and continues throughout childhood and adolescence until skeletal maturation occurs when growth ceases, as it does in all humans. Individuals with this genetic disturbance initially are low on the weight and length charts at birth, typically the first sign of the disorder. One study that compared birth weight and birth length of 4 individuals with 3-M syndrome showed an average of 3.28 standard deviation score (SDS) under the normal birth weight and an average of 5.14 SDS under the normal birth length. Clinical studies show that as development progresses, characteristic facies, radiological findings, and a lack of neurological and cognitive findings are noted as the major signs and symptoms of the disorder.

Characteristic facies typically observed in 3-M syndrome include the following:

- triangular face
- broad forehead
- frontal bossing
- short stature
- nostrils that are rotated into an anterior position
- disproportionate head-to-body ratio
- hypoplastic midface

The literature suggests that individuals with 3-M syndrome show abnormal radiological features including, but not limited to, the following:

- elongated and narrow vertebral bodies, particularly in the lumbar region
- broad thorax with slender and horizontal ribs
- flared metaphyses
- enlarged calcaneus
- slender, long bones
- Sprengel's deformity of the scapulae
- anterior wedging of thoracic vertebral bodies
- irregular upper and lower endplates
- thoracic kyphoscoliosis
- spina bifida occulta
- small pelvic bones
- small iliac wings
- slightly delayed bone age

QUESTIONS TO ASK YOUR DOCTOR

- What reproductive complications may I encounter during life, and how can this be rectified?
- Am I a candidate for rhGH treatment?
- How should I be evaluated for possible aneurysms and at what time in my life?
- Can my future spouse be tested for being a carrier for this gene to determine the chances of having a child with the syndrome?
- What options for treatment are available and applicable to me and my condition?
- Are there support groups for people who have similar syndromes?
- What are my limitations of activities of daily living? How can I improve my condition to decrease any limitations?

Diagnosis

A diagnosis of 3-M syndrome is suggested in children with low birth weight, severe growth retardation, characteristic facies, and characteristic radiological findings without any change to the abdomen, cardiovascular system, and/or nervous system. The signs and symptoms of the disorder have a high correlation to the diagnosis of the condition, although a genetic profiling test such as sequence analysis or deletion/duplication analysis is most important in the diagnosis of an individual thought to have the disorder. Genetic testing is helpful in differentiating 3-M syndrome from other genetic abnormalities showing dwarfism, such as Floating-Harbor syndrome, achondroplasia, spondyloepiphyseal dysplasia, diastrophic dysplasia, Russell-Silver syndrome, Dubowitz syndrome, Mulibrey nanism, and fetal alcohol syndrome. Bloodwork may also be a good diagnostic tool, but there is an inconsistency in cases with a deficiency in growth hormone.

Treatment and management

Individuals diagnosed with 3-M syndrome are screened and evaluated throughout life, though more so during skeletal immaturity. To evaluate the extent of the disease in an individual, a physical examination is performed. Joint mobility is evaluated to measure and control the development of arthritis. The level of arthritis noted may yield management as seen fit by orthopedic physicians or another healthcare physician. Individuals

are often screened throughout life to prevent brain aneurysms. In addition to physical examination, surveillance of growth every 6 to 12 months on standard growth charts, with special attention to growth rate, is recommended. A blood test for a growth hormone deficiency may also be recommended. If a blood test concludes a deficiency in growth hormone, the use of recombinant human GH (rhGH) for the treatment of short stature associated with 3-M syndrome may be used, as it has been documented in literature. However, significant individual variation is reported in relation to GH response. This variation may be accounted for by the variable response to GH based on the genotype, with a better response noted in patients that have a CCDC8 mutation as compared to an OBSL1 mutation.

In addition to physical examination and screening, males with 3-M syndrome should be referred for endocrinologic evaluation at puberty regarding gonad function.

Although treatment of 3-M syndrome is inconsistent, management of the disorder is positive. Adaptive aids for activities of daily living such as bathing, dressing, and driving vehicles have been established. Surgical bone lengthening may also be an option.

Genetic counseling may also be rendered, because there is a correlation between an individual with 3-M syndrome and future siblings developing the disorder. Prenatal screening can be done via ultrasound by checking for slow growth of all long bones. Carrier testing and prenatal testing may be administered for families with previously diagnosed family members as well.

Prognosis

The prognosis of individuals diagnosed with 3-M syndrome is good, due to the lack of signs and symptoms seen in other systems of the body aside from the skeletal system. The literature shows a small chance of early death occurring in infancy due to respiratory malfunctions associated with protein malformation, more specifically in the Yakut short stature syndrome variant. One study showed that of 43 diagnosed individuals in 37 Yakut families, approximately 42% of them had severe asphyxia and respiratory distress at birth associated with poor development of the cartilaginous lamina of the bronchi, leading to death.

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ORGANIZATIONS

- Genetic and Rare Diseases (GARD) Information Center, P.O. Box 8126, Gaithersburg, MD 20898-8126, (301) 251-4925, <http://rarediseases.info.nih.gov/GARD/>

Taryn Terry, DC, MSACN, BA

3-Methylglutaconic aciduria type 2

Definition

3-methylglutaconic aciduria type 2 (MGCA2) is a rare and serious X-linked metabolic and neuromuscular genetic disorder affecting males. It is one of five subtypes of 3-methylglutaconic aciduria (MGA), a group of disorders that affect the body's ability to make energy in the mitochondria of cells. As a result of this deficiency, two organic molecules called 3-methylglutaconic acid and 3-methylglutaric acid build up in the body and can be detected in the patient's urine. The disorder is also known as Barth syndrome, after the Dutch pediatrician who first reported on it in 1981 and demonstrated that it is an inherited disorder. It is also called BTHS and cardiomyopathy-neutropenia syndrome.

3-methylglutaconic aciduria type 2 is caused by a mutation in the tafazzin gene (referred to as *TAZ*) on the long arm of the X chromosome at Xq28. This mutation results in adverse effects on multiple systems of the body, including the cardiac and skeletal muscle systems. Severe infections and cardiac failure are common causes of death in individuals with 3-methylglutaconic aciduria type 2. There are over 160 different mutations of the *TAZ* gene that are known to cause 3-methylglutaconic aciduria type 2 as of 2015. The *TAZ* gene is also known as the *BTHS*, *CMD3A*, *EFE*, *G4.5*, or *LVNCX* gene.

Description

3-methylglutaconic aciduria type 2 was identified and described by Peter Barth (1932–) of the Netherlands in publications in 1981 and in 1983. Richard Kelley of Johns Hopkins University published an additional

description of the syndrome in 1991. The specific location of the gene on the X chromosome responsible for the disorder was identified in 1996.

Genetic profile

3-methylglutaconic aciduria type 2 is an X-linked recessive genetic condition that is usually transferred from mother to son. A mother who is a carrier of the syndrome will show no signs or symptoms of the disease. A female carrier has a 50% chance of giving birth to a son with 3-methylglutaconic aciduria type 2, while her daughters have a 50% chance of becoming carriers. Females with an X chromosome with a tafazzin mutation do not develop the syndrome as they have a second X chromosome with a normal tafazzin gene that is dominant over the recessive mutated tafazzin gene. All daughters of a male with 3-methylglutaconic aciduria type 2 will be carriers, but none of his sons.

Demographics

The prevalence rate of 3-methylglutaconic aciduria type 2 is estimated at between 1 in 300,000 to 1 in 400,000 male infant births and appears to occur in all ethnic groups. About 150 cases worldwide have been described in the medical literature. Fewer than ten new cases of the syndrome are identified each year in the United States. There are fewer than 500 individuals with 3-methylglutaconic aciduria type 2 listed on the registry of the Barth Syndrome Foundation.

3-methylglutaconic aciduria type 2 is listed as a rare disease by the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH) in the United States, which means that the syndrome affects fewer than 200,000 people in the U.S. population. Orphanet, a database of rare diseases and orphan drugs developed by a consortium of European partners, defines a condition as rare if it affects 1 in 2,000 people. 3-methylglutaconic aciduria type 2 is considered a rare disease by Orphanet. It is possible, however, that the incidence of the syndrome may be underestimated. Male infants and children who die of acute dilated cardiomyopathy are often thought to have viral myocarditis and may not have been tested for 3-methylglutaconic aciduria type 2.

Signs and symptoms

There is considerable variability in degree and type of conditions associated with individuals with 3-methylglutaconic aciduria type 2. The defining characteristics of the disease include the following conditions:

- Weak heart muscle
- Abnormally low level of neutrophils
- Muscles having a cellular deficiency

KEY TERMS

Cardiolipin—A type of lipid (fatty substance) found almost exclusively in the inner mitochondrial membrane where it is essential for the optimal function of numerous enzymes involved in mitochondrial energy metabolism.

Endocardial fibroelastosis (EFE)—An abnormal thickening of the lining of the heart tissue due to a concentration of elastic collagen-like fibers.

Heart arrhythmia—An abnormal heart rhythm, in which the heartbeats may be too slow, too rapid, too irregular, or too early.

Learning disability—Refers generally to a group of disorders manifested by significant difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning, or math abilities.

Mitochondria (singular, mitochondrion)—Specific compartments within cells that act as the cells' power plants. Mitochondria make and supply energy to cells to carry out all of the cells' jobs.

Tafazzin—A protein involved in modifying the structure of cardiolipin. Tafazzin adds a molecule of linoleic acid to the cardiolipin molecule, which enables cardiolipin to perform its functions. The protein was named for a comic character in an Italian television show by its discoverers, a team of Italian researchers.

Tafazzin gene (TAZ)—A human gene located on the X chromosome that encodes tafazzin, a protein expressed at high levels in cardiac and skeletal muscle. Mutations in this gene have been associated with a number of disorders, including 3-methylglutaconic aciduria type 2 and dilated cardiomyopathy.

Individuals with 3-methylglutaconic aciduria type 2 typically develop a weak heart muscle usually associated with enlargement of the heart. In most affected individuals, there is poor muscle tone at birth, with signs of cardiomyopathy typically developing during the newborn period or within the first few months of life. The left ventricle of the heart is often thicker than normal due to a concentration of elastic collagen-like fibers in its lining, a condition known as endocardial fibroelastosis (EFE). The thickening of the left ventricle leads to a reduced ability to pump blood from the heart to the lungs, thus increasing the risk of heart failure.

Individuals with the syndrome also have an abnormally low level of neutrophils, a type of white blood cell

that is important in fighting bacterial infections. This condition, referred to as neutropenia, can result in mouth ulcers, fevers, bacterial pneumonia, and skin abscesses. Neutropenia can be as dangerous to children with 3-methylglutaconic aciduria type 2 as cardiomyopathy.

3-methylglutaconic aciduria type 2 also results in muscles having a cellular deficiency that limits their ability to produce energy. Persons with the syndrome, therefore, exhibit muscular weakness, particularly in the muscles closest to the center of the body, and increased fatigue during movement, resulting in exercise intolerance. The children may exhibit a waddling gait and reduced muscle mass.

During childhood, individuals with 3-methylglutaconic aciduria type 2 are usually underweight and below average in height. Birth weight may be normal or slightly reduced, but by two years of age, children with the syndrome are noticeably below normal for height with a proportional or even much lower weight even when adequately nourished. However, they often reach normal or low-normal height during the mid- to late-teenage years. Males with the syndrome often have characteristic facial features that include chubby cheeks, deep-set eyes, and prominent ears.

3-methylglutaconic aciduria type 2 has adverse effects on the functioning of the mitochondria of cells, which are the primary energy producers in cells. Individuals with 3-methylglutaconic aciduria type 2 have an increase in the organic acid 3-methylglutaconic acid, which results in abnormal functioning of the mitochondria. The mitochondria also cannot make adequate amounts of tetralinoleoyl-cardiolipin, an essential lipid necessary for normal mitochondrial structure and activity.

The major problems associated with 3-methylglutaconic aciduria type 2 are congestive heart failure, heart arrhythmia, severe bacterial infections, gross and/or fine motor developmental delays, delay in growth, exercise intolerance, and lack of stamina. The heart arrhythmia often results in sudden death. Other problems that individuals with Barth syndrome may develop include frequent diarrhea, osteoporosis, chronic headaches, extreme fatigue, and feeding problems. Body aches also occur, especially during puberty. Most affected children have normal intelligence but may exhibit mild to moderate learning disabilities, especially in the areas of spatial and computational reasoning.

Diagnosis

An early diagnosis of 3-methylglutaconic aciduria type 2 is critical for survival. Any child or adult who has one or more of the characteristics of the condition should be evaluated. Genetic testing involving DNA

sequence analysis or mutation scanning of the entire coding region of the tafazzin gene is recommended. The diagnostic tests include:

- Urinalysis
- Cardiolipin analysis of muscle, blood platelets, or cultured cells
- A complete blood count and differential, which includes the total number of white blood cells as well as specific types of white cells. All indicate the presence of various types of infections or diseases
- An echocardiogram to create a moving picture of the heart

A complete family history should also be obtained, with emphasis on identifying cases of cardiac disease, failure-to-thrive, and unexplained infant or sudden deaths.

Treatment and management

There is no known cure for 3-methylglutaconic aciduria type 2. Treatment is supportive and palliative, and regular medical care tailored to the individual patient is essential to manage symptoms and conditions associated with the syndrome. Symptoms are treated as they occur. Antibiotics are used to treat infections. Granulocyte colony stimulating factor, or GCSF, can stimulate white cell production by bone marrow to fight infections. Various types of medicines can be used to control heart problems.

Diet should be monitored to assure that affected children do not become deficient in calcium or other nutrients. Overfeeding to encourage growth may lead to chronic diarrhea and increased acidosis. Children with 3-methylglutaconic aciduria type 2 have a lower level of potassium in their muscles and may become potassium-depleted during bouts of diarrhea. However, if the children are given intravenous fluids containing potassium to counteract potassium depletion, they may develop hyperkalemia (abnormally high levels of potassium in the blood), which can cause death.

Prognosis

In the past, males with 3-methylglutaconic aciduria type 2 usually died of heart failure or infection by three years of age. However, with improved detection of the syndrome and monitoring and treatment of symptoms, the survival rate and lifespan of affected children is increasing. In many children (estimated at up to 75%) affected by the syndrome who have been studied through puberty, cardiac disease has improved substantially. In some cases, it has even been cured by the end of the puberty growth spurt. Improved treatment with cardiac drugs and heart transplantation has eliminated progressive cardiac disease in many children. Between 1985

QUESTIONS TO ASK YOUR DOCTOR

- Which symptoms and conditions do we need to watch for in our child?
- Is heart transplantation an option in our child's case?
- Which medical specialists should we consult for our child's specific condition?
- What organizations and support groups are available?
- Where can we obtain genetic counseling for possible future pregnancies?

and 2005, in the United States, only 10% of children with 3-methylglutaconic aciduria type 2 have died, compared to 70% of their older relatives who were born before the diagnosis of the syndrome in their family was made.

In spite of advances in medical care, however, males with 3-methylglutaconic aciduria type 2 have shortened lifespans; those who survive into adulthood usually die in their late forties. Peter Barth reported in 2005 that no known female carriers of the defective *TAZ* gene show symptoms of the syndrome, and that their lifespans do not differ from that of the general population.

Prevention

There is no known prevention for 3-methylglutaconic aciduria type 2. Based on family history and known cases in family members and ancestors, parents may seek genetic counseling to determine their risk of having a child with the syndrome. They may seek genetic testing to evaluate the *tafazzin* gene status to determine whether the mother is a carrier of 3-methylglutaconic aciduria type 2. Based on the results of genetic testing, parents may choose to adopt, become pregnant with an egg from an unaffected donor, prevent pregnancy, or terminate an affected fetus. Counseling may also help parents prepare for treatment and care of an affected infant after birth.

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ORGANIZATIONS

American Academy of Pediatrics (AAP), 345 Park Boulevard, Itasca, IL 60143, (847) 434-4000, <http://www.2.aap.org/guestbook/contactus-form.cfm>

Barth Syndrome Foundation, 2005 Palmer Avenue, #1033, Larchmont, NY 10538, (914) 303-6323, <https://www.barthsyndrome.org/home>

Barth Syndrome Foundation of Canada, 162 Guelph Street, Suite 115, Georgetown, ON Canada L7G 5X7, (905) 873-2391, (888) 732-9458, <http://www.barthsyndrome.ca/home>

Children's Cardiomyopathy Foundation (CCF), 24 West Railroad Avenue, Suite 408, Tenafly, NJ 07670, (866) 808-CURE (2873), <http://www.childrenscardiomyopathy.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, <http://rarediseases.org>

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3-MSBN see **3-M syndrome**

46,XX testicular disorder of sex development

Definition

46,XX testicular disorder of sex development occurs when the affected individual appears as a normal male but has female chromosomes. Two types of 46,XX

Disorders associated with multiple X or Y chromosome inheritance

Disorder	Chromosome affected	Karyotype	Incidence	Symptoms
Turner syndrome	X	45,X (monosomy)	1 in 2,000	Growth retardation Infertility Cardiovascular malformations Learning disabilities
Klinefelter syndrome	X	47,XXY (trisomy)	1 in 500–800	Taller than average Poor upper body strength; clumsiness Mild intention tremor (20–50%) Breast enlargement (33%) Decreased testosterone production Infertility
Triple X	X	47,XXX (trisomy)	1 in 1,000	Dyslexia (50%) Mild delays in motor, linguistic and emotional development Learning disabilities
XYY syndrome	Y	47,XYY	1 in 1,000	Slightly taller than average Taller than average Lack of coordination Acne Some infertility Learning disabilities (50%) Behavior problems, especially impulse control
XX male syndrome	Y	46,X,t(X,Y) (translocation of the SRY gene [90%] or other gene responsible for male sex determination)	1 in 20,000–25,000	Usually normal male physical features but may have ambiguous genitalia, hypospadias or undescended testes Infertility Shorter than average

Disorders associated with multiple X or Y chromosome inheritance (Gale)

testicular disorder of sex development can occur: those with detectable *SRY* gene and those without detectable *SRY*. *SRY* is the main genetic switch for determining that a developing embryo will become male.

Description

46,XX testicular disorder of sex development is a condition in which the sex chromosomes of an individual do not agree with the physical sex of the affected person. Normally, there are 46 chromosomes, or 23 pairs of chromosomes, in each cell. The first 22 pairs are the same in men and women. The last pair, the sex chromosomes, may be two X chromosomes in females (XX) or an X chromosome and a Y chromosome in males (XY).

In 46,XX testicular disorder of sex development, the person has female chromosomes but male physical features. The majority of individuals with 46,XX testicular disorder of sex development have the Y chromosome gene *SRY* attached to one of their X chromosomes. The rest of the individuals with 46,XX testicular disorder of sex development do not have *SRY* detectable in their cells. Hence, other genes on other chromosomes in the pathway for determining sex must be responsible for their male physical features.

Genetic profile

If the 46,XX testicular disorder of sex development caused by the gene *SRY*, a translocation between the X chromosome and Y chromosome causes the condition. A translocation occurs when part of one chromosome breaks off and switches places with part of another chromosome. In 46,XX testicular disorder of sex development, the tip of the Y chromosome that includes *SRY* is translocated to the X chromosome. As a result, an embryo that has XX chromosomes with a translocated *SRY* gene will develop the physical characteristics of a male. Typically, a piece of the Y chromosome in the pseudo autosomal region exchanges with the tip of the X chromosome. In 46,XX testicular disorder of sex development, this crossover includes the *SRY* portion of the Y.

In individuals with 46,XX testicular disorder of sex development who do not have an *SRY* gene detectable in their cells, the cause of the condition is not known. Scientists believe that one or more genes that are involved in the development of the sex of an embryo are mutated or altered and cause physical male characteristics in a chromosomally female person. These genes could be located on the X chromosome or on one of the 22 pairs of autosomes that males and females have in common.

Approximately 20% of XX males do not have a known cause and are SRY negative. It is thought that SRY is a switch point. This means that the protein made by SRY regulates the activity of one or more genes (likely on an autosomal chromosome) that contribute to sex development. Some research has identified an autosomal recessive and autosomal dominant inheritance for the XX male.

Demographics

46,XX testicular disorder of sex development occurs in approximately 1 in 20,000 to 1 in 25,000 individuals. The vast majority, about 90%, have SRY detectable in their cells. The remaining 10% are SRY negative, although some research indicates that up to 20% can be SRY negative. As there is no ethnic or racial differences in occurrence, 46,XX testicular disorder of sex development can occur in any ethnic background. It usually occurs as a sporadic event, not inherited from the person's mother or father. However, some examples of more than one affected family member have been reported.

Signs and symptoms

SRY positive 46,XX testicular disorder of sex development

Males with SRY positive 46,XX testicular disorder of sex development look like and identify as males. They have normal male physical features including normal male body and genitalia. All males with 46,XX testicular disorder of sex development are infertile (cannot have biological children) because they lack the other genes on the Y chromosome involved in sperm production. Men with 46,XX testicular disorder of sex development are usually shorter than an average male. This is because they do not have certain genes on the Y chromosome involved in height. A similar syndrome that affects males with two X chromosomes is Klinefelter syndrome. Those individuals with Klinefelter syndrome present with symptoms such as small testes and infertility.

SRY negative 46,XX testicular disorder of sex development

People with SRY negative 46,XX testicular disorder of sex development are more likely to be born with physical features that suggest a condition. Many have hypospadias, where the opening of the penis is not at the tip, but further down on the shaft. They may also have undescended testicles, where the testicles remain in the body and do not drop into the scrotal sac. Occasionally, an SRY negative affected male has some female structures such as the uterus and fallopian tubes. Men with SRY-negative 46,XX testicular disorder of sex development

KEY TERMS

Autosomes—Chromosome not involved in specifying sex.

Chromosome—A microscopic thread-like structure found within each cell of the body consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or in their shape and size (structure) may lead to physical or mental abnormalities.

Embryo—The earliest stage of development of a human infant, usually used to refer to the first eight weeks of pregnancy. The term “fetus” is used from roughly the third month of pregnancy until delivery.

Gene—A building block of inheritance containing the instructions for the production of a particular protein and consisting of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

can also have gynecomastia, or breast development during puberty. Furthermore, puberty may be delayed. As with SRY positive 46,XX testicular disorder of sex development, these men are infertile and shorter than average because they lack other Y-specific genes. The physical features can vary within a family, but most affected people are raised as males.

A small portion of people with SRY negative 46,XX testicular disorder of sex development are true hermaphrodites. This means they have both testicular and ovarian tissue in their gonads. They are usually born with ambiguous genitalia, a condition where the genitals of the baby have both male and female characteristics. Individuals with 46,XX testicular disorder of sex development and true hermaphrodites can occur in the same family, suggesting there is a common genetic cause for both. Research indicates that 15% of 46XX true hermaphrodites have the SRY gene.

Diagnosis

For people with 46,XX testicular disorder of sex development who have ambiguous genitalia, hypospadias, and/or undescended testicles, the diagnosis is suspected at birth. For males with 46,XX testicular disorder of sex development and normal male features, the diagnosis can be suspected during puberty when breast development occurs. Many men do not know they have 46,XX testicular disorder of sex development until they try to

QUESTIONS TO ASK YOUR DOCTOR

- What are the risks and benefits of testicular surgery?
- At what point should I discuss the condition with my child?
- When should testing for SRY be performed?
- What are the risks of this condition occurring in future pregnancies?

have their own children, are unable to do so, and are evaluated for infertility.

When the condition is suspected in a male, chromosome studies can be done on a small sample of tissue such as blood or skin. The results show normal sex chromosomes, or XX chromosomes. Further genetic testing is needed to determine if the *SRY* gene is present.

Some affected individuals have had *SRY* found in testicular tissue but not in their blood cells. This is called mosaicism. Most males only have their blood cells tested for *SRY* and not their testicular tissue. Therefore, some men who think they have *SRY* negative 46,XX testicular disorder of sex development may actually be mosaic and have *SRY* in their gonads.

46,XX testicular disorder of sex development can be detected before a baby is born. This occurs when a mother-to-be has prenatal testing done that shows female chromosomes but on ultrasound male genitals are found. Often the mother has had prenatal testing for a reason other than 46,XX testicular disorder of sex development, such as for an increased risk of fetal Down syndrome due to her age. Genetic testing, such as fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR), can detect the presence of the *SRY* gene through amniocentesis. An amniocentesis is a procedure in which a needle is inserted through the mother's abdomen into the sac of fluid surrounding the baby. Some of the fluid is removed and used to test for the presence of the *SRY* gene. Amniocentesis slightly increases the risk of miscarriage.

Treatment and management

For those with 46,XX testicular disorder of sex development with normal male genitals and testicles, no treatment is necessary. Affected males with hypospadias or undescended testicles may require one or more surgeries to correct the condition. If gynecomastia is severe enough, breast reduction surgery is

possible. The rare person with true hermaphroditism usually requires surgery to remove the gonads, as they can become cancerous.

Parents who learn their child has been diagnosed with 46,XX testicular disorder of sex development are encouraged to seek both emotional and educational support. Issues such as explaining the condition to their child when they are grown may be easier with the help of both medical professionals and other parents whose children are living with the condition.

Prognosis

The prognosis for males with 46,XX testicular disorder of sex development is excellent. Surgery can usually correct any physical problems. Men with 46,XX testicular disorder of sex development have normal intelligence and a normal lifespan. However, all affected men will be infertile.

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ORGANIZATIONS

Accord Alliance, 3324 E. Ray Road, #578, Higley, AZ 08889, (602) 492-4144, <http://www.accordalliance.org>

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47,XXY syndrome see **Klinefelter syndrome**

4p minus syndrome see **Wolf-Hirschhorn syndrome**

5p deletion syndrome see **Cri du chat syndrome**

5p minus syndrome see **Cri du chat syndrome**

A-gammaglobulinemia tyrosine kinase see **Bruton agammaglobulinemia**

Aarskog syndrome

Definition

Aarskog syndrome is an inherited disorder that causes a distinctive appearance of the face, skeleton, genitals, hands, and feet. First described in a Norwegian family in 1970 by the pediatrician Dagfinn Aarskog, the disorder has been recognized worldwide in most ethnic and racial groups. Because the responsible gene is located on the X chromosome, Aarskog syndrome occurs almost exclusively in males. It is not known exactly how many people have the rare disorder.

Description

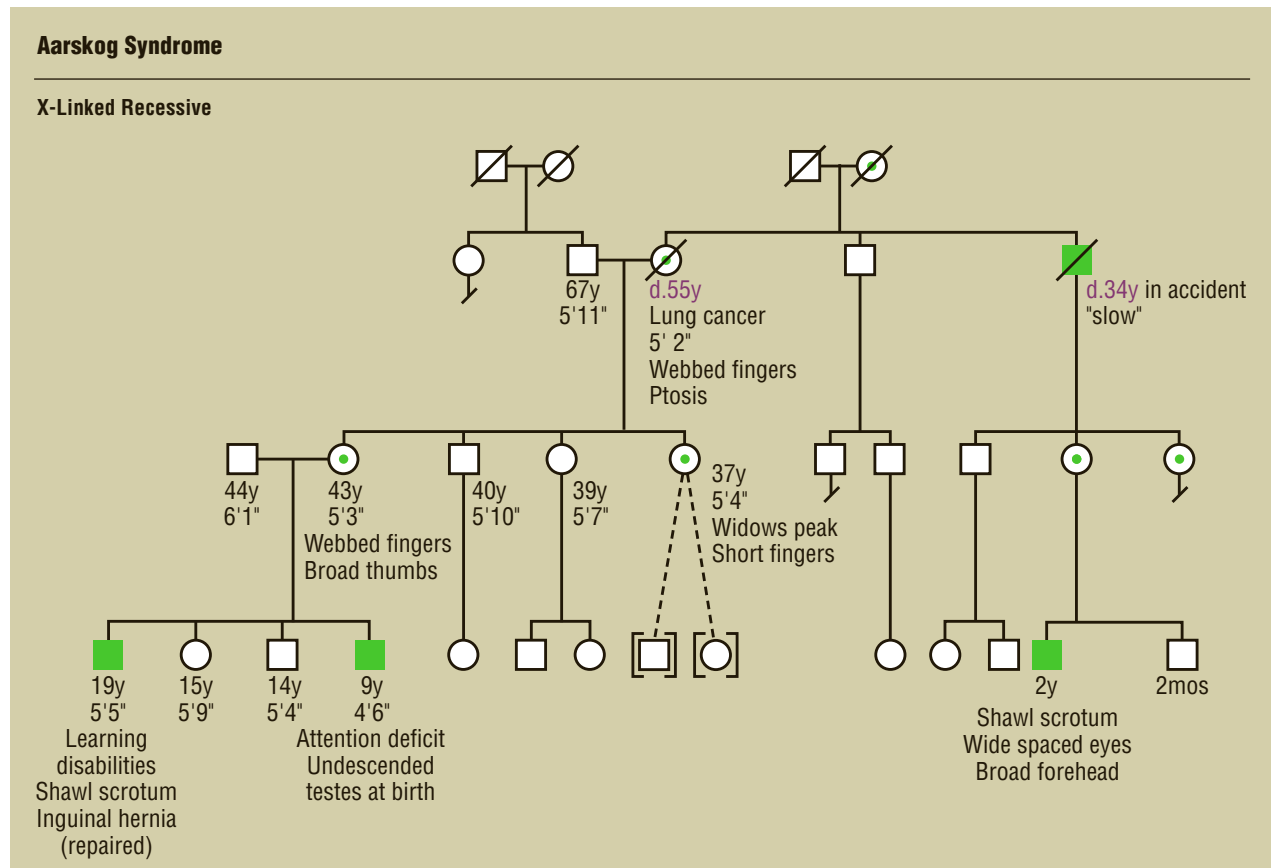
Aarskog syndrome is among the genetic disorders with distinctive patterns of physical findings. Signs are present at birth, which allows for early identification. The facial appearance and findings in the skeletal system and genitals combine to make a recognizable pattern. The diagnosis is almost exclusively based on recognition of these findings. Aarskog syndrome is also called

Faciogenital dysplasia, Faciogenitodigital syndrome, and Aarskog-Scott syndrome.

Genetic profile

About one-fifth of cases of Aarskog syndrome are caused by mutations in the *FGD1* gene, located on the short arm of the X chromosome (Xp11.21). As many as 20 different mutations in the *FGD1* gene have been identified as responsible for the syndrome. In most cases the altered gene in affected male offspring is inherited from a carrier mother. Since men have a single X chromosome, mutations in the *FGD1* gene produce full expression. Girls and women who carry a mutation of the *FGD1* gene on one of their two X chromosomes are usually unaffected, but may have subtle facial differences and less height than other female members of the family. There may be other causes of Aarskog syndrome, but they have not yet been identified.

Female carriers have a 50% chance of transmitting the altered *FGD1* gene to offspring. Affected men are fully capable of reproduction. They transmit their single X chromosome to all daughters who, therefore, are



Aarskog syndrome: pedigree analysis chart (Gale)

carriers. Since men do not transmit their single X chromosome to sons, all sons of male carriers are unaffected.

The gene affected in Aarskog, called *FGDI*, codes for a Rho/Rac guanine exchange factor. While the gene product is complex and the details of its function are incompletely understood, it appears responsible for conveying messages within cells that influence their internal architecture and the activity of specific signal pathways. *FDGI* also belongs to a family of genes called zinc fingers that provide instructions for making certain proteins. The precise way in which mutations in *FGDI* produce changes in facial appearance and in the skeletal and genital systems is not completely known, but research published in 2012 showed that the protein helps to regulate bone development. Therefore, the alteration in this protein could lead to the physical signs in those affected by Aarskog syndrome.

Demographics

Only boys and men are affected with Aarskog syndrome, although female carriers may have subtle changes of the facial structures and be shorter than noncarrier sisters. There are no high-risk racial or ethnic groups.

Signs and symptoms

Signs and symptoms of Aarskog syndrome are present from birth. The facial appearance is distinctive and in most cases is enough to help a doctor diagnose the disease. Changes are present in the upper, middle, and lower portion of the face. Increased width of the forehead, growth of scalp hair into the middle of the forehead (widow's peak), increased space between the eyes (ocular hypertelorism), a downward slant to the eye openings, and drooping of the upper eyelids (ptosis) are the major features in the upper part of the face. A boy also may have a short nose with forward-directed nostrils and simply formed small ears that may protrude. The mouth is usually wide and the chin is small. As the face elongates in adult life, the forehead becomes more prominent and the increased space between the eyes becomes less apparent. The teeth may erupt more slowly than normal, and the child may have missing teeth and broad upper incisors.

A person with Aarskog syndrome often holds his hand in a distinctive position flexed at the joint between the hand and the fingers, and the joints may appear lax or loose. This hand posturing becomes more obvious when there is an attempt to spread the fingers. There may also be some mild webbing between the fingers. The fingers are short, and there is often only a single crease across the middle of the palm. The person's toes are also shorter than normal, and the foot is often bent

KEY TERMS

Rho/Rac guanine exchange factor—Member of a class of proteins that appear to convey signals important in the structure and biochemical activity of cells.

inward at its middle portion. All of the joints may be unusually loose. Excessive movement of the cervical spine may cause it to press on the spinal cord. In some cases, the sternum (breastbone) may appear sunken (pectus excavatum).

Changes in the appearance of the genitals may also be helpful in diagnosis. At birth, one or both testes may remain in the abdomen area, rather than descending into the scrotal sac as they should. The scrotum tends to surround the penis giving a so-called "shawl scrotum" appearance. Hernias may appear in the genital and umbilical regions. In childhood and adulthood, the boy's or man's height is generally less than the height of unaffected brothers.

Although most affected males have normal intellectual function, some individuals have mild impairments. There does not appear to be any particular association with behavioral problems, although there are rare reports of them. However, attention deficit occurs among some affected boys with learning difficulties.

Diagnosis

Diagnosis of Aarskog syndrome is made based on clinical findings, primarily analysis of the family history and characteristic facial, skeletal, and genital findings. There are no specific laboratory or imaging tests that help doctors diagnose the syndrome. When necessary, the diagnosis can be confirmed by finding a mutation in the *FGDI* gene.

Families with a known history of Aarskog syndrome could consider prenatal diagnosis through ultrasound examination of the unborn child's face, hands and feet, or by testing for the *FGDI* gene. However, this is not generally sought since the condition is not considered medically severe.

Few other conditions are confused with Aarskog syndrome. Noonan syndrome, another single gene disorder that has symptoms of short stature, ocular hypertelorism, downslanting eye openings, and depression of the lower chest, poses the greatest diagnostic confusion. Patients with Noonan syndrome often have wide necks and heart defects, which is helpful in distinguishing them

QUESTIONS TO ASK YOUR DOCTOR

- How definite is the diagnosis?
- Is surgery in the umbilical or groin region recommended?
- What testing should my child have to be certain that developmental milestones are reached?
- At what point do you recommend testing for attention deficit disorder?

from patients with Aarskog syndrome. The disorder also can be confused with pseudohypoparathyroidism and Robinow's syndrome.

It may be more difficult to diagnose Aarskog syndrome in an older patient because facial symptoms are less obvious and scrotum is obscured by pubic hair.

As in many disorders, there is a range of severity of the clinical appearance even within the same family. In these cases, examination of several affected family members and attention to family history may be helpful.

Treatment and management

Since there are no major malformations or major mental disabilities in Aarskog syndrome, the diagnosis may be reassuring. Developmental milestones and school progress should be monitored, as there may be impairment of intellectual function in some individuals. Some children are treated with growth hormone therapy.

The X-linked inheritance pattern should be described to the family.

Prognosis

Short-term and long-term prognosis is favorable. Life threatening malformations or other health concerns rarely occur. Special educational attention may be necessary for those with learning difficulties. A few affected individuals have spinal cord compression, usually in the neck, causing pain or injury to peripheral nerves, and may need neurosurgery. Hernias in the umbilical and groin areas may be surgically repaired.

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ORGANIZATIONS

Genetic Alliance, 26400 Woodfield Road, #189, Damascus, MD 20872, (202) 966-5557, info@geneticalliance.org, <http://www.geneticalliance.org>

The MAGIC Foundation, 4200 Cantera Dr., #106, Warrenville, IL 60555, (630) 630-836-8200, (800) 362-4423, contactus@magicfoundation.org, <http://www.magicfoundation.org/>

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Abetalipoproteinemia

Definition

Abetalipoproteinemia (ABL) is a rare inherited disorder characterized by difficulty in absorbing fat during digestion. The result is absence of betalipoproteins in the blood, abnormally shaped red blood cells, and deficiencies of vitamins A, E, and K. Symptoms include intestinal, neurological, muscular, skeletal, and ocular problems, along with anemia and prolonged bleeding in some cases.

Description

An unusual sign first described in ABL is the presence of star-shaped red blood cells, which were dubbed "acanthocytes" (literally, *thorny cells*). Thus, ABL is also known by the name acanthocytosis. Less commonly, ABL may be referred to as Bassen-Kornzweig syndrome.

The underlying problem in ABL is a difficulty in absorbing fats (lipids) in the intestine. Most people with ABL first develop chronic digestive problems, and then progress to neurological, muscular, skeletal, and ocular disease. Disorders of the blood may also be present. Severe vitamin deficiency causes many of the symptoms in ABL. Treatments include restricting fat intake in the diet and vitamin supplementation. Even with early diagnosis and treatment, ABL is progressive and cannot be cured.

Fats are important components of a normal diet. Their processing, transport, and use by the body are critical to normal functioning. Lipids bind to protein (lipoprotein) so they can be absorbed in the intestine, transferred through the blood, and taken up by cells and tissues throughout the body. There are many different lipoprotein complexes in the body. One group, the betalipoproteins, must combine with another protein, microsomal triglyceride transfer protein (MTP). ABL is caused by abnormalities in the gene that codes for MTP. When MTP is nonfunctional or missing, then betalipoproteins will also be decreased or absent. The *MTP* gene has been localized to chromosome 4.

ABL is an autosomal recessive genetic disorder. This means that both copies of the *MTP* gene are abnormal in a person affected with the disorder. Since all genes are present at conception, a person cannot “acquire” ABL. Each parent of an affected child carries the abnormal *MTP* gene but also has a normally functioning gene of that pair. Enough functional MTP is produced by the normal gene so that the parent is unaffected (carrier). When both parents are carriers of the same recessive gene, there is a one in four chance in each pregnancy that they will have an affected child.

Demographics

ABL is rare; the true incidence of the disorder is unknown. Prior to the description of ABL in 1950, it is believed that people with ABL were diagnosed as having either Friedreich ataxia (a more common form of hereditary ataxia) or some other neurologic disorder. Misdiagnosis may still occur if all of the symptoms are not present or if they do not occur in a typical fashion. Most of the reported cases of ABL have been in the Jewish population, but individuals from other ethnic backgrounds have been described as well. As many as one-third of people with ABL have had genetically related (consanguineous) parents. Higher rates of consanguinity are often seen in rare autosomal recessive disorders.

Signs and symptoms

Too much fat left unabsorbed in the intestine results in the symptoms that are often noticed first in ABL, such as chronic diarrhea, loss of appetite, vomiting, slow weight gain, and slow growth due to reduced uptake of nutrients.

Various lipids, such as cholesterol and its components, are important in the development and normal functioning of nerve and muscle cells. Decreased lipid levels in the bloodstream, and thus elsewhere in the body, are partly responsible for the neuromuscular and ocular problems encountered in ABL. Neurological symptoms

KEY TERMS

Acanthocytosis—The presence of acanthocytes in the blood. Acanthocytes are red blood cells that have the appearance of thorns on their outer surface.

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Chylomicron—A type of lipoprotein made in the small intestine and used for transporting fats to other tissues in the body. MTP is necessary for the production of chylomicrons.

Clubfoot—Abnormal permanent bending of the ankle and foot. Also called talipes equinovarus.

Consanguinity—A mating between two people who are related to one another by blood.

Lipoprotein—A lipid and protein chemically bound together, which aids in transfer of the lipid in and out of cells, across the wall of the intestine, and through the blood stream.

Low density lipoproteins (LDL)—A cholesterol carrying substance that can remain in the blood stream for a long period of time.

Neuromuscular—Involving both the muscles and the nerves that control them.

Retinitis pigmentosa—Progressive deterioration of the retina, often leading to vision loss and blindness.

Triglycerides—Certain combinations of fatty acids (types of lipids) and glycerol.

Vitamin deficiency—Abnormally low levels of a vitamin in the body.

include ataxia (poor muscle coordination), loss of deep tendon reflexes, and decreased sensation to touch, pain, and temperature.

Muscular atrophy, the weakening and loss of muscle tissue, is caused by the decreased ability of nerves to control those muscles, as well as lack of nutrients for the muscles themselves. Weakened heart muscle (cardiomyopathy) may occur. Several severe cases of weakened heart muscle resulting in early death have been reported.

Retinitis pigmentosa is progressive especially without treatment. The typical symptoms are loss of night vision and reduced field of vision. Loss of clear vision, nystagmus (involuntary movement of the eyes), and eventual paralysis of the muscles that control the eye may also occur.

QUESTIONS TO ASK YOUR DOCTOR

- What specific foods should be eliminated to control triglycerides?
- What vitamin regimen do you recommend?
- Do you have specific recommendations to help with lipid absorption?
- Are there any therapies that can help with neuromuscular symptoms?

Skeletal problems associated with ABL include various types of curvature of the spine and clubfeet. The abnormalities of the spine and feet are thought to result from muscle strength imbalances in those areas during bone growth.

Severe anemia sometimes occurs in ABL and may be partly due to deficiencies of iron and folic acid (a B vitamin) from poor absorption of nutrients. In addition, because of their abnormal shape, acanthocytes are prematurely destroyed in the blood stream.

Vitamins A, E, and K are fat soluble, meaning they dissolve in lipids in order to be used by the body. Low lipid levels in the blood means that people with ABL have chronic deficiencies of vitamins A, E, and K. Much of the neuromuscular disease seen in ABL is thought to be caused by deficiencies of these vitamins, especially vitamin E.

Approximately one-third of all individuals with ABL develop mental retardation. However, since the proportion of cases involving consanguinity is also reported to be about one-third, it is difficult to determine if mental retardation in individuals with ABL is due to the disease itself or to other effects of consanguinity. Consanguinity may also be responsible for other birth defects seen infrequently in ABL.

Diagnosis

The diagnosis of ABL begins with observations of intestinal, neuromuscular, and ocular symptoms. It is confirmed by laboratory tests showing the presence of acanthocytes and the absence of betalipoproteins and chylomicrons in the blood. Other diseases resulting in similar intestinal or neurological symptoms, and those associated with symptoms related to malnutrition and vitamin deficiency must be excluded. There is no direct test of the *MTP* gene available in the United States for routine diagnostic testing. Accurate carrier testing and prenatal diagnosis are therefore not yet available. Any couple whose child is diagnosed with ABL should be

referred for genetic counseling to obtain the most up-to-date information.

Treatment and management

The recommended treatments for ABL include diet restrictions and vitamin supplementation. Reduced triglyceride content in the diet is suggested if intestinal symptoms require it. Large supplemental doses of vitamin E (tocopherol) have been shown to lessen or even reverse the neurological, muscular, and retinal symptoms in many cases. Supplementation with a water-soluble form of vitamin A is also suggested. Vitamin K therapy should be considered if blood-clotting problems occur.

Occupational and physical therapy can assist with any muscular and skeletal problems that arise. Physicians who specialize in orthopedics, digestive disorders, and eye disease should be involved. Support groups and specialty clinics for individuals with multisystem disorders such as ABL are available in nearly all metropolitan areas.

Prognosis

Because the condition ABL is rare, there have been few individuals on which to base prognostic information. The effectiveness of vitamin supplementation and diet restrictions will vary from person to person and family to family. Lifespan may be near normal with mild to moderate disability in some, but others may have more serious and even life-threatening complications. Arriving at the correct diagnosis as early as possible is important. However, this is often difficult in rare conditions such as ABL. Future therapies, if any, will likely focus on improving lipid absorption in the digestive tract. Further study of the *MTP* gene may lead to the availability of accurate carrier testing and prenatal diagnosis for some families.

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ORGANIZATIONS

March of Dimes Birth Defects Foundation, 1550 Crystal Drive, Arlington, VA 22202, (888) 663-4637, resourcecenter@modimes.org, <http://www.modimes.org>

National Foundation for Jewish Genetic Diseases, Inc, 1 Gustave L. Levy Place, New York, NY 10029-5674, (212) 241-6500, <https://icahn.mssm.edu/research/jewish-genetics>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06812-8923, (203) 744-0100, <http://www.rarediseases.org>

National Society of Genetic Counselors, 330 North Wabash Avenue, Suite 2000, Chicago, IL 60611, (312) 321-6834, <http://www.nsgc.org>

National Tay-Sachs and Allied Diseases Association, 2001 Beacon Street, Suite 204, Brighton, MA 02135, (617) 277-4463, ntasd-Boston@worldnet.att.net, <http://www.ntsad.org>

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Absence of vas deferens

Definition

Absence of vas deferens is a birth defect that causes male infertility. The vas deferens are the tubes that transport sperm from the testicle to the ejaculatory tube. Absence of vas deferens is most often associated with the genetic disorder cystic fibrosis (CF). The majority of men with CF (95%) are born without either vas deferens. This condition is referred to as congenital bilateral absence of vas deferens or CBAVD. Cystic fibrosis is caused by inheriting two defective CF genes, one from each parent. Absence of vas deferens can also occur in male carriers of a single defective CF gene who do not have symptoms of CF.

Description

The vas deferens (pl. vasa deferentia), also called the spermatic duct, is a thick-walled tube about 18 inches (45 cm) long that transports sperm from the testicle to the ejaculatory duct where the sperm is combined with semen. Absence of vas deferens is usually bilateral, meaning that the tubes on each side of the body fail to form. Absence of

vas deferens does not interfere with sperm production in the testicles or with semen production. However, the semen is ejaculated without the sperm required to fertilize an egg and thus is infertile. Absence of vas deferens can also be unilateral, meaning that the vas deferens is missing from only one testicle. The male retains his fertility. Congenital absence of the vas deferens is present at birth and is distinguished from similar conditions caused by an accident or surgery. An example of surgery would be vasectomy, where the vas deferens is cut to prevent sperm from reaching the semen as a form of birth control.

Absence of vas deferens has long been recognized as a symptom of CF. While males with CF present normal levels of sex hormones, they have azoospermia (absence of sperm). CF is an often-fatal, inherited disorder that affects the cells that produce mucus, sweat, and digestive enzymes. CF leads to progressive damage to the respiratory system and chronic digestive problems. Absence of vas deferens without CF was not recognized as a separate disorder until 1992, when it was identified by a team of doctors led by Arturo Anguiano and Robert Oates. Many men with one CF-causing gene have either unilateral or bilateral absence of vas deferens without other symptoms. Still, they sometimes have mild respiratory or digestive problems. A less common cause of absence of vas deferens is a prenatal abnormality that interferes with proper differentiation in the mesonephric duct, the primitive tube that develops into the vas deferens.

Genetic profile

CF and associated CBAVD are caused by mutations (changes) in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The *CFTR* protein forms a channel in cell membranes that enables chloride ions to move in and out of cells. Chloride ion flow helps control the water movement that is necessary for the production of thin, flowing mucus. If the *CFTR* protein is abnormal or absent, as in CF, chloride ions are prevented from exiting cells. This disrupts the normal movement of water in and out of cells and causes the production of thick, sticky mucus that blocks airways and ducts in the digestive system leading to progressive damage. CF also causes the formation of thick, sticky mucus in the male genital tract. This blocks the vasa deferentia as they are forming and causes them to deteriorate before birth.

Of the more than 1,900 known mutations that can occur in the *CFTR* gene, only 127 are known to cause CF. About 70% of CF cases in people of European ancestry are caused by a mutation called delta-F508. This is a deletion of three DNA bases in the *CFTR* gene that results in a *CFTR* protein missing a single amino acid—phenylalanine (F) at amino-acid position 508. This simple change results to all of the medical consequences of

KEY TERMS

Carrier—Having one abnormal gene for a trait, such as cystic fibrosis, and one normal gene for the trait (a heterozygote), without signs and symptoms of the disorder. A carrier can still pass the abnormal gene on to offspring.

Congenital bilateral absence of vas deferens (CBAVD)—The absence at birth of the vas deferens on each side of the male reproductive tract.

Cystic fibrosis (CF)—An inherited genetic disorder that affects many body systems, especially the lungs and digestive system, and produces absence of vas deferens in males.

Cystic fibrosis transmembrane conductance regulator (CFTR)—A protein responsible for regulating chloride movement across cells lining passageways and tubules in some tissues. Cystic fibrosis and absence of vas deferens can be caused by mutated *CFTR* genes.

Delta-F508—The most common cystic fibrosis-causing mutation in Caucasians, resulting in a defective CFTR protein due to the deletion of the amino acid phenylalanine (F) at amino-acid position 508 of the protein.

Epididymis—The mass of small ducts in which sperm mature before entering the vas deferens.

In vitro fertilization (IVF)—Fertilization of eggs removed from an ovary with male sperm using laboratory equipment, followed by implantation of the fertilized egg(s) into a woman's uterus.

Intracytoplasmic sperm injection (ICSI)—Fertilization process in which the sperm is injected directly into the cytoplasm of the egg using laboratory equipment.

Microsurgical epididymal sperm aspiration (MESA)—A surgical sperm retrieval method where a small needle is inserted into the epididymis and a syringe attached by tubing to the needle is used to withdraw the sperm under the observation of a microscope.

R117—A minor mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that can cause absence of vas deferens without causing cystic fibrosis.

Testicles—The testes and their enclosing structures.

Vas deferens (pl. vasa deferentia)—The tube that transports sperm from the testicle to the ejaculatory tube.

CF. However, this mutation is recessive, so that only children who inherit two copies of a defective *CFTR* gene—one from each parent—have CF, as well as CBAVD in males. Children who inherit a defective *CFTR* gene from one parent are “carriers” who can pass the defective gene on to their offspring. About one out of every 25 Caucasians carries a gene that can cause CF.

Stand-alone CBAVD without CF can occur in males who have inherited the delta-F508 mutation from one parent and a second mild mutation in the *CFTR* gene from the other parent. This second mutation, called R117H, changes the DNA sequence to replace the amino acid arginine (R) at position 117 of the CFTR protein with the amino acid histidine (H). This R117H mutation is dominant, so that the vas deferens may fail to develop even in males who have inherited a normal *CFTR* gene from the other parent. However, the R117H mutation does not always cause absence of vas deferens—it depends on certain other characteristics of the *CFTR* genes. A specific variant of the *CFTR* gene called 5T can also cause CBAVD. Men with CBAVD caused by *CFTR* mutations who father children through assisted reproductive technologies are at increased risk for having a child with CF or male children with CBAVD and/or CF.

Demographics

CBAVD is rare. It is responsible for only 1%–2% of all cases of male infertility. It almost exclusively affects males of European and Ashkenazi Jewish descent. It is very rare in males of African or Asian descent. When it does affect males of African or Asian descent, it is usually due to some other prenatal abnormality in the formation of the vas deferens.

Signs and symptoms

The cause of absence of vas deferens in males who do not have a mutation in the *CFTR* gene is often unknown. Some cases of absence of vas deferens are associated with other structural problems in the urinary tract.

There are no observable signs of absence of vas deferens. The first indication is usually male infertility in adulthood.

Diagnosis

The first step in determining the cause of male infertility is to ascertain if the semen contains any sperm or if the sperm are defective. If there are no sperm present,

QUESTIONS TO ASK YOUR DOCTOR

- How can you tell if my infertility is caused by absence of vas deferens?
- Should I be tested for cystic fibrosis?
- Should my partner and I have genetic testing?
- What information will genetic testing provide?
- Can I father a child by in vitro fertilization?
- How does intracytoplasmic sperm injection differ from in vitro fertilization?
- What are the chances that my child conceived through in vitro fertilization will have cystic fibrosis and/or absence of vas deferens?

the next step in diagnosis is to ascertain if sperm are produced. Determining that the testicles are of normal size and shape would suggest that they are producing sperm. With CBAVD, the testicles are normal, as are other parts of the reproductive system such as the epididymis (the tube that connects a duct at the rear of the testicle to the vas deferens). The key evidence from the physical exam is that the vasa deferentia are not palpable; they are not easy to find. Two other diagnostic indications are a low volume of semen and an acidic pH to the ejaculate.

Once a diagnosis of CBAVD has been made, the affected male should have a standard exam for CF. Tests may reveal previously unrecognized influences from *CFTR* mutations that may help in the diagnosis of future health problems. The standard diagnostic tests for CF include analysis of sweat for a high salt content and any signs of lung disease.

Genetic testing can reveal the most common mutations responsible for stand-alone CBAVD. However, it is prohibitively complicated to test for all *CFTR* mutations. Men with CBAVD who plan to use their sperm for in vitro fertilization (IVF) may undergo genetic testing to determine the risk of passing CF and/or CBAVD to their offspring.

Treatment and management

Although there is no treatment for CBAVD, the resulting infertility can be circumvented by removing sperm from the testicles for IVF. The sperm is usually retrieved by a surgical sperm retrieval method. The most effective method is microsurgical epididymal sperm aspiration (MESA). A small needle is inserted into the epididymis and a syringe attached by tubing to the needle is

used to withdraw the sperm under the observation of a microscope. Another method, called testicle sperm extraction, surgically removes a small amount of tissue from one of the testicles and extracts the sperm. This is less effective than MESA and is only used in extreme situations. The most effective method of artificial insemination for men with CBAVD is intracytoplasmic sperm injection (ICSI), in which the sperm is injected directly into the cytoplasm of the female's egg. Once the zygote (fertilized egg) starts to multiply, it is implanted in the woman's uterus.

Prognosis

Men with absence of vas deferens who do not also have CF lead normal healthy lives. They can usually father children using IVF or ICSI. Genetic testing of both parents can help prevent passing on CF and/or CBAVD to offspring. It is also possible to diagnose CF in a zygote before implantation into the uterus.

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Cystic Fibrosis Foundation, 4550 Montgomery Avenue, Suite 1100 N, Bethesda, MD 20814, (301) 951-4422, (800) FIGHT CF (344-4823), info@cff.org, <http://www.cff.org>

Family Equality, 475 Park Avenue, Suite 2100, New York, NY 10016, (646) 880-3005, <https://www.familyequality.org>
 RESOLVE, The National Infertility Association, 7918 Jones Branch Road, Suite 300, McLean, VA 22102, (703) 556-7172, (703) 506-3266, info@resolve.org, <http://www.resolve.org>

Ray F. Brogan, PhD
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Acanthocytosis see **Abetalipoproteinemia**

Accutane embryopathy

Definition

Accutane is the retinoid isotretinoin commonly used to treat severe acne that has not responded to other forms of treatment. Accutane embryopathy, or fetal retinoid syndrome, refers to the pattern of physical and mental birth defects that may be caused in an embryo that is exposed to synthetic vitamin A during development.

Description

Accutane is one of several synthetic drugs derived from vitamin A. The generic name for Accutane is isotretinoin. Accutane and other vitamin A derivatives are referred to as retinoids. Vitamin A is an essential nutrient for normal growth and development. It is found in foods such as green leafy and yellow vegetables, oranges, pineapple, cantaloupe, liver, egg yolks, and butter. It is also available in multivitamins and as a daily supplement. Vitamin A is important in a number of biological processes, including the growth and differentiation of the skin, bone development, and vision. Deficiency of vitamin A may lead to increased susceptibility to infection and problems with vision and growth of skin cells. The potential risks of supplemental vitamin A in a person's diet have been a matter of some debate; however, excess vitamin A during pregnancy does not seem to be associated with an increased risk for birth defects.

The same cannot be said for drugs derived from vitamin A like Accutane and other retinoids that display some of the same biologic properties as vitamin A. For this reason it is an effective method of treatment for severe cases of cystic acne, a condition characterized by painful scarring lesions. Four to five months of Accutane treatment usually leads to clearing of the acne for one year or more even after the medicine is stopped. Accutane may also be prescribed for moderate acne that has not responded to other forms of treatment. Milder cases of acne that produce scarring or other related skin disorders

may also be treated with this medication, but dermatologists prescribe Accutane only after other methods of treatment have been unsuccessful.

Common side effects of Accutane are chapped lips, dry skin with itching, mild nosebleeds, joint and muscle pain, and temporary thinning of hair. Although severe acne on its own is associated with lower self-esteem, depression including thoughts of suicide has been reported more recently as another much more serious potential side effect. No studies have been published to try to determine if Accutane use somehow makes it more likely for a person to be depressed or to attempt suicide.

The United States Food and Drug Administration (USFDA) approved the use of Accutane in September 1982 even though it had previously been shown to cause birth defects in animals. Consequently, its approval was granted with the provision that the drug label would describe its risk of causing birth defects. The patient information brochure also included information for women taking the medication about avoiding pregnancy.

The first report of an infant with Accutane-related birth defects was published in 1983. At least ten additional cases were subsequently reported to the USFDA and Centers for Disease Control and Prevention (CDC). In 1985, Dr. Edward Lammer reviewed a total of 154 pregnancies exposed to Accutane and discovered a pattern of birth defects involving the head, ears, face, and heart. Each of the pregnancies had reported the use of the drug during the first three months of pregnancy. This period is a critical and sensitive time during which the organs begin to develop. Chemical insults during this part of pregnancy often result in abnormal formation of internal organs with or without external abnormalities.

Each of the 154 pregnancies had been voluntarily reported to either the USFDA or CDC. The pregnancy outcomes included 95 elective pregnancy terminations and 59 continuing pregnancies. Of these, 12 (20%) ended in a spontaneous pregnancy loss or miscarriage, and the remaining 47 pregnancies resulted in 6 stillborn infants with obvious abnormalities, 18 live born infants with abnormalities, and 26 apparently normal infants. The abnormalities observed among the stillborn and living infants were similar, most frequently involving the head, face, heart, and central nervous system. Thus, use of Accutane during the first several months of pregnancy was shown to be associated with an increased risk of miscarriage or stillbirth, as well as with a significant risk of birth defects in living children. This pattern of abnormalities has since become known as Accutane embryopathy. The names retinoic acid embryopathy, isotretinoin embryopathy, or fetal retinoic syndrome are also occasionally used to describe the same condition, because other retinoids,

such as Tegison (etretinate), have been associated with a similar pattern of birth defects. Tegison is commonly used to treat severe psoriasis and can cause birth defects even if stopped years before becoming pregnant.

Genetic profile

Accutane embryopathy is not an inherited or hereditary type of abnormality. Rather, it is caused by exposure of a developing embryo to the drug Accutane during the first trimester of pregnancy. Accutane is a well-known, powerful teratogen, and its use any time after approximately four weeks of pregnancy is associated with a significantly increased risk for pregnancy loss or an infant with Accutane embryopathy. It is not known if the dosage of Accutane affects the occurrence of the embryopathy. If Accutane is stopped prior to conception, no increased risk for loss or birth defects is expected.

Demographics

The total number of women of reproductive age (15–44 years old) taking Accutane is unknown. However, since the 1990s, the overall number of prescriptions written for Accutane has increased over 200%. Prescriptions are evenly divided between men and women, but women 30 years old or younger account for 80% of the patients among their sex.

A Dermatologic and Ophthalmic Drug Advisory Committee was convened at the USFDA in September 2000. Patterns of Accutane use and the outcomes of Accutane-exposed pregnancies were presented at this meeting. Two overlapping sources of pregnancy data exist: one sponsored by the manufacturer of the drug, Roche Laboratories, and a second study maintained by the Slone Epidemiology Unit at the Boston University School of Public Health. Representatives from both institutions reviewed their outcome data up to that time. This data supports previous estimates of the frequency of Accutane embryopathy.

Studies were done in the 1980s through the early 2000s to measure the occurrence of embryopathy in women who used isotretinoin, usually in the context of how useful pregnancy prevention or risk management programs worked within this population. Similar to Lammer's initial findings, women taking isotretinoin had about a 25% chance of embryopathic events during pregnancy. The studies, however, focused on the pregnancy rates in women being treated with isotretinoin rather than the effects the use or dosage had on developing fetuses.

Between the years of 1999 and 2007, a population-based study in the Netherlands also evaluated compliance with pregnancy prevention protocols in women of child-bearing age taking isotretinoin and found similar

KEY TERMS

Embryo—The earliest stage of development of a human infant. The term “embryo” is usually used to refer to the first eight weeks of pregnancy. The term “fetus” is used from roughly the third month of pregnancy until delivery.

Miscarriage—Spontaneous pregnancy loss.

Psoriasis—A common, chronic, scaly skin disease.

Retinoid—A derivative of synthetic vitamin A.

Stillbirth—The birth of a baby who has died sometime during the pregnancy or delivery.

Teratogen—A factor that causes malformations in the growing embryo.

Thymus gland—An endocrine gland located in the front of the neck that houses and transports T cells, which help to fight infection.

pregnancy rates and embryopathic events. Neither the U.S. nor the Dutch studies evaluated the annual occurrence of Accutane embryopathy, but they did show that annual rates during the years the studies ran were about 1–2 per 1,000 pregnancies per year, which suggests a 26% risk of developing symptoms associated with Accutane embryopathy.

Signs and symptoms

Accutane embryopathy is characterized by a number of major and minor malformations. Each abnormality is not present in every affected individual.

Craniofacial

- Abnormalities of the ears, when present, involve both ears but may show different levels of severity ranging from mild external abnormalities to a very small or missing ear.
- Underdevelopment of the skull and facial bones that can lead to specific facial features, including a sharply sloping forehead, small jaw (micrognathia), flattened bridge of the nose, and an abnormal size and/or placing of the eye sockets and eyes.

Heart

- Structural defects, most of which require surgery to correct.

Central nervous system

- Hydrocephalus, or abnormal accumulation of fluid within the brain. This is the most common type of brain

abnormality and often is treated by placement of a shunt within the head to drain the fluid.

- Small head size (microcephaly)
- Structural or functional brain abnormalities
- Mild to moderate intellectual disability or learning disabilities later in life. Either may be present even in the absence of physical abnormalities.

Other

- Abnormal or very small thymus gland
- Cleft palate, or opening in the roof of the mouth

Diagnosis

A diagnosis of Accutane embryopathy is based on two pieces of information: (1) report of Accutane use by the mother during the first trimester of pregnancy, and (2) recognition of the physical abnormalities in an exposed infant. The latter is accomplished by a physical examination by a doctor familiar with the disorder. Special studies of the heart may be required after delivery to determine the specific nature of any structural heart defect.

Prenatal diagnosis is theoretically possible if there is knowledge of early pregnancy exposure. A prenatal ultrasound evaluation may detect abnormalities such as heart defects, hydrocephalus or microcephaly, or some craniofacial abnormalities. However, not all features of Accutane embryopathy will be apparent even with an ultrasound; thus, a careful examination after delivery is still needed for diagnosis.

Treatment and management

The care of an infant with Accutane embryopathy after delivery is primarily symptomatic. Infants with serious heart abnormalities will need to be evaluated by a heart specialist and may require surgery in order to survive. Infants with brain abnormalities such as hydrocephalus may require shunt placement soon after birth and monitoring by a brain surgeon on a regular basis. Ear malformations may be associated with hearing loss in affected children. Depending on the severity of the ear abnormality, sign language may be needed for communication. Some infants with very severe internal birth defects, particularly of the heart, may die at a young age.

Based on the features associated with Accutane embryopathy and the long-term medical care that may be required, the focus of the manufacturer of Accutane has long been on the prevention of as many pregnancies as possible. Roche Laboratories has made numerous efforts since 1982 to achieve this, including periodic changes in the drug label and attempts to increase doctor

QUESTIONS TO ASK YOUR DOCTOR

- If I take isotretinoin in the future, how long before conception should I stop taking the drug?
- What are the risks if my baby has heart surgery?
- How severe is my child's hearing loss?
- At what age can my baby's hearing be accurately checked?

and consumer awareness about the teratogenic nature of Accutane during pregnancy.

In 1988, Roche developed the Accutane Pregnancy Prevention Program (PPP), which was fully implemented in mid-1989. The goal of the PPP was to develop educational materials about Accutane for both patients and their doctors. A PPP kit included a consent form and a patient information brochure. Prescribing physicians were encouraged to obtain informed consent from all of their patients after a verbal discussion of the risks and benefits of the drug. Pregnancy tests were strongly encouraged prior to beginning treatment. The patient information brochure included information about the patient referral program sponsored by Roche. The program offered to reimburse women for the cost of a visit to their doctor to review effective methods of birth control. Finally, warnings about the risks associated with Accutane were printed directly on the box and the individual drug packages.

An Accutane tracking study was implemented to evaluate how often doctors were using the PPP kit and following other major components of the program. The results of the study revealed that many doctors were inclined to rely only on oral communication about Accutane with their patients rather than using each of the elements of the PPP kit. The patient brochure was frequently used, but other components of the kit were considered inconvenient and too time-consuming. Both Roche and the FDA agreed that certain parts of the PPP needed improvement.

Additional support came in the form of a report published in the CDC-sponsored periodical *Morbidity and Mortality Weekly Report* (MMWR) in January 2000. A group of 23 women was identified in California, all of whom had taken Accutane while pregnant. During March 1999, a representative from the CDC interviewed a total of 14 of these women in an attempt to learn why pregnancies exposed to Accutane continued to occur despite the efforts of the PPP. The factors that contributed to the occurrence of these pregnancies in the first place were

investigated. Some of the women had obtained Accutane from a source other than their doctor, such as in another country or from an associate. Another woman reported using medication left over from a previous prescription. In other cases, the prescription was filled before a pregnancy test was performed or was started before day two or three of her menstrual period.

Due to legal issues surrounding the serious side effects Accutane and its contribution to severe birth defects, Roche Pharmaceuticals discontinued its production in 2009. In 2012, lawsuits were brought against Roche by former users of Accutane who blamed the medication for their development of bowel disease.

Prognosis

Accutane embryopathy is a serious medical condition that is directly related to the maternal use of Accutane during the first trimester of pregnancy. Some individuals born with Accutane embryopathy will suffer from several different developmental disorders, but may have a normal lifespan, while others may die at a young age due to complex internal abnormalities. Mild or moderate mental disabilities are common even when there are no obvious physical features expressed.

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ORGANIZATIONS

- American Academy of Dermatology, P.O. Box 1968, Des Plaines, IL 60017, (866) 503-SKIN, (847) 240-1859, MRC@aad.org, <http://www.aad.org>
- MotherToBaby: A Service of the Organization of Teratology Information Specialists (OTIS), 5034A Thoroughbred Lane, Brentwood, TN 37027, (866) 626-OTIS, contactus@otispregnancy.org, <http://www.mothers-to-baby.org>

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Aceruloplasminemia

Definition

Aceruloplasminemia is an inherited disorder that causes iron in the body to slowly gather in the brain and in various internal organs of the body. The effects of the excess iron in the brain typically become apparent when a person reaches adulthood. These effects tend to get worse as the years go by. The three major manifestations include diabetes, degeneration of the retina in the eye, and neurological disease. The neurological disease includes shaking or jerking of the extremities and twitching of the eyelids, along with other muscular, coordination, and cognitive problems.

Alternate names associated with aceruloplasminemia include ceruloplasmin deficiency, familial apoceruloplasmin deficiency, ferrooxidase deficiency, and hereditary ceruloplasmin deficiency.

Description

Aceruloplasminemia results from the complete absence of iron-removing activity via ceruloplasmin, a copper-containing protein in the blood. Ceruloplasmin is important in removing iron from cells in the body. It is believed to do this by metabolizing iron, or oxidizing one form of iron (ferrous iron or Fe²⁺) into another (ferric iron, or Fe³⁺). Once it is in the ferric iron form, another protein in the blood plasma (called transferrin) can then carry it away in the bloodstream. Without ceruloplasmin, iron cannot be transported out and instead accumulates in the cells of various organs. These organs include parts of the brain, the pancreas, the liver, and the retina of the eye.

The iron builds up slowly, becoming more and more concentrated in the organs as the years pass. The iron overload not only damages organs, but may cause them

to stop working altogether. Most people who have this condition do not experience noticeable problems as children or teens. However, they begin showing symptoms once they reach adulthood, usually between the ages of 25 and 60 years of age. The symptoms typically worsen as the patient ages.

Genetic profile

Aceruloplasminemia results from a mutation in the ceruloplasmin (ferroxidase) gene (generally abbreviated CP). Aceruloplasminemia is an autosomal recessive disorder, it occurs when an individual inherits a mutated *CP* gene from each parent. Everyone has two copies of the *CP* gene. Individuals with aceruloplasminemia inherit two non-working (mutated) copies of the gene, one from each parent. Their parents are carriers when they have one mutated form of the *CP* gene and one working form of the *CP* gene. Carriers are individuals who do not develop the disorder themselves but may pass the gene for the disorder onto their children. If both parents are carriers, each of their children has a 50% chance of being a carrier, a 25% chance of inheriting the disorder, and a 25% chance of inheriting two normal *CP* gene copies. In the rare circumstance that both parents have aceruloplasminemia, all of their children will also have the disorder.

Located on chromosome 3, the *CP* gene carries the blueprint for making the protein ceruloplasmin, which actually comes in two forms. They are:

- Glycosylphosphatidylinositol-anchored (GPI-anchored) ceruloplasmin, which is made in supportive cells, called glial cells, of the nervous system. GPI-anchored ceruloplasmin metabolizes iron in the brain.
- Serum ceruloplasmin, which is made mainly in the liver. Serum ceruloplasmin metabolizes iron elsewhere in the body, but not in the brain.

Individuals who have inherited the mutated *CP* gene from both parents make ceruloplasmin that cannot function correctly. As a result, iron begins to accumulate in vital organs including the brain. These vital organs begin experiencing iron overload and eventually suffer damage.

Not all CP mutations are the same. Scientists have identified over 50 different mutations in the *CP* gene that can lead to aceruloplasminemia. More than half of all CP mutations may cause the gene to produce incomplete or otherwise ineffective ceruloplasmin proteins. In some other cases, the CP mutations may result in substitutions of amino acids, the building blocks of proteins. This leads to the production of ceruloplasmin that degrades soon after it is made and, therefore, is nonfunctional.

KEY TERMS

Anemia—A disorder resulting from insufficient red blood cells or hemoglobin in the blood.

Blood serum—The clear liquid portion of the blood.

Ceruloplasmin—A copper-containing protein that is involved in iron metabolism.

Diabetes mellitus—A group of metabolic diseases resulting from high blood-sugar concentrations.

Insulin—A hormone that is important in controlling blood-sugar levels.

Retina—The light-sensitive tissue at the back of the eyeball.

As of 2015, DNA sequencing of the *CP* gene can identify greater than 92% of the mutations that cause aceruloplasminemia. DNA sequencing is the molecular determination of the precise sequence of nucleotides in a specific gene or genes. DNA sequencing of the *CP* gene is done by reading the coding portion (exons), and the junctions between the non-coding and coding regions of the *CP* gene. By reading the genetic code at these important functional regions of the *CP* gene, over 92% of the mutations in this gene will be detected. It is important to remember that not all mutations can be detected by DNA sequencing. Other forms of DNA testing may be necessary.

Once the disease causing mutations are found in the affected individuals, it is possible to use DNA testing for carrier testing of other relatives, prenatal diagnosis for at-risk pregnancies, and predictive testing for asymptomatic adult relatives at risk to develop aceruloplasminemia.

Demographics

Aceruloplasminemia is a rare genetic disorder that affects individuals worldwide. According to the National Institutes of Health, its overall prevalence is unknown, although studies in Japan indicate that it affects approximately 1 in 2,000,000 individuals there. Aceruloplasminemia affects males and females equally.

Signs and symptoms

Individuals with aceruloplasminemia usually do not experience any problems as children or teens. The first symptoms may appear as early as age 25, but sometimes do not manifest until the individual is middle-aged or older. Symptoms vary from one individual to the next and often include neurological problems.

Symptoms may include one or more (typically several) of the following:

- tremors
- involuntary jerks of the body
- twitching of the eyelids (also known as blepharospasm)
- involuntary facial movements, especially grimacing
- difficulty speaking
- difficulty walking
- Stiffness
- coordination problems

Besides these more common symptoms, some individuals may experience attacks on their cognitive function. Some may develop depression or other psychiatric problems. Furthermore, they may face dementia once they reach middle age or older.

In addition to these symptoms, many individuals with aceruloplasminemia also develop the following conditions, often before other aceruloplasminemia symptoms appear:

- Anemia, resulting ultimately from a deficiency of iron in the blood
- Diabetes mellitus, resulting from damage to insulin-making cells in the pancreas. Insulin is important in controlling blood-sugar levels.

Both anemia and diabetes mellitus are associated with their own sets of symptoms.

Sometimes, a visit to the eye doctor for a routine exam can reveal a sign of aceruloplasminemia—a sign that is not evident to the patient. The disorder often causes damage to the retina, which is the light-sensitive tissue at the back of the eyeball. This is evident as small yellowish-white spots as well as damaged tissue that the doctor can readily see during an eye examination. The damage usually causes no vision problems and has no other noticeable effects on the patient.

Diagnosis

Examination

A doctor may suspect aceruloplasminemia if a patient reports one or more of the symptoms listed above, particularly when combined with already-diagnosed anemia or diabetes mellitus, or with retina damage as discovered in an eye examination. To make a diagnosis of aceruloplasminemia, however, the doctor will also order blood or other tests. DNA sequencing of the *CP* gene may be done to confirm the diagnosis.

Tests

A doctor will typically order blood tests, perhaps combined with magnetic resonance imaging (MRI) to rule out or confirm aceruloplasminemia. Blood tests serve several purposes, including whether any of the following apply:

- a lack of serum ceruloplasmin.
- too little iron (less than 45 5g/dL compared to a normal range of 60-180 5g/dL in males, and 60-140 5g/dL in females) and/or too little copper (less than 10 5g/dL compared to a normal range of 70-125 5g/dL) in the blood, which are signs of dysfunctional ceruloplasmin or its complete absence.
- a high concentration of the primary iron-storage protein, called ferritin (850-4000 ng/mL compared to a normal range of 45-200 ng/mL in males and 30-100 ng/mL in females).
- higher-than-normal concentration of hepatic iron (the normal level of iron in the liver is less than 36 μ mol/g).

The doctor may use MRI results to determine whether the patient's liver and parts of the brain show the presence of accumulated iron.

Treatment and management

No cure exists for aceruloplasminemia, but doctors can offer various treatment options. These may include the following:

- Iron chelating agents, which attract and bind with excess iron so that it can be removed from the body by way of the bloodstream and ultimately the urine and feces. Iron chelating agents are used to lower the concentration of iron in the brain and liver, to lessen the concentration of ferritin in blood serum, and to slow or stop the progression of neurologic symptoms. A commonly used iron chelating agent is desferrioxamine (also known as deferoxamine or desferol). Treatment with desferrioxamine typically involves nightly infusions by a pump over a course of days or weeks.
- Combination of plasma (given as fresh-frozen plasma or FFP) and an iron chelating agent.
- Repeated doses of plasma to ease neurologic symptoms.

The doctor may also recommend that the patient take zinc supplements and vitamin E or other antioxidants to help prevent damage to various organ tissues.

Prognosis

Most individuals who have aceruloplasminemia experience no symptoms until they are at least 25 years old and possibly not for three or four more decades after that. The various treatment options may slow the disease's progression or lessen, and possibly halt, some of

QUESTIONS TO ASK YOUR DOCTOR

- I have heard that other iron chelating agents are available besides desferrioxamine. Are the treatment regimens for these less demanding and will they work as well?
- My spouse and I are both carriers and would like to have a child. Is prenatal testing available to determine whether a baby has aceruloplasminemia?
- Is there a way, perhaps through preimplantation genetic diagnosis, to ensure that we have a baby that does not have the disorder?
- I have a relative with aceruloplasminemia. Should I be tested for this disorder? Should my children be tested?
- My child has just been diagnosed with aceruloplasminemia. Are there certain foods I should avoid serving?

the symptoms associated with it. The symptoms generally worsen with age. Many patients with this disorder also develop diabetes mellitus and anemia.

Prevention

There is no way to prevent aceruloplasminemia. It is an inherited disorder. Adults who are carriers may wish to undergo genetic counseling before deciding to have children so that they understand the risks. If parents who are carriers do have a child, they should inform their doctor and ask to have their child tested early for the disorder. If parents are not aware that they are carriers and have a child born with aceruloplasminemia, they should ask to have themselves and their other children tested. If necessary, parents should ask about possible preventative treatments, such as administration of desferrioxamine. Brothers and sisters of a child with the disorder have a 25% chance of having the disorder themselves, and a 50% chance of being a carrier for the disorder.

All individuals diagnosed with this condition should have yearly glucose testing for diabetes mellitus. This will allow the patient to begin diabetes treatment as early as possible. In children with aceruloplasminemia, this testing should start in the teen years.

Persons with aceruloplasminemia should avoid taking iron supplements even if they are anemic. Studies show that the added iron causes aceruloplasminemia to progress more quickly.

Caregivers of older patients should remain observant for signs of depression or dementia and report their concerns to the patient's doctor.

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ORGANIZATIONS

- National Heart, Lung, and Blood Institute, Building 31, 31 Center Drive, Bethesda, MD 20892, 877-645-2448, nhlbiinfo@nhi.gov, <http://www.nhlbi.nih.gov>
- National Organization for Rare Disorders, 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, orphan@rarediseases.org, <http://www.rarediseases.org>
- NBIA Disorders Association, 2082 Monaco Court, El Cajon, CA 92019-4235, (619) 588-2315, info@NBIAdisorders.org, <http://www.NBIAdisorders.org>

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Achondrogenesis

Definition

Achondrogenesis is a group of disorders of cartilage and bone formation in which skeletal growth is severely affected. The condition is usually fatal prenatally or early in life.

Description

Achondrogenesis is a name given to a group of disorders that represent the most severe form of congenital chondrodysplasia, or malformations of bones and cartilage that are present at birth. Achondrogenesis is considered a lethal form of infantile dwarfism. Dwarfism is a condition that leads to extremely short stature. In achondrogenesis, the abnormalities in cartilage formation lead to abnormalities in bone formation. The lethality of the disorder is thought to result from difficulty breathing, probably due to the infant's having a very small chest. Achondrogenesis usually results in a stillborn infant or death shortly after delivery.

Achondrogenesis is subdivided into two major types, type 1 and type 2. Type 1 can further be subdivided into type 1A and type 1B. Types 1A and 1B are distinguished by microscopic differences in the cartilage and cartilage-forming cells. Cartilage-forming cells (chondrocytes) are abnormal in type 1A, whereas the cartilage matrix itself is abnormal in type 1B. The current classification, introduced by Jürgen Spranger and colleagues in 1974, is based on genetic findings. The three classifications have different genetic causes.

Synonyms

Synonyms for achondrogenesis include chondrogenesis imperfecta; hypochondrogenesis; lethal neonatal dwarfism; lethal osteochondrodysplasia; and neonatal dwarfism. Achondrogenesis type 1A is also known as Houston-Harris-type achondrogenesis; achondrogenesis type 1B is also known as Fraccaro-type achondrogenesis; and achondrogenesis type 2 is also known as Langer-Saldino-type achondrogenesis.

Genetic profile

Achondrogenesis type 1A is the least common and least well understood form of the disorder. The gene responsible for type 1A was identified in 2010 as the *TRIP11* gene on chromosome 14 at 14q32.12. This gene encodes a protein known as the Golgi microtubule-associated protein 210 (GMAP-210). GMAP-210 is essential in moving proteins from the endoplasmic reticulum of a cell to the Golgi apparatus. Without GMAP-210, the proteins remain in the endoplasmic reticulum, which swells up. Loss of function in the Golgi apparatus is particularly damaging in cells responsible for bone and cartilage formation, which explains the connection between mutations in the *TRIP11* gene and achondrogenesis. Type 1A does follow an autosomal recessive pattern of inheritance.

Achondrogenesis type 1B also follows an autosomal recessive pattern of inheritance. It results from mutations

KEY TERMS

Chondrocyte—A specialized type of cell that secretes the material which surrounds the cells in cartilage.

Endoplasmic reticulum—A network of tubules and flattened sacs that serve a variety of functions within a cell, ranging from protein transport to the synthesis of carbohydrate and fat molecules.

Fetal hydrops—A condition in which there is too much fluid in the fetal tissues, fetal cavities, or both.

Golgi apparatus—An organelle within cells that packages proteins for secretion outside the cell. Also called the Golgi body, it is named for the Italian physician Camillo Golgi, who first identified it in 1897.

Micromelia—The state of having extremely short limbs.

Ossification—The process of the formation of bone from its precursor, a cartilage matrix.

Polyhydramnios—A condition in which there is too much fluid around the fetus in the amniotic sac, seen in about 1% of pregnancies.

in the diastrophic dysplasia sulfate transporter gene (*SLC26A2*), which is located on the long arm of chromosome 5 (5q32 specifically). Abnormalities in the *SLC26A2* gene (also known as the *DTDST* gene) result in the inability of cartilage cells to take up needed sulfate ions. Without these ions, cartilage structure and bone formation are severely disrupted.

The severity of mutation determines which disorder the patient will have. The most severe of these disorders is type 1B. Since both types 1A and 1B follow autosomal recessive patterns of inheritance, the chance of parents having another child with the disorder after having the first child is 25% for both disorders.

Similar to achondrogenesis type 1B, achondrogenesis type 2 represents the most severe form of a group of disorders resulting from the mutation of a single gene—the collagen type 2 gene (*COL2A1*), located on the long arm of chromosome 12 (12q13.11 specifically). In addition to its role in development and growth, collagen type 2 plays an important structural role in cartilage formation and in the ability of cartilage to resist compressive forces. Type 2 achondrogenesis, however, does not follow an autosomal recessive pattern of inheritance. Most of the mutations that cause type 2 are new mutations, meaning they are not passed from parents to children. Also, most of these

mutations are considered autosomal dominant. However, some family members of affected children may have the mutant gene without having the disease. This pattern is not a classical dominant pattern and implies the involvement of other genes in the disease process.

Demographics

Achondrogenesis is equally rare in males and females of all races in the United States and worldwide. Although the exact incidence is unknown, one estimate places the incidence at 1 case in every 40,000 to 60,000 live births.

Signs and symptoms

Traits found in all subtypes of achondrogenesis

All infants with achondrogenesis share these characteristics: an extremely short neck, underdeveloped lungs, a protuberant abdomen, low birth weight, extremely short limbs (micromelia) and other skeletal abnormalities. The most common defining feature of this condition is the extreme shortness of the limbs.

Fetuses with achondrogenesis may also have a condition known as polyhydramnios. The symptoms of polyhydramnios include too much fluid around the fetus in the amniotic sac, too much fluid in the fetal tissues, and too much fluid in the fetal cavities. Having too much fluid in the fetal tissues or fetal cavities constitutes a condition known as fetal hydrops (hydrops fetalis). Infants with achondrogenesis are also often born in the breech position (hindquarters first).

Differences in traits shared by all subtypes of achondrogenesis

Although all the subtypes of achondrogenesis share some characteristics, there are differences in some of these characteristics between subtypes. Type 1 achondrogenesis is generally considered to be more severe than type 2. This consideration is supported by the shorter limbs found in type 1 and the lower average birth weight of type 1 infants compared to type 2 infants. Although any birth weight below 5.5 lbs (2,500 g) is considered to be low, type 1 infants average 2.6 lbs (1,200 g), whereas type 2 infants average 4.6 lbs (2,100 g). In addition, both groups have a number of subtle skeletal abnormalities in addition to those already discussed.

Traits found in type 1 achondrogenesis not shared by type 2

Type 1 achondrogenesis has two non-subtle characteristics that type 2 does not. Type 1 is often accompanied by abnormal connections either on the inside of the infant's heart or in the major blood vessels leading to and away from

QUESTIONS TO ASK YOUR DOCTOR

- Can you recommend a support group?
- Are there any supportive or comfort measures I can offer my baby?
- What is the likelihood of having additional children with this disorder?
- What type of testing is recommended before conceiving future children?

the heart. These defects are formally known as either atrial septal defects, ventral septal defects, or a patent ductus arteriosus. These connections allow oxygenated blood and deoxygenated blood to mix. Normally, oxygenated and deoxygenated blood flows are separated in the circulatory system to ensure enough oxygen makes it to important tissues like the brain. Mixing the blood results in less oxygen being pumped into the body and insufficient oxygenation of tissues around the body.

The other type 1 characteristic is incomplete ossification. Ossification is the process of bone formation. In type 1A, incomplete ossification can be seen in many bones, including the skull. In type 1B, the skull is ossified, but bones other than the skull reveal incomplete ossification. No deficiency in ossification can be seen in type 2 achondrogenesis.

Diagnosis

Prenatal diagnosis of a skeletal disorder may be made by ultrasound. DNA testing may be used to determine the type of disorder or to confirm the presence of a suspected disorder. Genetic tests available for all three types of achondrogenesis include deletion/duplication analysis, target variant analysis, and sequence analysis of the entire coding region of the gene in question. Otherwise, diagnosis may be made by the physical appearance of the infant at birth, x-rays, or both. DNA analysis or a microscopic examination of cartilage tissues may be used to identify the type of disorder.

Treatment and management

There is no treatment for the underlying disorder. Parents should consider mental health and genetic counseling to deal with the grief of losing a child and to understand the risks of the disorder recurring in subsequent children. Support groups may be helpful in the pursuit of these goals. It is important for genetic counseling purposes to determine the type of achondrogenesis that

affected the child, since different types of achondrogenesis carry very different prognoses for future children.

Prognosis

This disorder is fatal at birth or soon after. Type 1 is considered more severe, partly because infants with type 1 are more likely to be stillborn and generally succumb to the disorder earlier than infants with type 2 achondrogenesis.

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ORGANIZATIONS

- Chromosome Disorder Outreach (CDO), P.O. Box 724, Boca Raton, FL 33429-0724, (561) 395-4252, info@chromodisorder.org, <http://www.chromodisorder.org>
- National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301)

402-0911, (301) 402-2218, <http://www.genome.gov/10005049>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, <http://rarediseases.org>

National Society of Genetic Counselors (NSGC), 330 N. Wabash Avenue, Suite 2000, Chicago, IL 60611, (312) 321-6834, nsgc@nsgc.org, <http://www.nsgc.org>

Society for Maternal-Fetal Medicine (SMFM), 409 12th Street, SW, Washington, D.C. 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

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Achondroplasia

Definition

Achondroplasia is a common form of dwarfism or short stature due to an autosomal dominant mutation (a mutation on one of the first 22 “non-sex” chromosomes) that causes an individual to have short stature with disproportionately short arms and legs, a large head, and distinctive facial features, including a prominent forehead and a flattened midface.

Description

Achondroplasia is a genetic form of dwarfism due to a problem of bone growth and development. There are many causes for dwarfism, including hormone imbalances and metabolic problems. Achondroplasia belongs to a class of dwarfism referred to as a chondrodysplasia or skeletal dysplasia. All skeletal dysplasias are the result of a problem with bone formation or growth. There are over 100 different types of skeletal dysplasia. Achondroplasia is the most common and accounts for half of all known skeletal dysplasias.

Achondroplasia is easily recognizable. Affected individuals have disproportionately short stature, large heads with characteristic facial features, and disproportionate shortening of their limbs. Most individuals with achondroplasia have a normal IQ. The motor development of infants is delayed due to hypotonia (low muscle tone) and their physical differences (large heads and small bones). The motor development of children with achondroplasia eventually catches up with that of their peers. Individuals with achondroplasia can have medical complications that range from mild to severe. Because of the differences in their bone structure, these individuals are prone to middle ear infections. They are also at risk for neurological problems due to spinal cord compression. The spinal canal (which holds the spinal cord) is smaller



A man with the characteristic physical features of achondroplasia. (Scott Camazine/Alamy)

than normal in people with achondroplasia. The American Academy of Pediatrics' Committee on Genetics has developed guidelines for the medical management of children with achondroplasia.

The short stature of achondroplasia can be socially isolating and physically challenging. Most public places are not adapted to individuals of short stature, which can limit activities. Children and adults with achondroplasia can be socially ostracized due to their physical appearance. Many people erroneously assume that individuals with achondroplasia have limited abilities. It is very important to increase awareness with educational programs and to take proactive steps to foster self-esteem in children with achondroplasia.

Genetic profile

Achondroplasia is caused by a mutation, or change, in the fibroblast growth factor receptor 3 gene (*FGFR3*) located on the short arm of chromosome 4.

Genes contain the instructions that tell a body how to form. They are composed of four different chemical bases—adenine (A), thymine (T), cytosine (C), and guanine (G). These bases are arranged like words in a sentence, and the specific order of these four bases provides the instructions that a cell needs in order to form a protein.

FGFR (fibroblast growth factor receptor) genes provide the instruction for the formation of a cell receptor. Every cell in the body has an outer layer, called a cell membrane, that serves as a filter. Substances are transported into and out of the cells by receptors located on the surface of the cell membrane. Every cell has hundreds of different types of receptors. The fibroblast growth factor receptor transports fibroblast growth factors into a cell. Fibroblast growth factors play a role in the normal growth and development of bones. When the receptors for fibroblast growth factors do not work properly, the cell does not receive enough fibroblast growth factors, which results in abnormal growth and development of bones.

Achondroplasia is caused by mutations in the *FGFR3* gene. Two specific mutations account for approximately 99% of achondroplasia. The *FGFR* gene is composed of 2,520 bases. In a normal (non-mutated) gene, base number 1138 is guanine (G). In most individuals with achondroplasia (98%), this guanine (G) has been replaced with adenine (A). In a small number of individuals with achondroplasia (1%), this guanine (G) has been replaced with cytosine (C). Both of these small substitutions cause a change in the fibroblast growth factor receptor (FGFR) that affects the function of this receptor.

Mutations in the *FGFR3* gene are inherited in an autosomal dominant manner. Every individual has two *FGFR3* genes—one from their father and one from their mother. In an autosomal dominant disorder, only one gene has to have a mutation for the person to have the disorder. Over 80% of individuals with achondroplasia are born to parents with average stature. Their achondroplasia is the result of a *de novo* or new mutation that arises spontaneously. No one knows the cause of *de novo* mutations or why they occur so frequently in achondroplasia. For reasons that are not yet understood, most new mutations occur in the *FGFR3* gene that is inherited from the average-size father.

An individual with achondroplasia has a 50% chance of passing on their changed (mutated) gene to their children. An achondroplastic couple (both parents have achondroplasia) has a 25% chance that they will have a child with average stature, a 50% chance that they will have a child with one achondroplasia gene (a heterozygote), and a 25% chance that a child will get two copies of the achondroplasia gene (a homozygote). Babies with homozygous achondroplasia are much more severely

affected than those with a single achondroplasia gene. These infants generally die very shortly after birth because of breathing problems caused by an extremely small chest.

Demographics

Because individuals with other forms of dwarfism are often misdiagnosed with achondroplasia, the exact incidence of achondroplasia is unknown. Estimates of the incidence of achondroplasia vary between one in 15,000 to one in 40,000 births. One European study found a prevalence of 3.72 per 100,000 births. It is estimated that there are approximately 15,000 individuals with achondroplasia in the United States and 65,000 worldwide. Achondroplasia affects males and females in equal numbers and occurs in all races and ethnic groups.

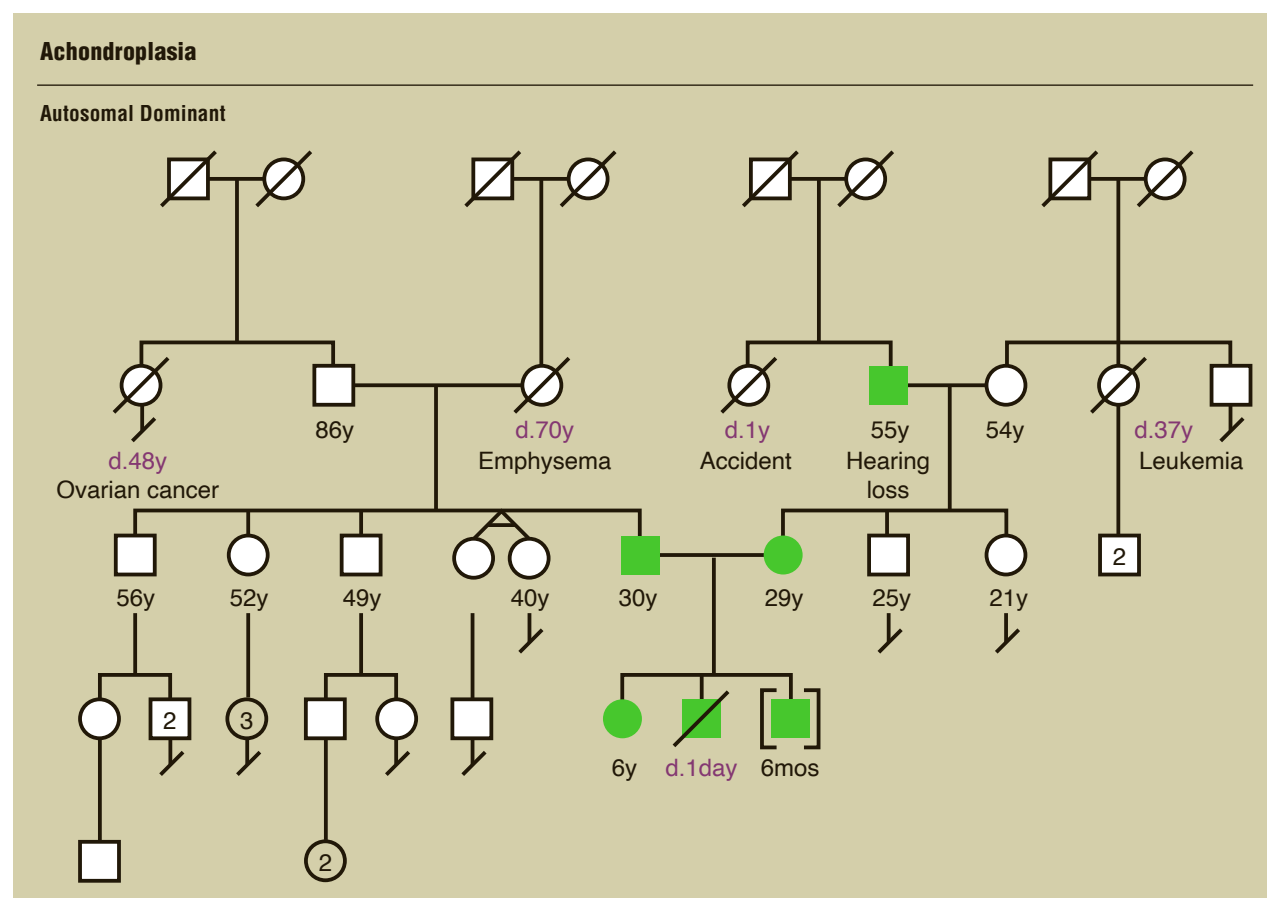
Signs and symptoms

Individuals with achondroplasia have disproportionately short stature, large heads with characteristic facial features, and rhizomelic shortening of their limbs.

(Rhizomelic means “root limb.”) Rhizomelic shortening of the limbs means that those segments of a limb closest to the body (the root of the limb) are more severely affected. In individuals with achondroplasia, the upper arms are shorter than the forearms, and the upper leg (thigh) is shorter than the lower leg.

In addition to shortened limbs, individuals with achondroplasia have other characteristic limb differences. They also have a limited ability to rotate and extend their elbows. They generally develop bowed legs and may have in-turned toes. Their hands and feet are short and broad, as are their fingers and toes. Their hands have been described as having a “trident” configuration. This term is based upon the trident fork used in Greek mythology and describes the unusual separation of their middle fingers. This unusual separation gives their hands a “three-pronged” appearance with the thumb and two small fingers on the side and the index and middle finger in the middle.

Individuals with achondroplasia have similar facial features and a large head (megalencephaly) due to the difference in the growth of the bones of the face and head.



Achondroplasia: pedigree analysis chart (Gale)

The exact reason for the increase in head size is not known, but it reflects increased brain size and can sometimes be due to hydrocephalus. People with achondroplasia have a protruding forehead (frontal bossing) and a relatively prominent chin, in part due to the relative flatness of their midface. While people with achondroplasia do resemble one another, they also resemble their family of origin.

Individuals with achondroplasia have shortening of their long bones. Women with achondroplasia have an average adult height of 48 in. (122 cm). Men have an average adult height of 52 in. (132 cm).

Diagnosis

Achondroplasia is generally diagnosed by physical examination at birth. The characteristic findings of short stature, rhizomelic shortening of the limbs, and specific facial features become more pronounced over time. In addition to being diagnosed by physical examination, individuals with achondroplasia have some specific bone changes that can be seen on an x ray including a smaller spinal canal and a small foramen magnum. The foramen magnum is the opening at the base of the skull. The spinal cord runs from the spinal canal through the foramen magnum and connects with the brain.

The diagnosis of achondroplasia can also be made prenatally either by ultrasound (sonogram) or by prenatal DNA testing. Sonograms use sound waves to provide an image of a fetus. The physical findings of achondroplasia (shortened long bones, trident hand) can be detected in the third trimester (last three months) of a pregnancy. Prior to the last three months of pregnancy, it is difficult to use a sonogram to diagnose achondroplasia, because the physical features may not be obvious. Because of the large number of skeletal dysplasias, it can be very difficult to diagnose achondroplasia definitively by sonogram. Many other dwarfing syndromes can look very similar to achondroplasia on a sonogram.

Prenatal testing can also be done using DNA technology. A sample of tissue from a fetus is obtained by either chorionic villus sampling (CVS) or amniocentesis. Chorionic villus sampling is generally done between 10 and 12 weeks of pregnancy, and amniocentesis is done between 16 and 18 weeks of pregnancy. Chorionic villus sampling involves removing a small amount of tissue from the developing placenta. The tissue in the placenta contains the same DNA as the fetus. Amniocentesis involves removing a small amount of fluid from around the fetus. This fluid contains some fetal skin cells. DNA can be isolated from these skin cells. The fetal DNA is then tested to determine whether it contains either of the two mutations responsible for achondroplasia.



X ray of achondroplasia, a common cause of dwarfism. It occurs as a sporadic mutation in approximately 80% of cases (often associated with advanced paternal age) or it may be inherited as an autosomal dominant genetic disorder. (Clinical Photography, Central Manchester University Hospitals NHS Foundation Trust, UK/Science Source)

Prenatal DNA testing for achondroplasia is not routinely performed in low-risk pregnancies. This type of testing is generally limited to high-risk pregnancies, such as those in which both parents have achondroplasia. It is particularly helpful in determining whether a fetus has received two abnormal genes (homozygous achondroplasia). This occurs when both parents have achondroplasia, and each of them passes on their affected gene. The baby gets two copies of the achondroplasia gene. Babies with homozygous achondroplasia are much more severely affected than those with heterozygous achondroplasia. Infants with homozygous achondroplasia generally die shortly after birth due to breathing problems caused by an extremely small chest. The prenatal detection rate is about 70%.

DNA testing can also be performed on blood samples from children or adults. This is usually done if there

is some doubt about the diagnosis of achondroplasia or in atypical cases.

Treatment and management

There is no cure for achondroplasia. The recommendations for the medical management of individuals with achondroplasia have been outlined by the American Academy of Pediatrics' Committee on Genetics. The potential medical complications of achondroplasia range from mild (ear infections) to severe (spinal cord compression). By being aware of the potential medical complications and catching problems early, it may be possible to avert some of their long-term consequences. An individual with achondroplasia may have some, all, or none of these complications.

All children with achondroplasia should have their height, weight, and head circumference measured and plotted on growth curves specifically developed for children with achondroplasia. Measurements of head circumference are important to monitor for the development of hydrocephalus—a known but rare (5%) complication of achondroplasia. Hydrocephalus (or water on the brain) is caused by an enlargement of the fluid-filled cavities of the brain (ventricles) due to a blockage that impedes the movement of the cerebrospinal fluid. Suspected hydrocephalus can be confirmed using imaging techniques such as a CT or MRI scan and can be treated with neurosurgery or shunting (draining) if it causes severe symptoms. Any child displaying neurologic problems such as lethargy, abnormal reflexes, or loss of muscle control should be seen by a neurologist to make sure they are not experiencing compression of their spinal cord. Compression of the spinal cord is common in individuals with achondroplasia because of the abnormal shape and small size of their foramen magnum (opening at the top of the spinal cord).

All children with achondroplasia should be monitored for sleep apnea, which occurs when an individual temporarily stops breathing during sleep. This can occur for several reasons, including obstruction of the throat by the tonsils and adenoids, spinal cord compression, and obesity. Individuals with achondroplasia are more prone to sleep apnea due to the changes in their spinal canal and foramen magnum, and because of their short necks. Treatment for sleep apnea depends on its cause. Obstructive sleep apnea is treated by surgically removing the tonsils and adenoids. Neurosurgery may be necessary to treat sleep apnea due to spinal cord compression. Weight management may also play a role in the treatment of sleep apnea.

Other potential problems in children with achondroplasia include overcrowding of the teeth (dental

KEY TERMS

Fibroblast growth factor receptor gene—A type of gene that codes for a cell membrane receptor involved in normal bone growth and development.

Rhizomelic—Describes disproportionate shortening of the upper part of a limb, compared to the lower part of the limb.

malocclusion), speech problems (problems with articulation), and frequent ear infections (otitis media). Dental malocclusion (overcrowding of teeth) is treated with orthodontics. All children with achondroplasia should be evaluated by a speech therapist by two years of age because of possible problems with the development of clear speech (articulation). Articulation problems may be caused by orthodontic problems. Due to the abnormal shape of the eustachian tube, individuals with achondroplasia are very prone to ear infections. Approximately 80% of infants with achondroplasia have an ear infection in the first year of life. About 78% of these infants require ventilation tubes in the ears to decrease the frequency of ear infections.

Weight management is extremely important for an individual with achondroplasia. Excess weight can exacerbate many of the potential orthopedic problems in an individual with achondroplasia, such as bowed legs, curvature of the spine, and joint and lower back pain. Excess weight can also contribute to sleep apnea. Development of good eating habits and appropriate exercise programs should be encouraged in individuals with achondroplasia. These individuals should discuss their exercise programs with their health care providers. Because of the potential for spinal cord compression, care should be used in choosing appropriate forms of exercise.

The social adaptation of children with achondroplasia and their families should be closely monitored. Children with visible physical differences can have difficulties in school and socially. Support groups such as Little People of America can be a source of guidance on how to face these issues. It is important that children with achondroplasia not be limited in activities that pose no danger. In addition to monitoring their social adaptation, every effort should be made to physically adapt their surroundings for convenience and to improve independence. Physical adaptations can include stools to increase accessibility, and lowering of switches and counters.

Two treatments have been used to try to increase the final adult height of individuals with achondroplasia—limb-lengthening and growth hormone therapy. There

QUESTIONS TO ASK YOUR DOCTOR

- What course of medical management is recommended?
- What specific form of exercise do you recommend?
- What are the benefits and risks of growth hormone therapy?
- What are the risks and benefits of limb lengthening?

are risks and benefits to both treatments, and they are still considered experimental.

Limb-lengthening involves surgically attaching external rods to the long bones in the arms and legs. These rods run parallel to the bone on the outside of the body. Over a period of 18 to 24 months, the tension on these rods is increased, which results in the lengthening of the underlying bone. This procedure is long and costly and has potential complications such as pain, infections, and nerve problems. Limb-lengthening can increase overall height by 12 to 14 inches (30.5–35.6 cm). It does not change the other physical manifestations of achondroplasia, such as the appearance of the hands and face. This is an elective surgery, and individuals must decide for themselves whether it would be beneficial to them. The optimal age to perform this surgery is not known.

Growth hormone therapy has been used to treat some children with achondroplasia. Originally, there was doubt about the effectiveness of this treatment, because children with achondroplasia are not growth hormone deficient. However, studies have shown that rate of growth in children with achondroplasia treated with growth hormone does increase during the first two years of treatment. For maximal effect, it is recommended that growth hormone therapy be started between ages one and six years. No studies suggest that long-term growth hormone therapy beyond two years spurs additional height gain.

Prognosis

The prognosis for most people with achondroplasia is very good. In general, they have minimal to moderate medical problems and normal IQ, and most achieve success and have a long life regardless of their stature. The most serious medical barriers to an excellent prognosis are the neurological complications that can arise in achondroplasia. Spinal cord compression is thought to increase the risk for sudden infant death syndrome (SIDS) to 7.5% in infants with achondroplasia and can

lead to life-long complications such as paralysis if untreated. Obesity can increase the risk for heart disease, and some studies have revealed an increased risk of unexplained death in the fourth and fifth decade of life.

Successful social adaptation plays an important role in the ultimate success and happiness of an individual with achondroplasia. It is very important that the career and life choices of an individual with achondroplasia not be limited by preconceived ideas about their abilities.

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Little People of America, 617 Broadway #518, Sonoma, CA 95475, (888) LPA-2001 or (714) 368-3689, (707) 721-1896, info@lpaonline.org, <https://www.lpaonline.org>

Kathleen Fergus, MS
Revised by Tish Davidson, AM

ACHOO syndrome

Definition

ACHOO syndrome is a generally benign condition characterized by sudden, uncontrollable sneezing after viewing a bright light.

Description

The ACHOO syndrome, standing for autosomal dominant compelling helio-ophthalmic outburst syndrome, is an inherited condition where a person will involuntarily sneeze after seeing a bright light. A person with this condition will sneeze multiple times, and in rare cases may sneeze 30–40 times. The syndrome is usually more intense if the person with the condition moves suddenly from darkness into an area with bright lights or sunlight.

Genetic profile

The ACHOO syndrome is thought to be inherited in an autosomal dominant pattern. This means that only one copy of the abnormal gene needs to be present for the syndrome to occur. If one parent has the condition, their children will have a 50% chance of also having the syndrome. One physician reported the condition in a family where it was observed in the father and his brother but not seen in the father's mother or his wife. Both the father and brother would sneeze twice when going from an area of darkness to an area of light. At four weeks of age, the father's daughter also started to sneeze whenever she was moved into bright sunlight.

Because of the relatively benign nature of the condition, there has been no reported scientific work trying to locate the gene responsible for the syndrome.

Demographics

Occurrence of the ACHOO syndrome is widespread in the general population. The few well-documented studies performed report the condition as being present in 23%–33% of individuals. Men seem to be affected more

KEY TERMS

Allergy—Condition in which immune system is hypersensitive to contact with allergens; an abnormal response by the immune system to contact with an allergen; condition in which contact with allergen produces symptoms such as inflammation of tissues and production of excess mucus in respiratory system.

Antibody—A protein produced by the mature B cells of the immune system that attach to invading microorganisms and target them for destruction by other immune system cells.

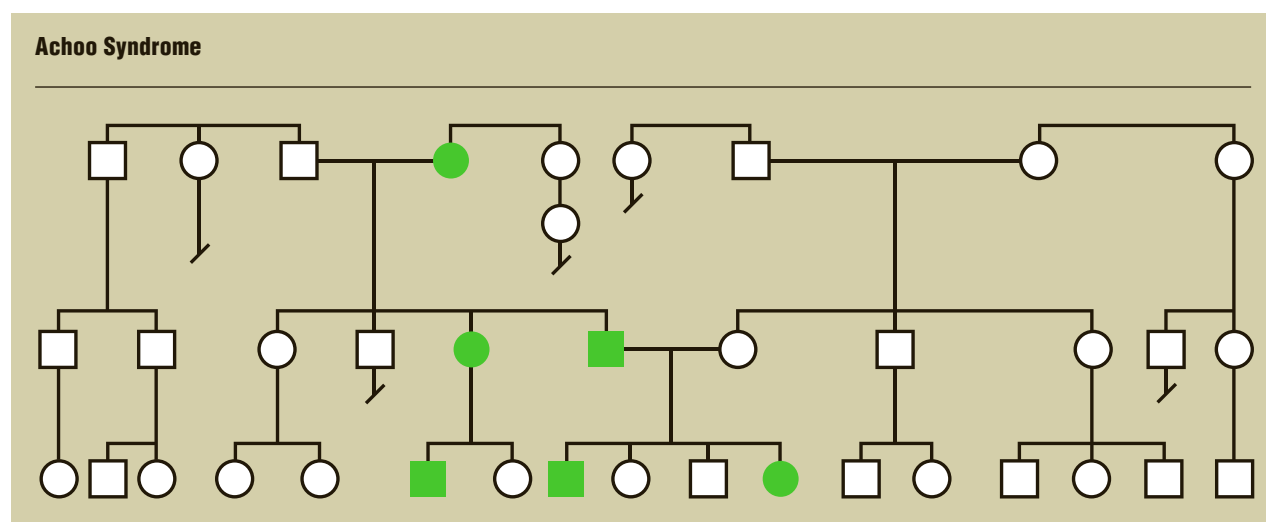
Antigen—A substance or organism that is foreign to the body and stimulates a response from the immune system.

Hypersensitivity—A process or reaction that occurs at above normal levels; overreaction to a stimulus.

Immune response—Defense mechanism of the body provided by its immune system in response to the presence of an antigen, such as the production of antibodies.

Immune system—A major system of the body that produces specialized cells and substances that interact with and destroy foreign antigens that invade the body.

than women. Studies on the occurrence of the syndrome in various ethnic groups are very limited. One study showed differences between whites and non-whites, while another study showed no difference.



ACHOO syndrome: pedigree analysis chart (Gale)

QUESTIONS TO ASK YOUR DOCTOR

- What allergy medications do you recommend?
- Should I take allergy medications on a regular basis?
- What is the risk of long-term allergy medication?
- Do you have a recommendation for decreasing the number of sequential sneezes?

Signs and symptoms

The prominent symptom of people with the ACHOO syndrome is sudden, involuntary sneezing when they see a bright light or sunlight. The way in which sneezing is triggered is not very well understood, but there are several theories that attempt to explain the syndrome.

One theory is that people who have the ACHOO syndrome have a hypersensitive reaction to light, just as some people have a sensitivity to cat hairs or pollen. When a person with the syndrome is exposed to a bright light, the same mechanism in the body that triggers a sneeze due to an irritant such as pollen somehow confuses light with that irritant and causes a sneeze to occur. Another idea is that the sneeze reflex in people with the ACHOO syndrome is somehow linked to real nasal allergies, although this does not explain the syndrome in people without nasal allergies. A third theory is that people with the ACHOO syndrome are very sensitive to seeing bright light. The sneeze reflex of the syndrome can then be thought of as an involuntary defense reaction against bright light; when the person sneezes, they automatically close their eyes.

Diagnosis

The ACHOO syndrome is diagnosed simply by observing the sneezing pattern of a person and by looking into the sneezing patterns of the person's close relatives. If the person seems to sneeze every time they are exposed to a bright light, and if their parents and offspring do the same, then the diagnosis of the ACHOO syndrome can be made.

Currently, there are no known blood tests or other medical tests that can help diagnose the syndrome.

Treatment and management

There are no specific treatments for the ACHOO syndrome. Common measures, such as wearing sunglasses, can help people who are severely affected.

There have been reports that people who have nasal allergies have a higher incidence of the ACHOO syndrome. Therefore, it is sometimes assumed that medications that are used for allergies, such as antihistamines, could perhaps play a beneficial role in the ACHOO syndrome. However, no studies have successfully demonstrated that the syndrome is relieved by this type of medication. Alternative medicine, including homeopathy and herbal medicine, recommends a wide range of remedies for nasal allergies; these may accordingly also be helpful for the ACHOO syndrome.

Prognosis

People with the ACHOO syndrome generally have the condition for life. There is no evidence showing that the ACHOO syndrome in any way affects a person's lifespan.

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American Optometric Association, 1505 Prince Street, Suite 300, Alexandria, VA 22314, (703) 739-9200, <http://www.aoa.org>

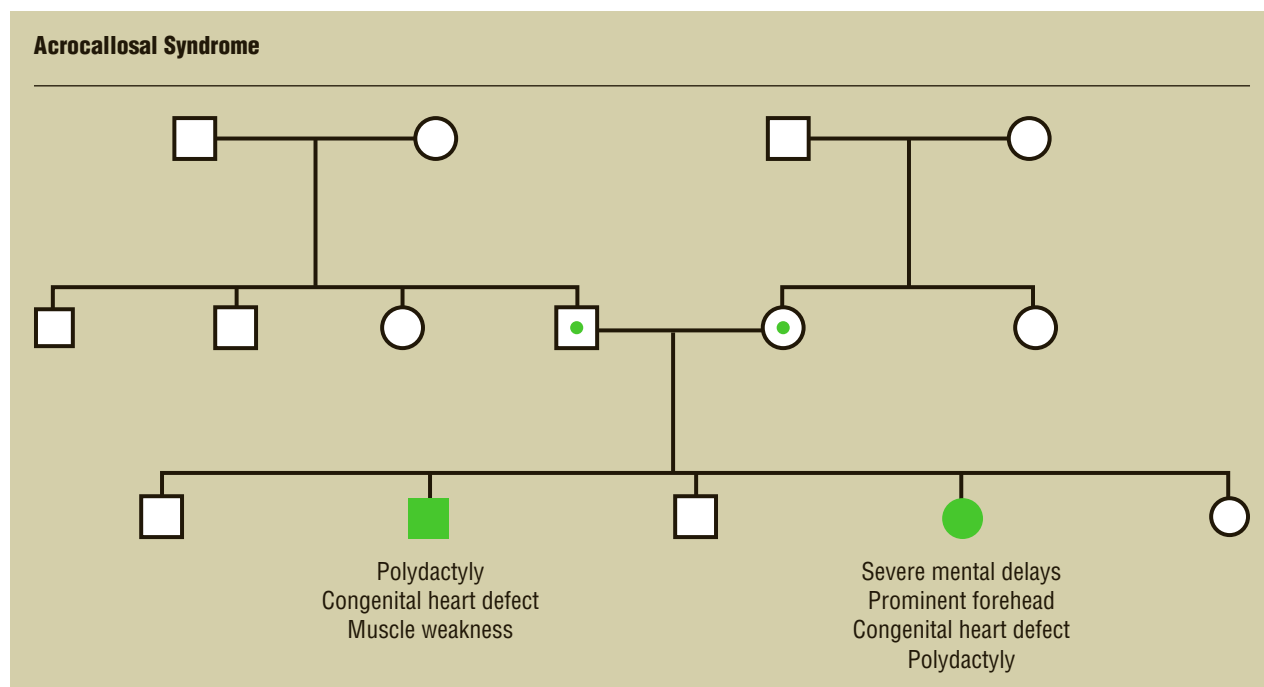
Edward R. Rosick, DO, MPH, MS

Achromatopsia see **Color blindness**

Acrocallosal syndrome (ACLS), Schinzel type; Joubert syndrome; and related disorders

Definition

Acrocallosal syndrome, Schinzel type is a rare congenital disorder in which the individual has absence or only partial formation of the corpus callosum. This is accompanied by skull and facial malformations with some degree of finger or toe malformations. Individuals



Acrocallosal syndrome: pedigree analysis chart (Gale)

may display motor delay and intellectual disability. The cause of this genetic disorder is unknown, and the severity of the symptoms varies by individual.

Description

Acrocallosal syndrome, Schinzel type also called Schinzel Acrocallosal Syndrome, was first described by Schinzel in 1979. Related syndromes include: Joubert Syndrome, Joubert Syndrome 12, Hallux duplication, postaxial polydactyly, and absence of corpus callosum. The term “acrocallosal” refers to the involvement of the acra (fingers and toes) and the corpus callosum, the thick band of fibers joining the hemispheres of the brain. Reported in both males and females, the cause of the disorder is unknown. The major characteristic of the syndrome is the incomplete formation (hypoplasia) or absence (agenesis) of the corpus callosum. Facial appearance is typically similar among affected people. This includes a prominent forehead, an abnormal increase in the distance between the eyes (hypertelorism), and a large head (macrocephaly). Individuals have a degree of webbing or fusion (syndactyly), or duplication (polydactyly) of the fingers and toes. Occasionally, those affected may have a short upper lip, cleft palate, cysts that occur within the cranium (intracranial), hernias, or may develop seizure disorders. Less frequently, affected children have congenital heart defects, internal organ (visceral) or kidney (renal) abnormalities.

Moderate to severe intellectual disability is reported with acrocallosal syndrome. Individuals usually display some form of poor muscle tone (hypotonia) with an expected delay or absence of motor activities, walking, and talking. There is great variation of functioning with this disorder, ranging from normal development to severe mental and motor disability.

Genetic profile

Acrocallosal syndrome, Schinzel type; Joubert syndrome; and related disorders are a group of autosomal recessive syndromes. This means that both parents must contribute the altered form of the gene for the affected child to inherit the disorder. This syndrome and the related disorder, hydroletharus syndrome, have recently been reported to be caused by mutations in the *KIF7* gene and over 19 other individual gene mutations.

In some rare cases of Joubert syndrome, an X-linked recessive pattern of inheritance has been seen. In these cases, the mutated gene is located on the X chromosome (one of the two sex chromosomes). Since males have only one X chromosome, one altered copy of the gene will cause the syndrome. Females have two X chromosomes; therefore, a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders more frequently than females. A characteristic of

X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Acrocallosal syndrome-related disorders are extremely rare. Isolated individuals with similar symptoms have shown over 19 unique individual genetic mutations. Overall, approximately 50% of individuals with Acrocallosal syndrome (ACLS) Schinzel type-Joubert syndrome have mutations on one of the identified genes. However, in many families, this syndrome is not linked to any of the known mutations that cause this phenotype. For this reason, researchers believe that Acrocallosal syndrome, Schinzel type; Joubert syndrome; and related disorders demonstrate locus heterogeneity, meaning that there are multiple genetic locations for mutations that cause similar symptoms.

Demographics

Acrocallosal syndrome (ACLS) Schinzel type-Joubert syndrome and related disorders are extremely rare. Joubert Syndrome is estimated to affect 1 in 100,000 newborns. Reports of this disorder may occur within family lines or without any pattern. It affects both males and females. There are some reports of webbing of the fingers or toes (syndactyly) and relatedness (consanguinity) of the parents of affected children. However, affected children may also have unrelated, healthy parents and unaffected siblings.

Signs and symptoms

At birth, those with acrocallosal syndrome present the characteristic pattern of facial and limb malformations. Limb appearance ranges from minor webbing between the fingers or toes to near duplication of the hands or feet. Forehead prominence, increased distance between the eyes, and an enlarged head are the main features of facial appearance. X-ray tests will reveal the absence or incomplete formation of the corpus callosum, and the presence of any cysts within the cranium. The infant will usually display reduced muscle tone (hypotonia). This may lead to a drooling condition or feeding difficulties. Hypotonia can also contribute to a delay in growth and motor skills. Severe hypotonia is usually associated with a form of mental disability.

Progress and functioning during the first year of life is dependent upon the severity of the symptoms. There have been wide ranging variations reported. The degree to which symptoms affect each child may differ. Some children develop normally and will walk and talk within normal age limits; others may experience a delay or absence of certain motor activities. Intellectual disability may be mild to severe. Some children may develop

KEY TERMS

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Consanguinity—A mating between two people who are related to one another by blood.

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

Hypertelorism—A wider-than-normal space between the eyes.

Hypotonia—Reduced or diminished muscle tone.

Polydactyly—The presence of extra fingers or toes.

Syndactyly—Webbing or fusion between the fingers or toes.

seizure disorders. The degree and progression of intellectual disability also varies by individual.

Diagnosis

The diagnosis of acrocallosal syndrome is based initially on the distinct pattern of facial and limb malformations. Computed tomography (CT), or a similar radiographic procedure, of the head is used to reveal the absence of the corpus callosum. Hand and foot x rays can be taken to confirm finger or toe abnormalities and to determine the extent of fusion, webbing, or duplication of the fingers and toes.

Prenatal diagnosis may not be possible due to the variability of the condition. However, prenatal ultrasound can detect duplication of the digits (polydactyly) and cerebral malformations. This may be especially informative for women who have affected children. There is a 25% risk of having another affected child.

Treatment and management

Beginning in infancy, physical therapy may assist in the development of motor skills and muscle tone. Surgery to remove extra fingers and to release fused fingers may improve movement and grasp, although the muscle tone may remain poor. Surgery to separate or remove affected toes may assist in walking and increase the comfort of footwear. Anti-epileptic therapy should be considered if a seizure disorder develops. Special-needs education

QUESTIONS TO ASK YOUR DOCTOR

- How many physical therapy sessions are required?
- Does my child's development appear delayed?
- What are the risks of surgery?
- What is the surgery's success rate in improving movement in the hands or feet?

may be required, depending on the level of intellectual impairment.

Prognosis

At present, there are no preventative measures for acrocallosal syndrome. The severity of symptoms and outcomes varies by individual. The quality of life for an individual with acrocallosal syndrome, Schinzel type is dependent upon the degree of intellectual disability and reduced muscle tone, rather than the extent of facial and limb malformations.

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ORGANIZATIONS

FACES: The National Craniofacial Association, P.O. Box 11082, Chattanooga, TN 37401, (800) 332-2373, faces@faces-cranio.org, <http://www.faces-cranio.org>
National Organization for Disorders of the Corpus Callosum (NODCC), 18032-C Lemon Drive, Yorba Linda, CA 92886, (714) 747-0063, info@nodcc.org, <http://nodcc.org>

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Acrocephalopolysyndactyly type II see

Carpenter syndrome

Acrocephalosyndactyly type I see **Apert syndrome**

Acrocephalosyndactyly type III see

Saethre-Chotzen syndrome

Acromegaly

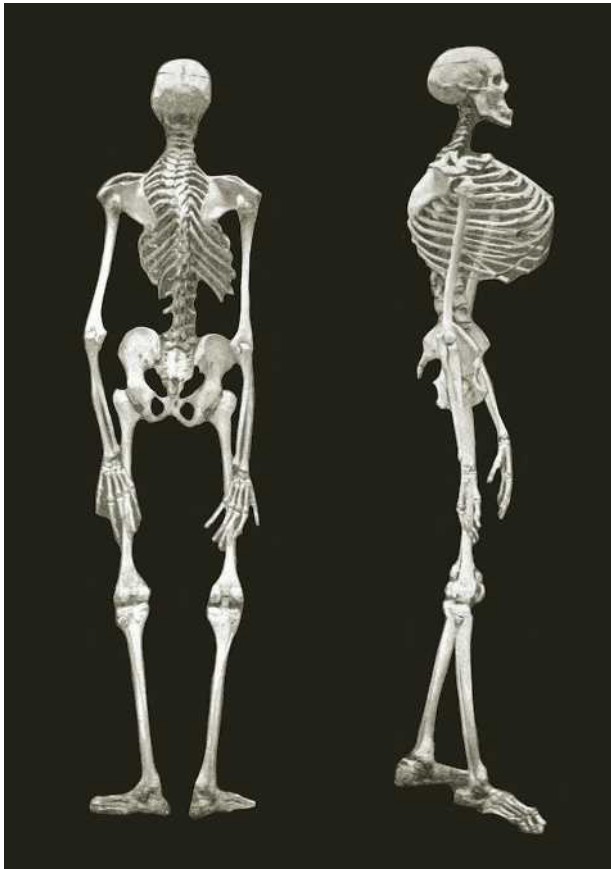
Definition

Acromegaly is a rare condition caused by abnormally high amounts of human growth hormone (HGH). An organ in the brain known as the pituitary gland secretes this chemical. An average range of HGH is needed for normal growth and physical maturity in children. However, with acromegaly, there is an increased amount of HGH released, generally due to a tumor that forms in the pituitary gland. If left untreated, acromegaly can lead to numerous disabling conditions as well as a decreased lifespan.

Description

Acromegaly was first described in scientific detail by the French physician Pierre Marie. In 1886, Dr. Marie, along with his assistant, J.D. Souza-Leite, described two patients, designated cases I and II, and reviewed previously published case studies on patients III through VIII, all with acromegaly. These patients exhibited a rapid growth in their height as well as significantly enlarged hands and feet, a coarsening change in the appearance of their faces, frequent headaches, and a high incidence of visual problems. Dr. Marie believed that all of these problems were due to a defect in the patients' pituitary gland, a small glandular structure located in the middle of the brain.

While Dr. Marie was the first to state formally that a problem in the pituitary gland was responsible for the condition of acromegaly, the link between pituitary defects and acromegaly remained controversial for many



A photograph from 1898 showing the skeleton of an unknown person who had acromegaly. The person was 7 feet 6 inches tall. Acromegaly is a disorder that results from the production of excess growth hormone after the growth plates have closed. (Science Source)

years. It was not until 1909, when Dr. Harvey Cushing introduced the concept of hyperpituitarism in reference to acromegaly, that the association became generally accepted. Dr. Cushing believed that acromegaly caused the pituitary gland to secrete high levels of HGH, resulting in abnormal growth and, as time progressed, the development of acromegaly.

Acromegaly is a rare condition, with only about 1,000 cases per year in the United States among a total population of 330 million. If the condition presents before adulthood, it is also referred to as gigantism, because individuals grow much taller than usual because of their excessive levels of growth hormone. Some individuals with acromegaly may be as tall as seven or eight feet. Its striking consequence of excessive height has caused acromegaly to remain a fascinating disease among scientists, doctors, and the public. Besides potentially causing great height and unusual facial features, it is now known that acromegaly also causes serious conditions that can be life-threatening, such as

heart disease, respiratory disease, arthritis, neuromuscular problems, thyroid disease, and diabetes. Colon polyps are also more common in individuals with acromegaly, although it is not known whether colon cancer is more common. Other symptoms may include obstructive sleep apnea, a sleep disorder, as well as a deep voice, both of which are caused by soft tissue swelling and an enlarged tongue.

The genetics behind the majority of cases of acromegaly is still poorly understood. The most common cause of acromegaly is a benign (non-cancerous) tumor in the pituitary gland that secretes HGH. It is known that the tumor arises from cells in the pituitary gland, possibly due to a defect in the pituitary gland itself. Tumors larger than 1 centimeter in size can cause headaches and impede vision. The gene responsible for this tumor formation is unknown.

Even though the genetics of tumor formation in the pituitary gland leading to most cases of acromegaly are not yet known, there are other conditions that lead to acromegaly in which the genetic causes of the conditions are known. In a very rare condition called familial acromegaly, there is a gene on chromosome 11 believed to cause the formation and growth of an HGH-secreting tumor in the pituitary gland. Familial acromegaly is transmitted in an autosomal dominant pattern, which means that it has an equal chance of affecting both boys and girls in a single family. This condition can also cause tumors in other areas of the body besides the pituitary, including the parathyroid gland, which controls the amount of calcium in the bloodstream, and the pancreas, which regulates insulin in the body needs in order to process sugars.

Another uncommon condition causing HGH-secreting tumors in the pituitary gland is called multiple endocrine neoplasia-1, or MEN-1. This is an autosomal dominant condition characterized by a combination of pituitary, parathyroid, and pancreatic tumors. The gene for this condition has also been found on chromosome 11 and is known as the *MEN-1* gene. About half of the patients with this abnormal gene will eventually develop acromegaly.

Carney syndrome is a rare autosomal dominant disorder that can cause HGH-secreting pituitary tumors and acromegaly in about 20% of patients who have the syndrome. It is associated with a defective gene on chromosome 2. Besides acromegaly, people with Carney syndrome frequently have abnormal skin pigmentation, heart tumors, and tumors of the testicles and adrenal glands.

McCune-Albright syndrome is a very rare disorder that can cause acromegaly through HGH-secreting tumors in the pituitary. Other conditions associated with this syndrome include polycystic fibrous dysplasia (affecting bone growth, especially in the pelvis and long

bones of the arms and legs), abnormal skin pigmentation, early puberty, and thyroid problems. The gene for the syndrome, named *GNAS1*, is located on chromosome 20.

Demographics

Acromegaly is a very rare condition. It is estimated to occur in about 30–60 individuals per million people. Both males and females seem to be affected equally, and the condition more frequently presents when individuals are in their forties or fifties. These individuals do not grow taller, but there is an enlargement of the bones and a thickening of the soft tissues, such as of the tongue, the lips, and the heart. Some internal organs may enlarge, such as the spleen, the thyroid, the liver, and the kidneys. There also does not seem to be any difference in the secondary complications of acromegaly experienced by males and females. The condition has been recorded at all ages of life, from early childhood into old age. The frequency of chronic complications increases with age in both men and women.

Many cases of acromegaly are detected on an initial visit to a family physician, although some early or mild cases may be missed, causing a delay as long as years in the diagnosis. Some patients with acromegaly are initially diagnosed in specialty clinics, such as cardiology clinics or diabetic clinics, where they present with secondary problems caused by their acromegaly.

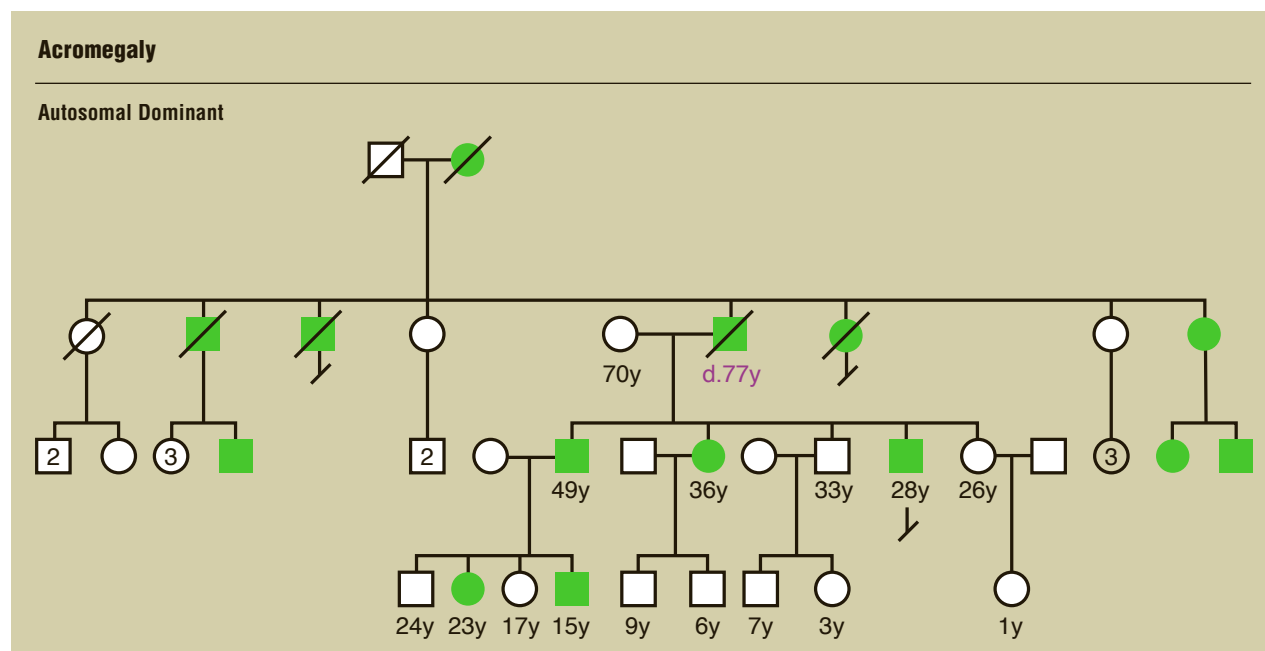
There is very little data on the differences of the occurrence of acromegaly among various ethnic and

racial lines. The few studies that have been done show no real difference among racial or ethnic groups, with acromegaly showing up equally in Caucasians, African Americans, and Asian Americans.

Signs and symptoms

The signs and symptoms of acromegaly can range from striking to almost unseen. The most visible signs of the condition are greatly increased height and coarse facial features that were caused by the abnormal growth of the facial bones. Another very noticeable feature is enlargement of both the hands and feet, which, as with the abnormal facial features, is the product of an excessive level of growth hormone and results in increased bone growth. The jaw may lengthen, causing malocclusion of the teeth as well as temporomandibular joint pain. Carpal tunnel syndrome is common, as is an early onset of osteoarthritis triggered by the condition. Individuals may notice that their rings no longer fit their fingers, and they may also need a larger shoe size, although successful treatment will decrease the size of the fingers and feet.

Other less visible, yet common, signs of acromegaly are increased sweating (hyperhidrosis), constant and at times debilitating headaches, visual disturbances, and increase in hair growth. Loss of sexual desire is often seen in both men and women. Amenorrhea, the cessation of menses (stopping of menstruation), is often a secondary condition associated with acromegaly in women. Females may also experience an abnormal milk flow



Acromegaly: pedigree analysis chart (Gale)



An acromegalous hand (left) beside and normal hand (right). This disorder causes uncontrolled growth, caused by excessive production of the growth hormone somatotrophin. (Biophoto Associates/Science Source)

from the breasts. Men may experience a lowered sexual drive or impotence. The pituitary tumor may press on the optic nerve, which may be revealed by testing such as magnetic resonance imaging.

There are further secondary complications of acromegaly that are not visible but can be life threatening. People with acromegaly are at greater risk for developing high blood pressure, cardiac disease, high cholesterol levels, arthritis and other degenerative diseases of the joints and spine, and diabetes. In addition, about 25% of individuals with this disorder experience hypertension. Acromegaly also increases the risk of other tumors, some of them cancerous, in other areas of the body, especially the breast, colon, and to a lesser degree, prostate.

With adequate treatment, especially early in the course of the condition, many of the secondary symptoms of acromegaly can be halted or even reversed. Less life-threatening complications, such as headaches, visual problems, and increased sweating, can be almost eliminated after adequate and timely treatment. More serious conditions, such as heart disease, high blood pressure, and diabetes, can be brought under control with treatment, although many times they cannot be totally eliminated.

Diagnosis

For most forms of acromegaly, there are no genetic tests yet available to diagnose the condition in newborns or before birth. Diagnosis is made by recognizing the clinical signs and symptoms previously described. Imaging tests may be used to identify the presence of a tumor in the pituitary. The patient's blood may be tested for elevated levels of insulin-like growth factor 1 (IGF1) or growth hormone. In certain very rare conditions, such as multiple endocrine neoplasia-1 and Carney syndrome, the genetics of the conditions are known and can theoretically be tested for. However, the conditions are so seldom encountered that unless a family member has the condition, genetic testing is usually not done until clinical signs and symptoms are apparent.

Treatment and management

The treatment and management of acromegaly have evolved over the past 100 years from crude surgery to genetically engineered medications. Today, through precise surgery and medications, a large percentage of patients with acromegaly can have their symptoms brought under control and in some cases totally cured.

KEY TERMS

Dopamine—A neurochemical made in the brain that is involved in many brain activities, including movement and emotion.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Somatostatin—A body chemical, known as a cyclic peptide, involved in the release of human growth hormone from the pituitary gland.

The goal of any therapy, be it surgery, medications, or radiation therapy, is a reduction in the level of HGH to levels seen in people without acromegaly. This goal may be achieved either through the removal or destruction of the tumor that is secreting the growth hormone, inhibition of HGH from the tumor, or blocking the effects of increased HGH on organs and other body systems outside the pituitary.

Surgical removal of the pituitary tumor is still the first treatment of choice for acromegaly. The rate at which a cure is achieved is determined by several factors, including the size of the tumor, whether or not it has spread outside the pituitary, and the level of HGH before the surgery. In patients with small tumors confined to the pituitary and exhibiting only moderately high HGH levels, the cure rate can be as high as 80% to 90%. In patients with larger tumors, especially those extending out of the pituitary, cure rates with surgery can be reduced to 40% to 60%.

Radiation therapy is often a second-line choice of treatment for acromegaly, especially in patients who have not achieved a cure with surgery. The treatment of acromegaly with radiation was used early on in the history of the condition, with the first report being written in 1909. Careful application of radiation can significantly reduce the size of pituitary tumors, subsequently decreasing high HGH levels. However, this decrease is often very slow, and it can take years for the HGH levels to drop to normal. Treatment with radiation can also have significant side effects, including damage to the pituitary gland itself, visual loss, and brain damage. Some studies have also suggested that treatment with radiation can lead to tumor formation in other areas of the brain.

The use of medications in the treatment of acromegaly has gained importance over the past few decades. The three key types of medications used to treat

acromegaly are somatostatin analogs, growth hormone receptor antagonists, and dopamine agonists. The somatostatin analog suppresses growth hormone and includes such drugs as octreotide, lanreotide, and pasireotide. Next, pegvisomant, a genetically engineered medication, is the GH receptor antagonist drug that may be used for treatment. Last, a dopamine agonist, such as bromocriptine, may be used to suppress GH. All of these medications are generally used in combination with surgery or radiation therapy.

Bromocriptine is known as a dopamine agonist and was one of the first pharmaceutical agents to be used to lower HGH levels in acromegaly. However, bromocriptine is not effective in the majority of cases, and consequently the medications octreotide and lanreotide have supplemented its use. These medications, both somatostatin analogues, decrease both the size of HGH-secreting pituitary tumors and the secretion of HGH itself. In multiple studies, they have been shown to normalize HGH levels in about 50% of cases and have been shown to shrink tumors in 45% of cases. The drawbacks to using both octreotide and lanreotide include multiple weekly dosing over a 12-month period, as well as acute side effects such as nausea, stomach pain, and diarrhea. Long-term use of these medications also results in an increased risk of developing gallstones.

Pegvisomant is a unique, recently developed genetically engineered HGH receptor antagonist. This medication does not decrease the amount of HGH secreted from pituitary tumors; rather, it desensitizes other organs of the body to the effects of the increased HGH circulating in the body. In medical trials, pegvisomant was well tolerated and resulted in significant symptomatic improvement. It is hoped that with a combination of surgery to decrease the tumor size and the use of an HGH antagonist like pegvisomant, both the acute and chronic debilitating symptoms of acromegaly can be greatly diminished, if not totally eliminated. The Pituitary Society reported in 2021 that patients with both acromegaly and diabetes, as well as a higher body mass, may need higher doses of medications such as pegvisomant. Some patients need combination therapy, and one option is a low dose or octreotide long-acting release medication or lanreotide, along with weekly dosages of pegvisomant.

Prognosis

The prognosis for patients with acromegaly who receive prompt treatment is good, although there are still possible complications. Patients who do not receive treatment, or those who receive it late in the course of the condition, have frequent and debilitating secondary complications as well as a greater chance for early death.

QUESTIONS TO ASK YOUR DOCTOR

- Are minimally invasive procedures available for removal of pituitary tumors?
- Is medication, rather than pituitary tumor surgery, an option?
- What risks are associated with medications?
- Based on my post-operative HGH level, what is my long-term prognosis?

There are only a few reliable studies examining the overall health benefits of treatment versus no treatment for patients with acromegaly. One study showed that those who received treatment before age 40 had a much better chance of not developing serious complications than those who were treated after age 40. Those who received earlier treatment had less chance of developing heart disease, high blood pressure, and diabetes, as well as other secondary complications of the condition.

Even with treatment, mortality rates for people with acromegaly are higher than those of the rest of the population. The principal causes of early death are cardiac disease, strokes, cancer, and respiratory failure. The level of HGH after treatment appears to offer the best data for predicting early mortality, with higher levels of post-treatment HGH corresponding to a greater, earlier mortality risk.

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ORGANIZATIONS

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Adams-Oliver syndrome

Definition

Adams-Oliver syndrome (AOS) is a congenital condition that involves a combination of scalp defects (called aplasia cutis congenita) and a specific type of limb defect.

Description

Adams-Oliver syndrome is a genetic condition characterized by aplasia cutis congenita and abnormal outer limbs. People who have the syndrome often have malformed or missing hands, fingers, feet, and toes. Sometimes the abnormalities are noticeable in the fingernails and toenails; some people have fused fingers or toes. Congenital heart disease has also been reported in individuals with this condition. Several genes have been identified as probable causes of Adams-Oliver syndrome, but there are likely other genes that cause the syndrome that are not yet identified. The severity of problems among families with AOS varies a great deal.

Genetic profile

There have been both familial and non-familial cases of Adams-Oliver syndrome reported. Most genetic cases have been inherited in an autosomal dominant manner with the *ARHGAP31*, *RBPJ*, *DLL4* and *NOTCH1* gene mutations. Autosomal recessive and sporadic inheritance

forms have also been reported. These are associated with the *DOCK6* and *EOGT* gene mutations.

Autosomal dominant inheritance means that only one abnormal gene copy is required for the disorder to occur. For persons with a copy of the gene, the risk of passing it to their offspring is one in two, or 50%.

Autosomal recessive inheritance means that two defective gene copies must be inherited, one from each parent, for the disorder to be present. A person with only one gene mutation is a carrier for the disorder. Individuals who are carriers for the recessive type of Adams-Oliver syndrome do not have any symptoms (asymptomatic) and do not know that they are carriers unless they have a child with the syndrome. The likelihood that each member of a couple would be a carrier for a mutation in the same gene is higher in people who are related. When both parents are carriers for the recessive type of Adams-Oliver syndrome, there is a one in four chance (25%) in each pregnancy for a child to have the disorder. There is a 50% chance that a healthy-appearing child is a carrier of the mutation and a 25% chance that the child does not have the gene mutation.

A sporadic genetic disorder is one that occurs for the first time in a family. The disorder can either become inherited by subsequent generations in an autosomal manner or occur just once because of a chance mutation. Different mechanisms have been postulated to explain how the sporadic form of Adams-Oliver syndrome occurs. They include trauma, uterine compression, amniotic band sequence, vascular disruption, and a large blood clot in the placenta. Amniotic band sequence is a condition resulting from strands of the amnion membrane causing amputation of parts of the fetus. Vascular disruption is blockage of blood flow to a developing part or parts of the fetus. A large blood clot in the placenta could possibly block certain important blood vessels and interrupt blood supply to developing structures. Recently, Adams-Oliver syndrome has been hypothesized to occur as a result of abnormalities in small vessel structures that occur very early in embryo formation. The vascular anomaly could be the result of a genetic defect causing decreased stability of embryonic blood vessels in the presence of specific forces.

Researchers have identified several genes responsible for Adams-Oliver syndrome. These include:

- ***ARHGAP31* gene mutations.** The *ARHGAP31* is a Rho GTPase activating protein gene, which helps to regulate proteins that signal chemicals within cells. The chemicals associated with the *ARHGAP31* protein are critical for certain parts of an embryo's development, especially the skull, heart, and limbs. In people with Adams-Oliver syndrome, the mutated protein is too short, making it

KEY TERMS

Aplasia cutis congenita (ACC)—A group of disorders with different causes and a common characteristic of absence of skin in a defined area.

Congenital—Refers to a disorder that is present at birth.

more active. This decreases the signals to the cells involved in development and impairs them.

- ***DOCK6* gene mutations.** The *DOCK6* gene instructs a protein called guanine nucleotide exchange factor, which also helps activate GTPase proteins. *DOCK6* is important in development of fibers that extend from nerve cells during development of the skull, heart, and limbs. Mutations in the *DOCK6* gene alter the way skin develops on the top of the head and how bones of the feet and hands develop.
- ***EOGT* gene mutations.** The *EOGT* gene provides instructions to proteins that modify other proteins. The alterations in proteins affect cell processes and how genes produce proteins. These changes can affect development of tissues throughout the body. Researchers are still learning precisely how the *EOGT* gene mutation influences Adams-Oliver syndrome. However, they know that at least three mutations in this particular gene exist in people with the disease. The most common mutation leads to an abnormally short protein.
- ***RBPJ* gene mutations.** The RBP-J protein produced by the *RBPJ* gene is important to the Notch signaling pathway aiding how certain cells develop in an embryo. If the gene has mutations, the proteins cannot properly signal how skin on top of the head or bones in the hand and feet develop. These abnormal developments are common symptoms of Adams-Oliver syndrome.
- ***NOTCH1* gene mutations.** The *NOTCH1* gene makes a specific receptor protein that is involved in signaling the specialization of certain cells.

Demographics

Adams-Oliver syndrome was first described in 1945. There have been more than 125 cases reported in the medical literature. There does not appear to be any ethnic or sex difference in prevalence of this condition.

Signs and symptoms

Limb defects are the most common occurrence in Adams-Oliver syndrome, affecting about 84% of patients. The type of limb defect is usually asymmetrical

(not the same on both sides). The tendency to involve both sides of the body (bilateral) is seen more often in the lower limbs than the upper limbs. There is a wide range of severity in the limb defects, from minimal problems such as a small or missing finger or toenail (called nail hypoplasia), to the more severe absence of hands, feet, or lower legs. Other more moderate limb defects that have been reported include webbing (syndactyly) of the skin (cutaneous syndactyly) or bones (bony syndactyly) of the fingers or toes, claw-hand malformation (ectrodactyly), and brachydactyly (shortened fingers or toes). Brachydactyly is the most common limb defect in AOS.

Congenital cutis aplasia is the second most common problem and is present in about 75% of patients with Adams-Oliver syndrome. In 64% of patients with congenital cutis aplasia, there is also an underlying skull defect. More rarely, skull defects can be seen without scalp defects and may be mistaken for an enlarged soft spot (fontanelle).

Congenital heart defects have been reported to occur in 13% to 20% of patients with Adams-Oliver syndrome.

Many different types of vascular (involving the blood vessels) and valvular (heart valves) problems have been reported in these patients.

Other clinical features seen with AOS include short stature, kidney (renal) malformations, cleft palate, small eyes (microphthalmia), spina bifida occulta, extra (accessory) nipples, undescended testes, skin lesions, and neurological abnormalities. Intellectual disability is present in a few cases.

Diagnosis

Aplasia cutis congenita is a physical finding that has many causes. To determine whether an individual has Adams-Oliver syndrome clinically, all infants with aplasia cutis congenita should have a complete pregnancy and family history taken, as well as a complete medical evaluation. When possible, relevant family members should be examined for evidence of the condition. When aplasia cutis congenita is discovered at birth, the placenta should be evaluated. Physical examination of the affected infant includes evaluation of other related structures, specifically teeth, hair, other areas of skin, nails, and the central nervous system. Once this evaluation has been completed and a specific diagnosis of Adams-Oliver syndrome has been established or refuted, genetic counseling can be provided. Several different genetic tests are available for Adams-Oliver syndrome.

Prenatal diagnosis by ultrasound of the limb defects and possible other abnormalities associated with AOS is possible, but clinical confirmation of the diagnosis usually occurs after birth.

QUESTIONS TO ASK YOUR DOCTOR

- Does my child show signs of having a disorder related to AOS?
- At what age should my child start wearing corrective shoes?
- What type of full-body work up is recommended?
- Which family members should undergo genetic testing?
- What are the chances that I might have another child affected with AOS?

Treatment and management

The treatment for AOS is different for each individual and is tailored to the specific symptoms present. If leg-length discrepancy is present, corrective shoes that increase the sole for the affected leg to prevent scoliosis and ambulation difficulties can be worn. Orthopedic devices such as prostheses are sometimes recommended. Patients should be referred to a physician specializing in treating patients with limb defects early in life. Surgery for congenital defects and skin grafting for scalp defects may be necessary. (About 30% of patients required skin grafting in one study.)

Treatment

All children diagnosed with Adams-Oliver syndrome should have a thorough medical evaluation to check for possible heart abnormalities.

About 30% of patients in one study experienced a major hemorrhage from the scalp defect. Twenty percent of patients had local infection of the scalp defect. Treatment such as transfusion or antibiotic therapy may be required in these cases.

Special devices for writing or other activities may be necessary if hand malformations are present. Appropriate special-needs services are available for those with intellectual disability. Counseling and support related to limb deficiency issues are essential for coping. Support groups can provide valuable peer referrals and information.

Prognosis

AOS does not usually alter lifespan, although complications from associated abnormalities such as intellectual disability can cause problems. About 5% of the scalp defects that hemorrhaged severely were fatal. Rare cases of meningitis as a result of infection of the scalp

defect have been reported. Asymmetry of the limbs can interfere with their proper function and cause pain. Psychological issues relating to disfigurement are possible.

Clinical trials are experimental new drug treatments and procedures for a disease or disorder. Participation is voluntary and at no cost to the participant. All clinical trials receiving U.S. government funding, and some supported by private industry, are posted at <https://www.clinicaltrials.gov>.

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ORGANIZATIONS

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Birth Defect Research for Children, Inc, 976 Lake Baldwin Lane, Suite 104, Orlando, FL 32814, (407) 895-0802, staff@birthdefects.org, <https://birthdefects.org>

Genetic and Rare Disease Information Center, P.O. Box 8126, Gaithersburg, MD 20898-8126, (888) 205-2311, <https://rarediseases.info.nih.gov>

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Revised by Tish Davidson, AM

Adaptive immunity

Our skin, saliva, and mucous are parts of the nonspecific immune system that serve to eliminate parasites,

perform phagocytosis (the process by which infected cells are engulfed and destroyed), and produce inflammation (the process used to defend the body from harmful or disease-causing agents). The non-specific immune system also aids in the development of adaptive and specific immune responses against infectious agents to which an individual has been exposed previously.

Adaptive immunity describes the specific defenses targeting foreign or infectious agents that have been encountered before. A key characteristic of the adaptive immune system is its ability to learn to recognize and attack pathogens (disease causing agents such as bacteria and viruses). Humans adapt to surroundings over time with specific immunity by selectively promoting the development of white blood cells and the products they make in response to specific threats. The body can use millions of combinations of cell surface or excreted proteins called antibodies, plus specialized cells to eliminate a toxic or infectious agent through specific immunity. The body develops specific immunity by using both humoral (antibody-mediated) and cell-mediated immune components over time.

Humoral Immunity, B cells, and Antibodies

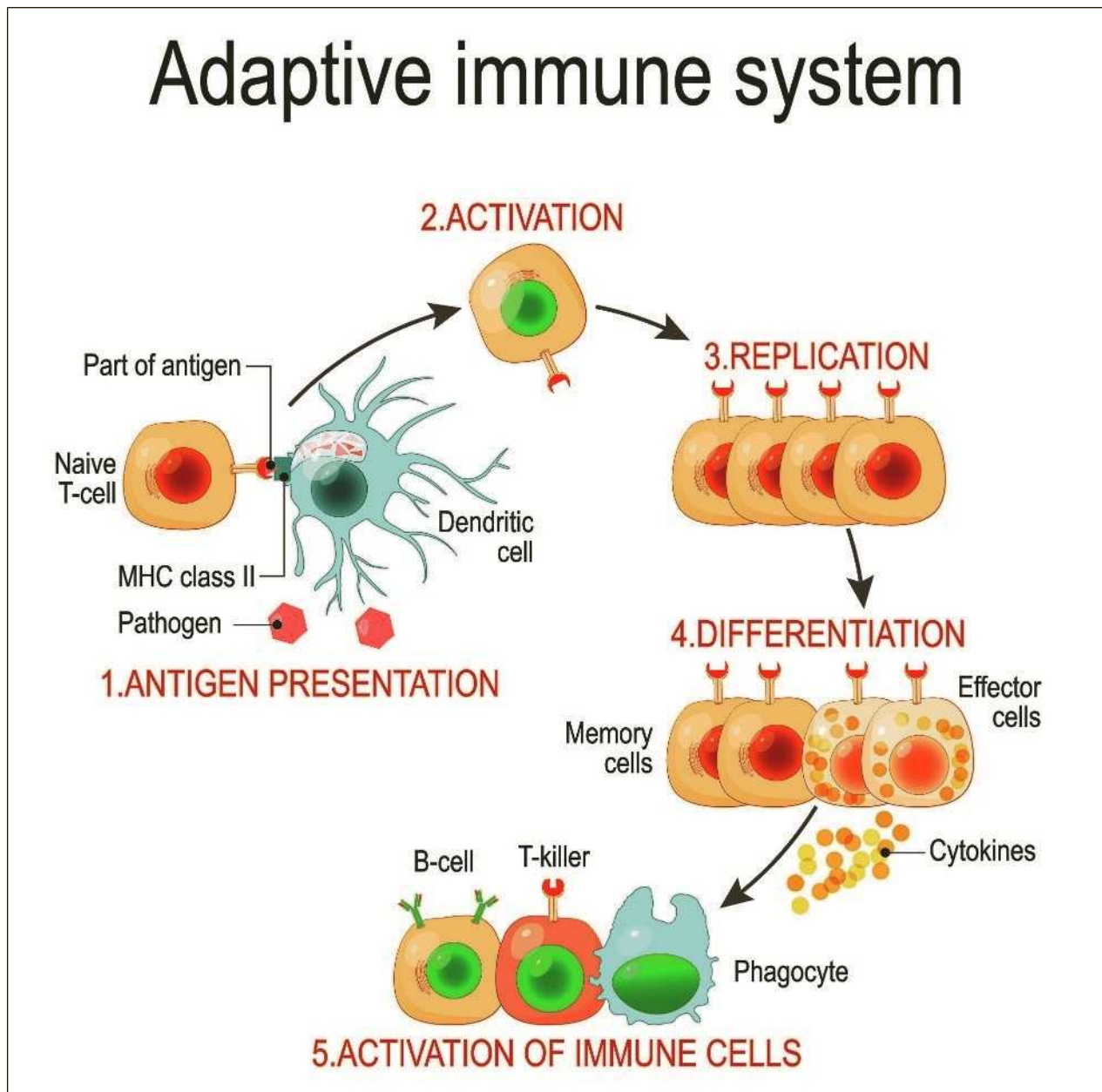
The humoral immune system is also known as antibody-mediated immunity because it relies on the actions of white blood cells called B cells and the antibodies they make after maturing in the bone marrow. The antibodies are globular proteins made from several polypeptide chains with carbohydrate structures bound to them. There are several classes of antibodies, with IgG, IgM, IgA, and IgE antibodies in different proportions in different locations of the body; each antibody serves a slightly different functions from each other.

Antibody Clonal Selection

Clonal selection involves only those B cells whose surface-bound antibody-like protein can bind to a foreign invader in precise a lock-and-key-type fit. Those B cells with proteins that cannot bind do not participate. When a B cell is bound, activation begins. The B cell replicates and changes characteristics into antibody secreting, or plasma cells. The foreign invader that originally bound the B cell is called an antigen.

Antibody Functions in Adaptive Immunity

In neutralization, a large number of antibodies bound on the surface of a microbe or particle can block the invaders' access to their targets in the body. In complement-mediated killing, factors (collectively called complement) that can kill bacterial cells locate the bacteria due to the bound antibodies.



Adaptive immune system diagrammed from antigen presentation to activation of other immune cells. (Shutterstock/Designua)

Agglutination, or clumping together of multiple invaders through their bound antibodies, allows lethal cells to locate numerous linked invaders at once. Opsonization, also called enhanced attachment, is a process in which bacteria or other antigens are coated with opsonins, facilitating more efficient phagocytosis, or cell eating, by white blood cells. It is more efficient when many antibodies are bound to the surface of a microbe. Antibodies also attract white blood cells that kill parasites when they release lethal enzymes.

White blood cell functions in adaptive immunity

Cell-mediated immunity was discovered 50 years after antibodies were first identified. We know now that some functions of adaptive immunity are performed by one of several T cells, which leave the bone marrow and migrate to the thymus to mature, then around to the lymphatic tissues of the body. Virus- or other parasite-infected cells or cancer cells with foreign antigens exposed on their surfaces are the preferred antigens of cellular immunity.

Classes of T cells and their Products

In humoral immunity, T helper cells stimulate B cells to produce antibodies by releasing chemical signals called cytokines. T helper cells also act in cell-mediated immunity by binding antigens with their surface receptors. Usually, the antigen is a fragment of an invader that has been digested by an immune cell and then pushed to the outer surface of the cell. In addition to binding an antigen presented on the surface of the human cell, a chemical signal from the antigen-presenting cell causes only the bound T cell to multiply, become further specialized, and form memory T cells.

Cytokines made by T cells of the T helper 1 variety act to control cells of the cell-mediated immune system and T helper 2 cells produce cytokines that participate in the allergic response and in responding to parasites. Cytokines that transmit signals between white blood cells are called interleukins. As of July 2021, twenty-nine interleukins have been discovered, characterized, and named.

Cytotoxic T cells differentiate to cytotoxic T lymphocytes (CTLs) once exposed to cytokines from T helper cells. The CTLs then recognize foreign antigens on human cell surfaces and destroy the cells to eliminate virus-infected or cancer cells. Regulatory T cells suppress the activity of other T cells. They regulate inflammation, the autoimmune response, and transplant organ rejection. Since each of these functions is vitally important for health, this cell population is the subject of much research.

Antigen-presenting cells

Dendritic cells and activated macrophages are antigen-presenting cells that function in cellular immunity. Both engulf and digest invaders and then present bits of the invaders' molecules on their own surfaces, offering them as examples to the rest of the immune system. After taking up invaders, antigen-presenting cells migrate to lymphatic tissues. There, they encounter T cells with receptors ready to bind an antigen and to begin to multiply and mature.

Development of Immunologic Memory

Four to seven days after exposure to a foreign body, human sera (the clear liquid separated from coagulated blood that contains antibodies) will have measurable antibody titers, or relative units of IgM antibodies. IgG antibodies soon replace the IgM as titers peak in a couple of weeks. This is the first or primary response.

After a second exposure, weeks to decades later, the secondary or anamnestic response occurs. The humoral development is triggered by memory B cells that remain

in circulation from the first exposure until the second. When the memory B cells detect the second exposure, they give rise to plasma cells, which rapidly produce large quantities of antibodies against the invader rapidly and in large quantities. The intensity and speed of the secondary response prevent people from becoming sick a second time. That protection is due to our adaptive immunity.

T cell-mediated adaptive immunity functions mainly in cancer prevention. T cells undergo a maturation after the first exposure also. The secondary response upon re-exposure is also specific, fast, strong, and adaptive.

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Addison disease see **Adrenoleukodystrophy (ALD)**

Adelaide-type craniosynostosis

Definition

Adelaide-type craniosynostosis is an autosomal dominant disorder that is characterized by premature

closing of certain bones in the skull, causing deformations in head shape and appearance of the face.

Description

Adelaide-type craniosynostosis is one of at least ten types of craniosynostosis caused by genetic abnormalities affecting the development of the fibroblast growth factor, transforming growth factor beta, and Eph/ephrin signaling pathways. The disorder is also called Muenke syndrome, FGFR3-associated coronal synostosis, Pro250Arg, and P250R mutation. The first of these terms honor Maximilian Muenke, German-American geneticist, who first described the condition in 1996. The last three designations indicate the gene at which the mutation causing the disorder has occurred, the *FGFR3* gene.

At birth, the human skull consists of a number of sections separated by narrow fissures. These fissures allow the skull to expand as the brain grows; they eventually grow together, forming the closed skull of a physically mature person. In cases of craniosynostosis, one or more fissures close prematurely, often with the result that other portions of the skull grow to a greater extent than usual. This unbalanced growth may result in the malformation of the head and the face. In the case of Adelaide-type craniosynostosis, uneven growth may be so minimal as to be almost undetectable, or it can be serious enough to produce significant malformations and the appearance of a ridge along the coronal suture, the fissure that runs across the skull from ear to ear. In addition to a misshaped head, other manifestations of the condition may be wide-set eyes and flattened cheekbones. Other physical conditions tend to be absent, thus explaining an alternative (and now discouraged) name for the disease, nonsyndromic coronal craniosynostosis. In about 5% of all cases of Adelaide-type craniosynostosis, growth of the head is significant enough to qualify as macrocephaly, but such growth is so modest as to be essentially absent in a quarter of all cases. Other physical manifestations of the disease include:

- short, crooked, or webbed fingers and toes in about 50% of all cases
- abnormally broad toes
- developmental delay in about one-third of all cases
- significant hearing loss in about 30% of all cases
- modest learning disabilities in about 20% of all cases
- less-than-average height in less than 5% of all cases

Genetic profile

Adelaide-type craniosynostosis is caused by a mutation on the fibroblast growth factor receptor 3 (*FGFR3*) gene, which is responsible for the production of a protein with the same name, fibroblast growth factor receptor 3.

KEY TERMS

Autosomal dominant—A genetic trait that is expressed when only a single copy of a gene is present.

Cartilage—A tough connective tissue attached to the ends of bones that may, early in the development of the body, be converted to bone.

CAT scan—Acronym for a computed axial tomography, a computerized x-ray examination of internal organs.

Coronal suture—A fissure between two bony plates in the skull that runs across the top of the head from one ear to the other ear.

Craniosynostosis—Premature closure of any one of the sutures of the skull.

Macrocephaly—Having an unusually large head.

Mutation—An alteration in the chemical structure of a gene.

Syndrome—A set of symptoms that suggest the presence of a disease or the possibility of contracting a disease.

The protein plays an important role in controlling the rate at which cartilage is converted to bone. The mutation responsible for Adelaide-type craniosynostosis occurs at position 250 in the *FGFR3* gene, resulting in the replacement of the amino acid proline by the amino acid arginine, thus accounting for another name for the condition, Pro250Arg, or more simply, P250A. This change in molecular structure inactivates the protein, removing a factor that slows down the conversion of cartilage to bone. Without this moderating factor, bone growth accelerates and skull segments on either side of the coronal suture close more rapidly than normal.

The mutation responsible for Adelaide-type craniosynostosis may either be transmitted as an autosomal dominant trait or it may appear as a *de novo* (new) mutation. Patterns of inheritance may also be unclear because of the possibility of reduced penetrance of the mutation. Reduce penetrance refers to the possibility that carriers of a mutant gene do not actually express symptoms of the disorder associated with that gene. In such a case, parents of a child with Adelaide-type craniosynostosis may appear to be less severely affected by the mutation.

Demographics

Adelaide-type craniosynostosis occurs in 1 out of about every 30,000 births, qualifying its listing by the Office of Rare Diseases of the National Institutes of

Health as a “rare disease.” An estimated 9,000 individuals in the United States have the condition at the present time. Adelaide-type craniosynostosis accounts for about 8% of all cases of craniosynostosis. Studies tend to suggest that the condition is somewhat more severe in females than in males.

Signs and symptoms

The characteristics of Adelaide-type craniosynostosis are very similar to those of other forms of craniosynostosis, primarily malformed head and face, such as ocular hypertelorism, ptosis or proptosis (usually mild), midface hypoplasia, and a highly arched palate. In fact, prior to Muenke’s discovery in 1996, the condition was misidentified as one or another form of craniosynostosis. Today, the only way to distinguish it from other types of craniosynostosis is through blood tests that identify a mutation in the *FGFR3* gene.

Diagnosis

Examination

As with all forms of craniosynostosis, visible examination of the skull and face are the first steps in diagnosis of Adelaide-type craniosynostosis. An enlarged skull (macrocephaly), malformed head, and/or misshapen facial features strongly suggest some form of the disease. Other physical evidence, such as shortened stature and malformed digits, may support this diagnosis, but are frequently not present.

Procedures

Visual evidence for the presence of Adelaide-type craniosynostosis is typically confirmed by a CAT scan, which confirms the presence or absence of prematurely closed sutures in the skull.

Tests

Unlike other types of craniosynostosis, the Adelaide type of the condition is identified conclusively and unambiguously entirely on the basis of a single blood test for the *FGFR3* gene. The presence of a mutation in that gene conclusively provides a diagnosis for the disorder.

Treatment and management

Treatment for Adelaide-type craniosynostosis depends on the severity of the patient’s condition and its prognosis. In many cases, the condition is so mild, with little or no effect on the patient’s physical or mental health, no treatment at all is necessary. In a few cases, some effort may be made to adjust the shape and appearance of the patient’s skull for cosmetic reasons, a step that can be taken with the

QUESTIONS TO ASK YOUR DOCTOR

- How do I know if my child has Adelaide-type craniosynostosis?
- What is the prognosis for a child with Adelaide-type craniosynostosis?
- What types of treatment are available for Adelaide-type craniosynostosis?
- Is it possible to predict whether my spouse (partner) and I are likely to have a child with Adelaide-type craniosynostosis in the future?
- What causes Adelaide-type craniosynostosis?

use of a supportive frame worn while the skull is still developing. In more severe cases, surgery may be required to re-open the prematurely closed coronal sutures. The primary reason for such surgery is to relieve pressure on the growing brain. In the absence of craniosynostosis, the skull is able to grow as the brain grows, providing sufficient room for the brain to reach its normal size. When sutures in the skull seal prematurely, however, intracranial pressures build up, potentially causing damage to the brain and possibly retarding mental growth. Early surgery may reduce the risk of later complications, such as hydrocephalus. If that condition does develop, additional surgery may be required.

Prevention

As with any genetic disease, it is not possible to eliminate the possibility of having a child with Adelaide-type craniosynostosis. However, it is possible for prospective parents to have a blood test that determines whether or not they carry copies of the mutant gene that is responsible for the condition. Partners can then decide whether or not they want to have children, based on the information obtained from such a test. Prenatal tests (amniocentesis or chorionic villus sampling) are also available to determine whether a fetus carries the mutant gene responsible for Adelaide-type craniosynostosis. Individuals with Adelaide-type craniosynostosis may wish to have genetic counseling to understand the risks associated with having children who may inherit the mutated gene. Siblings of affected individuals may also wish to have genetic counseling to understand the risks associated with having children who also carry the mutated gene.

Prognosis

The prognosis for Adelaide-type craniosynostosis varies widely. The condition may improve, may deteriorate, or may not change in severity.

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- Craniosynostosis and Positional Plagiocephaly Support, Inc. (CAPPS), 208 NY-109, #205, Farmingdale, NY 11735, (888) 572-5526, info@cappskids.org, <http://www.CAPPSkids.org>
- March of Dimes, 1550 Crystal City Drive, Suite 1300, Arlington, VA 22202, (888) 663-4637, <http://www.marchofdimes.org>
- World Craniofacial Foundation (WCF), 7777 Forest Lane, Suite C-616, Dallas, TX 75230, (972) 566-6669 or (800) 533-3315, info@worldcf.org, <https://www.worldcf.org>

David E. Newton, Ed.D

Adenomatous polyposis of the colon (APC)
see **Familial adenomatous polyposis**

Adenylosuccinate lyase deficiency

Definition

Adenylosuccinate lyase deficiency is a rare autosomal recessive metabolic disorder characterized by a number of nonspecific symptoms that may include psychomotor and mental disability, seizures, and autistic behavior. Common synonyms for the disease are adenylosuccinase deficiency,

KEY TERMS

Amyotrophy—Wasting of the muscles.

Autism—Abnormal brain development characterized by impaired social interaction and communication and by restricted and repetitive behavior.

Autosomal recessive—A genetic trait that appears only when two copies of a mutated gene are present.

Brachycephaly—A genetic condition characterized by a flattened skull.

Psychomotor—Pertaining to muscle functions that are controlled by the brain.

Purine—A nitrogen-containing organic compound whose basic molecular structure consists of two rings joined to each other.

Sign—An indication of disease, injury, or other physical problem that can be observed by someone other than the person experiencing these conditions.

Strabismus—Abnormal alignment of the eyes.

Symptom—An indication of disease, injury, or other physical problem reported by the person experiencing these conditions, but not by some outside observer.

succinylpurinemic autism, and the abbreviation ASL deficiency.

Description

Patients with ASL deficiency have a variable mixture of symptoms that include impaired psychomotor development, epilepsy, autistic features, feeding problems, and amyotrophy. (Amyotrophy is the medical term for muscle wasting.) Abnormal physical features may also be evident, including reduced head size, flattened head (brachycephaly), abnormal alignment of the eyes (strabismus), reduced upper lip, and low-set ears. The severity of these symptoms differs considerably from person to person, to the point that individuals with more moderate conditions may be able to live essentially normal lives.

ASL deficiency disorder is commonly divided into four subcategories. Type I is by far the most common and is characterized by poor muscle tone, severe mental disability, and epileptic seizures. Type II is characterized by impaired mental and visual development and poor hearing. Type III is characterized by muscle wasting and poor mental and physical development. Type IV is a mixture of types I and II.

QUESTIONS TO ASK YOUR DOCTOR

- What is the most recent research on the use of purine supplements for the treatment of ASL deficiency?
- Have any new palliative or therapeutic treatments been developed for use with ASL deficiency?
- Given the current condition of the patient, what is his or her prognosis?
- What support services are available for patients with ASL deficiency and their families?

Demographics

Fewer than 100 cases of the disorder have been unambiguously confirmed throughout the world. However, some authorities believe that a much larger number of cases have not been identified or have been misidentified because of confusion about signs and symptoms.

Signs and symptoms

ASL deficiency is caused by mutations in the gene responsible for the production of the enzyme adenylosuccinate lyase. The gene responsible for ASL deficiency occurs on chromosome 22 and many mutations have been found to be associated with the condition. The enzyme adenylosuccinate lyase is responsible for two essential steps in the synthesis of purine products in the body. Purines are nitrogen-containing organic ring compounds with a number of important functions in the body, one of which is the synthesis of nucleic acids, such as DNA and RNA. They are also involved in the conversion of energy into forms that can be used by the body, as signaling agents for a number of biochemical reactions, and as antioxidants that protect cells from carcinogenic agents. Adenylosuccinate lyase catalyzes two reactions in the synthesis of purines. The first is the conversion of succinylaminoimidazole ribonucleotide to aminoimidazole carboxamide ribonucleotide which is important for protein enzyme activity. The second is the conversion of adenylosuccinate to adenosine monophosphate (AMP) which is important for molecular bonding of RNA.

The precise manner in which this disruption produces the symptoms of ASL deficiency had not been determined as of 2015. The lack of adenylosuccinate lyase or its presence in an altered form does, however, result in the formation of two compounds that normally do not appear in the human body, succinylaminoimidazole

carboxamide riboside (SAICA riboside) and succinyladenosine. The presence of these substances in cerebrospinal fluid, urine, or (less commonly) blood serves as an unambiguous indication of the medical condition. It is believed that these substances are toxic and that their build-up leads to the associated neurological problems.

Diagnosis

Initial diagnosis of ASL deficiency is based on overall observations of a person's physical and mental features. Some indicators might be the presence of seizures, one's mental development, one's current characteristics, any muscular abnormalities, or other physical abnormalities. The condition can be unambiguously diagnosed only with the detection of SAICA in plasma, urine, or cerebrospinal fluid.

Treatment and management

No effective treatment is currently available for ASL deficiency.

Prognosis

The prognosis for ASL deficiency patients is generally poor, especially for those with Type I ASL deficiency. Most of these individuals die during infancy. Individuals with less severe conditions may do relatively well, however, and some have been able to live relatively normal lives well into adulthood.

Prevention

As with all genetic disorders, there are no preventative steps for ASL deficiency disorder. However, genetic counseling may be advisable.

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ORGANIZATIONS

- European Organization for Rare Diseases, 96, rue Didot, Paris, France 75014, +33 (1) 56.53.52.10, +33 (1) 56.53.52.15, eurordis.org, <http://www.eurordis.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (800) 999-6673, orphan@rarediseases.org, <https://rarediseases.info.nih.gov/organizations/2159>

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Adrenoleukodystrophy

Definition

Adrenoleukodystrophy is a progressive condition that affects the adrenal glands, the glands atop the kidneys responsible for the production of adrenalin, and myelin, which insulates the nerves in the brain and spinal cord.

Description

Adrenoleukodystrophy (ALD) was first described in the early 1900s and was originally called Schilder-Addison disease. It is named for the different parts of the body that are affected; “adreno” refers to the adrenal glands, “leuko” is the Greek word for white (myelin is often called the white matter in the brain and spinal cord) and “dystrophy,” meaning impaired growth. Therefore, this disease primarily affects the adrenal glands and the growth of the myelin in the brain and spinal cord. There is a wide range in the severity of symptoms. ALD mainly affects males, but occasionally females have mild or moderate symptoms.

Causes and effects

ALD is caused by problems in the peroxisomes. The peroxisomes are tiny structures in cells that help break down large molecules of fats into smaller ones so that they can be used by the body. In ALD the peroxisomes cannot break down saturated fats with very long chain fatty acids (VLCFA). There are two types of problems that occur because the VLCFA are not broken down. First, because

the VLCFA cannot be broken down, they accumulate throughout the body, especially in the brain and the adrenal glands. Very high levels of VLCFA are also seen in the blood. The second type of problem occurs because the fats that are usually made when VLCFA are broken down are not produced. This is in part what happens in the adrenal glands and in the myelin.

The adrenal glands are located on top of each kidney in the abdomen. Part of the job of the adrenal glands is to use cholesterol (a sterol made in the body when VLCFA are broken down) to make a few different steroids—chemical combinations that form the basis of hormones, body acids, and anabolic agents. The steroids are used to help the body properly use sodium and potassium and to break down proteins, carbohydrates, and other fats. Some of these steroids are also involved with sexual development and function.

The insulation that surrounds the nerves is called myelin and is also affected by the VLCFA not being broken down. Myelin is made up of a number of different proteins and fats. Normally the VLCFA break down and produce lipids that make up part of the myelin. When the VLCFA cannot break down, the fats necessary to make the myelin are not made, and the myelin is abnormal. In addition, for reasons not well understood, there is also active breakdown of myelin, also known as demyelination.

Genetic profile

ALD is caused by a mutation in a gene called the *ALD* gene. Genes contain the instructions for how the body grows and develops before and after a person is born. The *ALD* gene makes a protein called ALDP (ALD protein). Different proteins put together make the tissues and organs in the body such as myelin. ALDP is important because it helps VLCFA get into the peroxisomes. When there is a mutation in the *ALD* gene, the ALDP is abnormal or not present at all. As a result, the VLCFA cannot get into the peroxisomes and the VLCFA accumulate in other places in the body.

Genes are organized on structures called chromosomes. Hundreds to thousands of genes are found on each chromosome. There are 46 chromosomes in each cell of the body. These are grouped into 23 pairs. The first 22 pairs are the same in both males and females. The 23rd pair is called the sex chromosomes; having one X chromosome and one Y chromosome causes a person to be male; having two X chromosomes causes a person to be female. People get one member of each pair from the mother’s egg and one member from the father’s sperm.

The *ALD* gene is located on the X chromosome. Since males only have one X chromosome, they only

have one copy of the *ALD* gene. Thus, when a male has a mutation in his *ALD* gene, he will have ALD. However, females have two X chromosomes and therefore have two copies of the *ALD* gene. If they have a mutation in one copy of their *ALD* genes, they may only have mild symptoms of ALD or no symptoms at all. This is because their normal copy of the *ALD* gene does make normal ALD protein. Females who have one copy of the *ALD* gene with a mutation and one normal copy are called carriers.

Inheritance

ALD is passed on through families by X-linked recessive inheritance. This means that affected males are related through females in the family and there are no males in the family that have passed ALD onto their sons. Females pass on one of their X chromosomes to their children—sons or daughters. For a female carrier, if her normal X chromosome is passed on, her son or daughter will be unaffected and cannot pass ALD onto their children. However, if the X chromosome with the ALD mutation is passed on, a daughter will be a carrier and the son would have ALD. Therefore, a female carrier has a 50% or one in two chance of having an unaffected child (son or daughter), a 25%, or one in four, chance of having a carrier daughter, and a 25% or one in four chance of having an affected son.

When males pass on an X chromosome, they have a daughter. When they pass on a Y chromosome, they have a son. Since the ALD mutation is on the X chromosome, an affected male will always pass the ALD mutation on to his daughters. However, when he has a son, he passes on the Y chromosome, and the son is not affected. Therefore, an affected male passes the *ALD* gene mutation on to all of his daughters, but none of his sons.

Demographics

ALD has been described in people from all different ethnic groups. Approximately 1 in 20,000 to 1 in 42,000 people have ALD.

Signs and symptoms

Adrenal insufficiency

Almost all individuals affected with ALD have problems with their adrenal glands not working properly. This is called adrenal insufficiency. These problems include sluggishness, weakness, weight loss, hypoglycemia, nausea, vomiting, darkening of the skin color, and mental changes. Because adrenal insufficiency can cause problems with regulating the balance of sodium and potassium in the body, a person can go into shock and a coma, which can be potentially life threatening. Since this

aspect of ALD is readily treatable, it is important to identify these patients in order to prevent these complications.

Types of ALD

There is a wide range in the severity of symptoms and age of onset of ALD. All different severities have been seen within the same family. Therefore, a family who has many mildly affected members could still have a more severely affected member. ALD is roughly divided into three different types according to severity and age of onset. However, some patients do not fall neatly into one of these categories and instead fall somewhere in between. Each type is given a different name, although all have mutations (changes in the genetic code) in the same gene and the same type of inheritance.

The most severe form of ALD is called childhood ALD. About 35% of people with ALD have this type. These children usually have normal development in the first few years of life. Symptoms typically begin between four and eight years of age. Very rarely is the onset before the age of three or after the age of 15. In some boys, the first symptom may be seizures. In other children, they become hyperactive and have behavioral problems that may initially be diagnosed as attention deficit disorder. Early signs may also include poor school performance due to impaired vision that is not correctable by eye-glasses. Although these symptoms may last for a few months, other more severe problems develop. These include increasing problems with schoolwork and deterioration in handwriting and speech. They usually develop clumsiness, difficulty in reading and comprehension of written material, aggressive or uninhibited behavior, and various personality and behavioral changes. Most of these boys have problems with their adrenal glands by the time their first symptoms are noticed.

A milder form of ALD called adrenomyeloneuropathy (AMN) usually has a symptom onset at the age of 20 or later. Approximately 40%–45% of people with ALD have this type. The first symptoms are typically a progressive stiffness and weakness in the legs. Problems with urination and sexual function may also develop. Symptoms slowly progress over many years. Less than 20% of men with AMN will develop significant brain involvement that leads to cognitive and behavioral problems that are severe and may cause a shortened lifespan. About 70% of men with AMN will have problems with their adrenal glands when other symptoms are first noticed.

A third type of ALD is called Addison disease and affects about 10% of all of those with ALD. In this condition, people do not have the neurologic symptoms

associated with ALD and AMN, but do have problems resulting from adrenal insufficiency. Symptoms typically begin between two years of age and adulthood. The first symptoms are often vomiting, weakness or coma. People with Addison disease may or may not have darker skin. Many who are initially diagnosed with Addison disease will later develop symptoms of AMN.

In female carriers, about 20% will develop mild to moderate progressive stiffness and weakness in the legs and sometimes problems with urination. Rarely do they develop adrenal insufficiency. Symptoms in women generally do not begin before middle age.

Diagnosis

When the diagnosis of ALD is suspected, a test called magnetic resonance imaging (MRI) is usually required. In this test, pictures of the brain are taken and the amount of white matter (myelin) in the brain is measured. In people with symptoms of ALD, there are usually characteristic changes in the white matter. An MRI can be helpful in making the diagnosis of ALD, but if changes are seen on MRI, it does not confirm the diagnosis of ALD. Changes in the white matter may only be seen after 1–2 years of age when the brain has matured.

A definitive diagnosis of ALD can be made by measuring the level of the VLCFA in the blood. In 99.9% of males with all types of ALD, the level of the VLCFA in blood is very high. This is diagnostic of ALD.

When ALD is suspected, testing should also be performed to measure the adrenal function. In 90% of boys with symptoms of ALD and 70% of men with AMN, the adrenal glands are affected.

Approximately 85% of female carriers will have higher than normal levels of VLCFA in their blood. However, 15%–20% of female carriers will have normal levels of VLCFA in their blood, which gives a “false negative” result. If a woman wants to be certain about her carrier status, genetic testing to look for a specific mutation in the ALD gene can be performed. This testing usually involves drawing a small amount of blood. Before a woman could have testing to determine her carrier status, a mutation in the ALD gene must have already been found in an affected member of the family. If a mutation in the ALD gene has already been found in another family member, testing on another child suspected on having ALD would be done to look at the mutation known to cause ALD in the family.

Treatment and management

When the diagnosis of ALD is made, an important first step is to measure the level of adrenal function. If

KEY TERMS

Adrenal insufficiency—Problems with the adrenal glands that can be life threatening if not treated. Symptoms include sluggishness, weakness, weight loss, vomiting, darkening of the skin and mental changes.

Central nervous system (CNS)—In humans, the central nervous system is composed of the brain, the cranial nerves and the spinal cord. It is responsible for the coordination and control of all body activities.

Leukodystrophy—A disease that affects the white matter called myelin in the CNS.

Myelin—A fatty sheath surrounding nerves in the peripheral nervous system, which helps them conduct impulses more quickly.

Peroxisomes—Tiny structures in the cells that break down fats so that the body can use them.

Very long chain fatty acids (VLCFA)—A type of fat that is normally broken down by the peroxisomes into other fats that can be used by the body.

there is adrenal insufficiency, treatment should be given by steroid replacement, which can prove to be lifesaving. Adrenal function should be tested periodically.

Early on, it was thought that reducing the VLCFA in a person’s diet would help reduce the symptoms of ALD. Although some VLCFA does come from diet, most of it is produced in the body. Therefore, altering the diet alone does not cure ALD.

Lorenzo’s oil

A film called *Lorenzo’s Oil* told an embellished account of a real life family who had a young son with ALD and their search to find a cure for him. A possible treatment was found and was named Lorenzo’s oil, after their son, Lorenzo. The Lorenzo’s oil therapy worked to reduce the level of VLCFA in the blood. The idea was that if the level of VLCFA could be reduced, perhaps it would cure or help the symptoms. After a number of years of use, Lorenzo’s oil unfortunately does not seem to be an effective treatment, at least in those with advanced signs and symptoms. Although it does reduce the level of VLCFA in blood, it does not seem to alter a person’s symptoms.

Bone marrow transplant

One promising treatment is bone marrow transplant. However, this is a potentially dangerous procedure that

has a 10%–20% rate of death. Information is available on a limited number of patients. In the very small number of patients who have had a bone marrow transplant, a few have had their condition stabilize and a few have even made slight improvements. However, all of these people had the bone marrow transplant at an early stage of their disease. This treatment does have drawbacks, including the fact that there are limited numbers of donors who are a suitable “match” and a significant chance that complications will develop from the transplant. Early data suggests that bone marrow transplant is most effective when it is performed at an early stage of the disease when abnormalities are first seen through MRI. Additional long term studies are necessary to determine the overall success of these procedures.

Other treatments

Research is being done with other treatments such as lovastatin and 4-phenylbutyrate, both of which may help lower VLCFA levels in cells, but more work is necessary to determine their effectiveness. Gene therapy, a possible method of treatment, works by replacing, changing, or supplementing non-working genes. Although different gene therapy methods are being testing on animals, they are not ready for human trials.

Other types of therapy and supportive care are of benefit to both affected boys and their families. Physical therapy can help reduce stiffness and occupational therapy can help make the home more accessible. Support from psychologists and other families who have been or are in a similar situation can be invaluable. Many men with AMN lead successful personal and professional lives and can benefit from vocational counseling and physical and occupational therapy.

Prenatal diagnosis

Prenatal testing to determine whether an unborn child is affected is possible if a specific ALD mutation has been identified in a family. This testing can be performed at 10–12 weeks gestation by a procedure called chorionic villus sampling (CVS), which involves removing a tiny piece of the placenta and examining the cells. It can also be done by amniocentesis after 14 weeks gestation by removing a small amount of the amniotic fluid surrounding the baby and analyzing the cells in the fluid. Each of these procedures has a small risk of miscarriage associated with it, and those who are interested in learning more should check with their doctor or genetic counselor. Couples interested in these options should have genetic counseling to carefully explore all of the benefits and limitations of these procedures.

QUESTIONS TO ASK YOUR DOCTOR

- How often should adrenal function be tested?
- What are the risks of bone marrow transplant?
- At what point would you recommend starting physical or occupational therapy?
- Do you recommend genetic testing?

An experimental procedure, called preimplantation diagnosis, allows a couple to have a child that is unaffected with the genetic condition. This procedure is only possible for those families in which a mutation in the *ALD* gene has been identified. Those interested in learning more about this procedure should check with their doctor or genetic counselor.

Prognosis

The prognosis for people with ALD varies depending on the type of ALD. Those diagnosed with childhood ALD usually have a very rapid course. Symptoms typically progress very fast, and these children usually become completely incapacitated and die within three to five years of the onset of symptoms.

The symptoms of AMN progress slowly over decades. Most affected individuals have a normal lifespan.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 263-9938, <http://www.rarediseases.org>

United Leukodystrophy Foundation, 224 North Second Street, Suite 2, DeKalb, IL 60115, (800) 728-5483, (815) 748-0844, office@ulf.org, <http://www.ulf.org>

Karen M. Krajewski, MS, CGC

Aganglionic megacolon see **Hirschsprung disease**

Agnesis of clavicales and cervical vertebral and talipes equinovarus see **Crane-Heise syndrome**

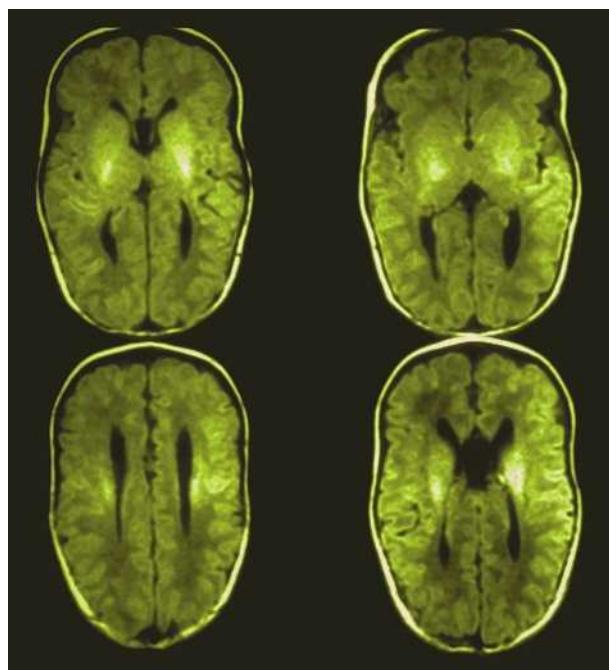
Agenesis of the corpus callosum

Definition

Agenesis of the corpus callosum is the complete or partial absence of the corpus callosum, the structure within the brain that connects the two hemispheres.

Description

Agenesis of the corpus callosum is a congenital anomaly occurring during the first trimester of pregnancy. During this time, the fetal brain is developing, and bundles of nerve fibers that create the corpus callosum are forming. This process may be interrupted if the mother is exposed to toxic substances or certain medications during pregnancy. Genetic abnormalities in the fetus may prevent the nerve fibers from growing correctly. In most cases, the exact cause of agenesis of the corpus callosum is unknown.



MRI images of the brain of a newborn, showing the typical appearance when there is agenesis of the corpus callosum. For example, the lateral ventricles are more widely separated. (Living Art Enterprises/Science Source)

In some people with agenesis of the corpus callosum, these nerve fibers are formed, but grow from front to back rather than from side to side. When the anomaly forms from front to back, groups of nerve fibers known as bundles of Probst form. These bundles stay within each hemisphere, never crossing the midline, and the two sides of the brain cannot share information. This lack of communication causes the symptoms of agenesis of corpus callosum.

The term “agenesis of the corpus callosum” usually refers to a complete absence of the corpus callosum. In some individuals, the corpus callosum is partially formed, and the condition is referred to as dysgenesis of the corpus callosum. There are two types of dysgenesis of the corpus callosum, partial and atypical. Partial dysgenesis occurs when the front, or anterior, portion of the corpus callosum does not form. In atypical dysgenesis of the corpus callosum, the rear, or posterior, portion of the corpus callosum is not formed.

The corpus callosum is not essential for life or for normal intellectual functioning. Many people who have agenesis of the corpus callosum as an isolated condition have no symptoms at all, and some may only experience mild difficulties with skills that require matching visual patterns. Since the two hemispheres of the brain cannot communicate, images seen by one eye cannot be connected to images processed by the other.

The more severe symptoms experienced by people with agenesis of the corpus callosum are most often caused by other brain malformations, chromosomal abnormalities, and genetic syndromes of which agenesis of the corpus callosum is only one component. Especially in children who have agenesis of the corpus callosum in addition to other brain malformations, the effects can be severe, including mental retardation, seizures, hydrocephalus, and impairment of motor functioning.

Agenesis of the corpus callosum often occurs along with other brain malformations, such as Arnold-Chiari malformation, Dandy-Walker malformation, and other defects of the midbrain. It may also be found in patients with defects of the size and shape of the brain, such as schizencephaly, lissencephaly, pachygyria, and hydrocephalus.

Individuals with anomalies of the formation of the forebrain, such as frontal encephalocele and holoprosencephaly, will usually have agenesis of the corpus callosum as well. In this case, the forebrain does not develop into two distinct hemispheres, and the corpus callosum does not form. These are severe birth defects and are usually incompatible with life.

Agenesis of the corpus callosum may occur as an isolated birth defect; in such cases, a genetic cause has not been identified. However, it often occurs as part of a syndrome. Agenesis of the corpus callosum has been associated with more than 30 inherited syndromes caused by chromosomal and single-gene anomalies and may result from prenatal exposure to anticoagulant medication during the first trimester of pregnancy.

Agenesis of the corpus callosum may also be known as absent corpus callosum, corpus callosum hypoplasia, ACC, CCA, callosal agenesis, or callosal dysgenesis.

Genetic profile

Agenesis of the corpus callosum is a component of many different genetic syndromes and chromosomal abnormalities, most of which are extremely rare.

Examples of autosomal malformation syndromes that include agenesis of the corpus callosum are:

- acrocallosal syndrome
- Andermann syndrome
- craniofacial dysmorphism-absent corpus callosum-iris colobomas-connective tissue dysplasia syndrome
- Fryns syndrome
- Joubert syndrome
- Larsen syndrome
- Miller-Dieker syndrome
- Rubinstein-Taybi syndrome

- Seckel syndrome
- Varadi-Papp syndrome

Agenesis of the corpus callosum is found in X-linked malformation syndromes such as:

- Aicardi syndrome
- Berry-Kravis and Israel syndrome
- Brooks syndrome
- CRASH syndrome
- Opitz-Kaveggia syndrome (FG syndrome)
- Proud syndrome
- Toriello-Carey syndrome
- X-linked hydrocephalus

Agenesis of the corpus callosum occurs more frequently in individuals with trisomies, such as trisomy 3, trisomy 13, trisomy 15, and trisomy 18. It has also been associated with chromosomal rearrangements, such as Wolf-Hirschhorn syndrome (del(4)(p16)).

Demographics

Researchers estimate the frequency of individuals affected with agenesis of the corpus callosum in the United States to be approximately 5.3%. It is more common in females than males, and is often seen in individuals with other brain malformations and as a part of many complex chromosomal and genetic syndromes.

Signs and symptoms

The symptoms of agenesis of the corpus callosum can range from virtually no difficulties to significant delays in reaching developmental milestones, mental retardation, and limited mobility.

Agenesis of the corpus callosum may be asymptomatic if occurring as an isolated brain malformation. With the increased use of imaging studies, many cases of absence of the corpus callosum are inadvertently discovered when a patient has a test to diagnose an unrelated condition. For many people with agenesis of the corpus callosum, however, symptoms of other clinical and genetic syndromes and brain malformations can be severe, especially in infants.

Symptoms of agenesis of the corpus callosum may include:

- seizures
- delays in reaching developmental milestones, such as sitting up, crawling, and walking
- intellectual disability
- poor hand-to-eye coordination
- impairments in auditory and visual memory

KEY TERMS

Autosomal—Pertaining to one or more of the 22 chromosomes that are not involved in determining gender.

Arnold-Chiari malformation—A congenital anomaly in which parts of the brain protrude through the opening in the base of the skull into the spinal column.

Bundles of Probst—Abnormally developed nerve fibers in the brain.

Congenital anomaly—A defect that is present at birth.

Computed tomography (CT) scan—A diagnostic imaging procedure in which x-ray and computer technology are used to generate slices or cross-sectional images of the body.

Dandy-Walker malformation—A congenital anomaly of the brain that causes a specific type of hydrocephalus.

Encephalocele—A congenital anomaly in which part of the brain is herniated through the skull.

Forebrain—The anterior of the front section of the brain.

Holoprosencephaly—A congenital anomaly of the front sections of the brain.

Hydrocephalus—The excess accumulation of cerebrospinal fluid within the skull.

Lissencephaly—Abnormality of the brain in which the surface is smooth, lacking the normal folds and grooves known as gyria.

Magnetic resonance imaging (MRI)—A diagnostic procedure that uses a combination of high powered magnets, radio frequencies, and computers to generate detailed images of structures within the body.

Pachygyria—Abnormality of the surface of the brain in which the gyria, or folds and grooves, in the surface of the brain are too large.

Schizencephaly—Abnormality of the brain in which there are deep ruts and clefts in the surface of the brain.

Trisomy—Three copies of an individual chromosome as opposed to the normal set of two chromosomes.

X-linked—Located on the X chromosome.

Although agenesis of the corpus callosum can be asymptomatic, it is considered a risk factor for neurological impairment. Agenesis of the corpus callosum may be suspected in children who have seizures, especially a specific type of seizures called infantile spasms. Agenesis of the corpus callosum may also be suspected in children with feeding problems, poor muscle control, and difficulties sitting, standing, and walking. It may be diagnosed later in children who experience other symptoms, such as frequent headaches or repetitive speech, in addition to seizures.

Diagnosis

Agenesis of the corpus callosum is diagnosed primarily by computed tomography (CT) scan and magnetic resonance imaging (MRI). MRI is the preferred imaging method for identifying abnormalities of the structures of the brain.

Agenesis of the corpus callosum may be diagnosed prenatally after week 20 of gestation, using prenatal ultrasound.

Treatment and management

There is no treatment for agenesis of the corpus callosum; however, the symptoms may be managed. Most

symptoms associated with agenesis of the corpus callosum are caused by other anomalies that occur along with the defect.

Symptoms, such as seizures, may be treated with anticonvulsant medications. Another common associated condition, hydrocephalus, may be treated by the surgical installation of a medical device called a shunt. A shunt relieves the pressure of excess fluid in the brain by draining that fluid away from the brain.

For infants and young children with agenesis of the corpus callosum and syndromes that include agenesis of the corpus callosum, early intervention programs may be helpful in assisting these children to reach developmental milestones. Other treatments, such as occupational therapy, physical therapy, and speech therapy, may help individuals improve deficits caused by the accompanying malformations.

Prognosis

The prognosis for individuals with agenesis of the corpus callosum varies widely. If agenesis of the corpus callosum occurs alone, the prognosis is usually excellent. Depending on the other associated birth defects and the

severity of the syndrome affecting the patient, intellectual disability, impaired neuromuscular functioning, and a shortened life expectancy may result. In rare cases, syndromes that may include agenesis of the corpus callosum are incompatible with life.

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ORGANIZATIONS

March of Dimes, 1550 Crystal Drive, Suite 1300, Arlington, VA 10605, (888) 663-4637, <http://www.marchofdimes.org>
National Organization for Disorders of the Corpus Callosum, PMB 363, 18032-C Lemon Drive, Yorba Linda, CA 92886, (714) 747-0063, info@nodcc.org, <http://www.corpuscallosum.org>

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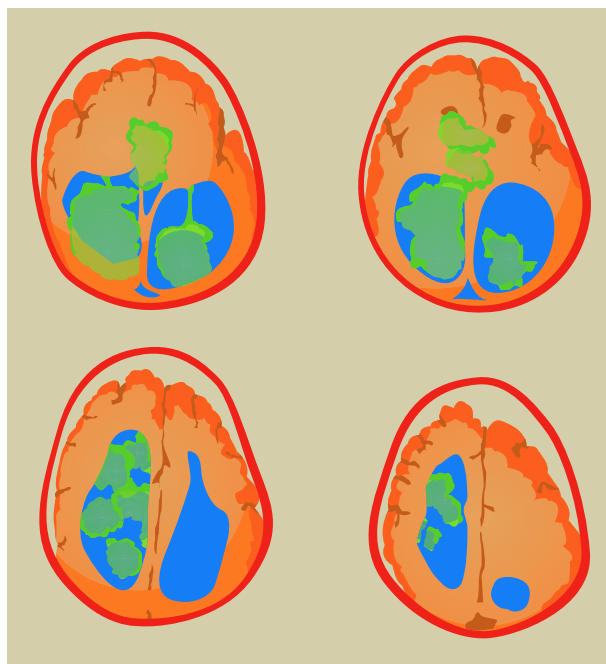
Aicardi syndrome

Definition

Aicardi syndrome is a rare genetic disorder that causes defects of the eyes and brain. It is believed to be an X-linked dominant genetic trait. The syndrome is named after Dr. Jean Aicardi, who first described it in 1965.

Description

Aicardi syndrome is an X-linked dominant genetic condition primarily found in females because males with the disease do not survive to birth. It is alternately called agenesis of the corpus callosum (ACC) with chorioretinal abnormality because of the associated abnormal



Brains with Aicardi syndrome (Gale)

formation of the connection between the right and left hemispheres of the brain (the corpus callosum) and abnormal development of the choroid and retinal sections of the eye.

The eye is composed of three layers: the sclera, the choroid, and the retina. The sclera is the tough, white outer coat of the eyeball; it is unaffected in individuals with Aicardi syndrome. The choroid is the middle layer of the eye. It serves to nourish the retina and absorb scattered light. The retina is the inner, light-sensitive layer of the eye. The retina receives the image produced by the lens and contains the rods and cones that are responsible for color vision. Both the choroid and the retina are abnormally formed in individuals affected with Aicardi syndrome.

Genetic profile

The location of the gene mutation responsible for Aicardi syndrome has been localized to Xp22.3. At or near this same locus is the gene responsible for microphthalmia with linear skin defects (MLS) and the gene responsible for Goltz syndrome. It is assumed that Aicardi syndrome is dominant and X-linked with near 100% fetal mortality in males. Nearly all of the cases of Aicardi syndrome are believed to result from *de novo* mutations (new mutations that occur after conception) since parents of affected individuals have normal chromosomes.

KEY TERMS

Absence seizure—A brief seizure with an accompanying loss of awareness or alertness.

Choroid—A vascular membrane that covers the back of the eye between the retina and the sclera and serves to nourish the retina and absorb scattered light.

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

De novo mutation—Genetic mutations that are seen for the first time in the affected person, not inherited from the parents.

Focal seizure—A seizure that causes a brief and temporary change in movement, sensation, or nerve function.

Grand mal seizure—A seizure that causes a loss of consciousness, a loss of bladder control, generalized muscle contractions, and tongue biting.

Infantile spasms—The form of grand mal or focal seizures experienced by infants prior to the development of many voluntary muscular controls.

Post-ictal state—A period of lethargy, confusion, and deep breathing following a grand mal seizure that may last from a few minutes to several hours.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Retinal lacunae—Small abnormal cavities or holes in the retina.

Demographics

Approximately 4,000 individuals, predominantly female, have been diagnosed with Aicardi syndrome worldwide. Aicardi syndrome is not associated with any particular sub-populations. It appears with equal frequency in all races and across all geographies. Because it is an X-linked dominant trait, it is observed almost exclusively in females.

Signs and symptoms

Aicardi syndrome is characterized by abnormalities in the connection between the left and right hemispheres of the brain (the corpus callosum), infantile spasms in affected infants and seizures in older affected individuals, developmental delays, lesions and other abnormalities of

the eye, and possible other defects in the brain such as holes where healthy brain tissue should be (brain cysts) and an enlargement of the connecting cavities (ventricles) of the brain. It is these abnormalities of the brain, including the corpus callosum, that lead to the observable symptoms of seizures and developmental delays. Aicardi syndrome may also be complicated by brain tumors, benign tumors of the scalp (lipomas), and cancer of the blood vessels (angiosarcoma).

The onset of infantile spasms in individuals with Aicardi syndrome is generally observed between the third and fifth months of life. It is at this time that the final connections (neural synapses) are made in the developing human brain. These infantile spasms are a form of the full seizures that are experienced by older affected individuals. A seizure is the result of sudden abnormal electrical activity in the brain. This electrical activity can result in a wide variety of clinical symptoms including muscle twitches; tongue biting; fixed, staring eyes; a loss of bladder control resulting in involuntary urination; total body shaking (convulsions); and/or loss of consciousness.

There are several types of seizures. Focal, or partial, seizures are characterized by a brief and temporary change in movement, sensation, or nerve function. Examples of this type of seizure include drooling, head turning, eye movements, lip biting, or rhythmic twitching of muscles. Focal seizures usually cause no change in awareness or alertness. An absence seizure is a brief seizure with an accompanying loss of awareness or alertness such as a staring spell. Focal and absence seizures are types of petit mal seizures. A grand mal seizure is characterized by a loss of consciousness, a loss of bladder control, generalized muscle contractions, and tongue biting. Grand mal seizures are also followed by a period of lethargy, confusion, and deep breathing (post-ictal state) that may last from a few minutes to several hours.

Individuals affected with Aicardi syndrome also have vision problems including blindness. These vision problems are the result of abnormal development of the two inner layers of the eye (the choroid and the retina). The most common type of malformation in the eyes of individuals with Aicardi syndrome is the appearance of small cavities or holes in the retina (retinal lacunae). Instances of small eyes (microphthalmia) and missing structures of the eye (coloboma) are also common.

Diagnosis

Aicardi syndrome is generally first diagnosed between the ages of three and five months. It is at this age that the final connections in the brain are completed. Once these connections are completed in an affected individual, the individual will begin to have infantile spasms.

QUESTIONS TO ASK YOUR DOCTOR

- What supportive measures can we provide at home?
- How many feedings a day should be given?
- How often should vision exams be done?
- What are the risks and benefits of the medications that you recommend?

These spasms are akin to seizures in older children. Infantile spasms combined with defects of the retina and choroid of one or both eyes is sufficient evidence for the diagnosis of Aicardi syndrome. Magnetic resonance imaging (MRI) can confirm the brain malformations, including the absence of the corpus callosum. Prenatal diagnosis is not yet available, but connection to the Xp22.3 locus makes genetic testing for this dominant trait theoretically possible.

Treatment and management

Treatment of an individual with Aicardi syndrome generally consists of seizure management, vision treatment for those individuals born with sight or partial sight, and early and continuing intervention programs for developmental delays. Because of the severe neurological damage, many individuals are unable to chew and swallow and must be fed with pureed food. The most common medications for affected individuals are anticonvulsive drugs such as valproic acid (brand names: Depakene, Valproate, Valrelease), clonazepam (brand names: Klonopin and Rivotril), phenobarbital (available as a generic drug), and phenytoin (brand name: Dilantin).

Prognosis

Aicardi syndrome is lethal in males prior to birth. The prognosis in females varies on a case-by-case basis. The estimated survival rate is 76% at 6 years of age and 40% at 14 years of age. There has been a report of a surviving individual with Aicardi syndrome in her late forties. Most individuals with Aicardi syndrome are either born blind or will become blind. Developmental delays and intellectual disability ranging from mild to severe are seen in all individuals affected with Aicardi syndrome.

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ORGANIZATIONS

Aicardi Syndrome Foundation, P.O. Box 3202, St. Charles, IL 60174, (630) 397-9728, research@aicardisyndrome.org, foundation.org, <https://aicardisyndromefoundation.org>

Paul A. Johnson

ALA dehydratase deficiency

Definition

ALA dehydratase deficiency is a very rare autosomal recessive type of porphyria. Porphyrrias are disorders caused by disruptions in the metabolic pathway by which a class of biochemicals known as porphyrins are converted to heme, the oxygen-carrying component of hemoglobin that gives blood its red color. The condition is also known as ALAD deficiency porphyria (ADP). It was first described in 1979.

Description

Heme is produced in a series of biochemical reactions that requires eight different enzymes, one of which is delta-aminolevulinic acid dehydratase, which catalyzes the second stage of this sequence (abbreviated as ALAD, for aminolevulinic acid dehydratase). More than ten possible mutations have been discovered within the gene responsible for the production of ALAD. When mutations occur in both alleles of the gene, ALA dehydratase deficiency disorder may develop.

Like other types of porphyria, neurological signs and symptoms are prominent. However, the descriptions of ADP for the very small number of individuals for whom data are available vary widely. In one case, an infant who contracted the disorder died at a young age. In another case, a 63-year-old man did not develop symptoms until late in life; his primary symptoms were then

KEY TERMS

Autosomal recessive—A genetic trait that appears only when two copies of a mutated gene are present.

Enzyme—A protein that catalyzes biochemical changes in the body without itself undergoing permanent change.

Heme—An organic molecule that contains a single atom of iron and is responsible for the oxygen-carrying ability of hemoglobin.

Neuropathy—A disorder of the peripheral nervous system.

Polyneuropathy—A disorder in which a number of nerves in the peripheral nervous system malfunction simultaneously.

Porphyria—Any one of a number of diseases, usually genetic in character, in which the conversion of porphyrins to heme is disrupted; usually associated with neurological problems.

Psychosis—A severe mental disorder that results in a distorted view of reality.

Sign—An indication of disease, injury, or other physical problem that can be observed by someone other than the person experiencing these conditions.

Substrate—A compound on which an enzyme works in a biochemical reaction.

Symptom—An indication of disease, injury, or other physical problem reported by the person experiencing these conditions, not by an outside observer.

severe polyneuropathy. Two German males experienced an onset of the disease in their teens and experienced neuropathy and, in one case, paralysis of the arms, legs, and respiratory system. In spite of these serious symptoms, both patients survived to live a somewhat satisfactory life for more than 20 years.

Genetic profile

Mutations in the *ALAD* gene cause a reduction in the amount of delta-aminolevulinic acid dehydratase in the bloodstream. Without this enzyme, the substrate on which it normally acts, delta-aminolevulinic acid (ALA), begins to accumulate. Excess ALA, a neurotoxin, is responsible for the neuropathies associated with the disease.

Demographics

Only one case of ADP has ever been diagnosed in the United States, and six more cases have been found in other countries: three in Germany, two in Sweden, and one in Belgium.

Signs and symptoms

In addition to the neuropathy associated with all forms of porphyria, patients with ADP may also experience abdominal pain, nausea, vomiting, constipation, diarrhea, urinary retention, weakness in the arms and legs, seizures, respiratory impairment, and, in extreme cases, psychoses.

Acute attacks of ADP may be triggered by a number of factors, including the ingestion of substances that stimulate the P-450 system, such as barbiturates and sulfonamides, psychological or physical stress, decreased caloric intake, and use of estrogen or progesterone products.

Diagnosis

Initial diagnosis of ALA dehydratase deficiency is based on a physical examination in which the physician looks for abdominal tenderness and neuropathy. Weakness of arms and legs may also be apparent. Confirmatory tests are based on urine samples in which the levels of ALAD are severely depressed (usually less than 5% of their normal concentrations) and levels of porphyrin are elevated. Elevated levels of other proteins, such as coproporphyrin III and zinc protoporphyrin IX, by as much as a factor of 100 are also common, although the reason for this phenomenon is not known.

Treatment and management

The most severe manifestations of an acute ADP attack can be mitigated by removing factors responsible for such attacks, such as increasing caloric intake, relieving physical or psychic stress, and avoiding use of chemicals involved in the P-450 cytochrome system. Long-term maintenance for the disease requires a high-caloric diet that includes a minimum of 300 g of glucose daily. For treatment of acute ADP attacks, heme replacement therapy can be instituted, in which hematin, a modified form of heme, is administered intravenously. Metalloporphyrins, synthetic compounds of a porphyrin with a metal such as copper, silver, or magnesium, can also be used to reduce neurological damage, although such agents are not successful in reversing existing neurological damage. A liver transplant was attempted as a way of treating ADP with a six-year-old Swedish boy, but the procedure was unsuccessful, and the boy died three years later.

QUESTIONS TO ASK YOUR DOCTOR

- Given the patient's current status, what is the likely prognosis for the disease?
- What steps should I take to reduce the conditions resulting from an acute attack of ADP?
- Where can I obtain additional information about ADP?

Although it is not possible to prevent the onset of ADP when a person has two copies of the damaged *ALAD* gene, it may be possible to avoid or reduce the severity of acute attacks. The patient should maintain a proper diet, high in calories; avoid physical and psychic stress; and avoid the ingestion of substances known to be associated with an ADP attack, such as certain drugs and hormone products.

Prognosis

Prognosis differs dramatically for patients with ADP, with some surviving many years after their original diagnosis and others surviving for only a short time. This differential prognosis may be the consequence of different genetic conditions leading to onset of the disease.

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ORGANIZATIONS

- American Porphyria Foundation, 4900 Woodway, Suite 780, Houston, TX 77056-1837, (713) 266-9617 or (866) APF-3635, (713) 840-9552, porphyrus@aol.com, <http://www.porphyrifoundation.com>

CLIMB (Children Living with Inherited Metabolic Diseases), Climb Bldg., 176 Nantwich Rd., Crewe, Cheshire UK CW2 6BG, enquiries@climb.org.uk, <http://www.CLIMB.org.uk>

David E. Newton, Ed.D

Alagille syndrome

Definition

Alagille syndrome is a genetic condition characterized by liver disease, characteristic facial features, heart murmurs or defects, vertebral changes, and eye changes, as well as a variety of less frequently noted features. Alagille syndrome is also called arteriohepatic dysplasia, cholestasis with peripheral pulmonary stenosis, syndromic hepatic ductular hypoplasia, and Alagille-Watson syndrome.

Description

Alagille syndrome is a rare condition occurring either sporadically or in an autosomal dominant pattern of inheritance. Approximately 90% of cases are caused by changes in the *Jagged1* gene on chromosome 20. However, the diagnosis of Alagille syndrome is based on clinical features and family history. Obtaining medical information about family members can be difficult, as some people with Alagille syndrome are so mildly affected or have such variable symptoms that the condition may go unrecognized. Prognosis depends on the extent of major organ involvement, especially of the liver, heart, and kidneys. Liver transplantation is needed in some cases. Prenatal testing is available to families in which a genetic change has been identified. The interpretation of this testing is limited by the variability of clinical features, even within the same family. People with the same genetic change can have a wide range of medical problems with varying degrees of severity. Alagille syndrome is named for Dr. Daniel Alagille (1925–2005) who specialized in treating childhood liver diseases. International Alagille Syndrome Awareness Day is observed on January 24 in honor of Dr. Alagille's birthday.

Genetic profile

Alagille syndrome occurs sporadically in 15%–56% of cases, but it has been noted to follow an autosomal dominant pattern of inheritance in some families. In sporadic cases, the gene change occurred for the first time in the affected individual, and neither parent had the same gene change. In autosomal dominant inheritance, multiple generations of a family are affected with the condition. In either case, people who have the genetic change have a

50% chance of passing the altered gene on to each of their children. Since the gene is dominant, passing on one copy of the gene is enough to cause symptoms. However, the condition exhibits variable expressivity, which means that different people with the condition may experience different features of the disease or different levels of severity. One explanation is that different changes in the gene may cause different features of the syndrome. However, even when family members all have the same genetic change, different features and degrees of severity can occur. In addition, the condition is not fully penetrant. Some people who have the gene mutation, due to an affected parent and child, do not show any features of the disease.

Changes in a gene called the jagged1 (*Jag1*) gene on the short arm of chromosome 20 have been shown to be the underlying defect in many patients. The *Jag1* gene encodes a cell surface protein that plays a role in the regulation of fetal development. The protein is active in many cell types and directs cells to their proper place in the embryo. Seventy to 75% of Alagille syndrome probands have had an identifiable change within this gene. Of that 70%, 6% have been shown using a laboratory technique called fluorescent in situ hybridization to have a small deletion of a piece of the short arm of chromosome 20 (20p), which includes the *Jag1* gene. A variety of other molecular changes in the gene have been detected by sequencing the gene. Thirty percent of people with the condition do not have an identifiable change in (*Jag1*). It is possible that there are other genes that cause the disease in these families.

Demographics

Alagille syndrome is rare, occurring in one in 70,000 to 100,000 live births. The condition affects males and females equally. Most patients with Alagille syndrome come to medical attention in the first four months of life because of jaundice, an enlarged liver, severe itching of skin, or multiple raised nodular areas on the skin.

Signs and symptoms

Liver manifestations

One of the most common and most serious symptoms of Alagille syndrome is liver disease, which occurs in 90% to 100% of patients and often leads to growth delay or failure as a result of malnutrition. Because there is a reduction in the number of bile ducts in the liver, there are elevated bile acids in the blood and limited bile excretion from the body, causing jaundice, pruritus (severe skin itching), and xanthomas (raised nodules on the skin, especially at skin creases or areas of friction). Some patients have mild or no liver problems, while others have progressive liver failure.

KEY TERMS

Amniocentesis—A procedure performed at 16 to 18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from it can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10 to 12 weeks of gestation. Under ultrasound guidance, a needle is inserted through either the mother's vagina or her abdominal wall, and a sample of cells is collected from around the early embryo. These cells are then tested for chromosome abnormalities or other genetic diseases.

First-degree relative—A parent, child, or sibling is a first-degree relative. First-degree relatives have one half of their genes in common.

Hemivertebra—A defect in which one side or half of a vertebra fails to form.

Proband—The person in the family who is affected by a genetic disorder and who brings the family to the attention of a healthcare provider.

Second-degree relative—Aunts, uncles, nieces, nephews, grandparents, grandchildren, and half-siblings are second-degree relatives. These individuals have one-quarter of their genes in common.

Spina bifida occulta—The failure of vertebrae to close into the neural tube without nerves protruding. This is most often asymptomatic.

Cardiac manifestations

Heart defects and murmurs have been noted in 85% to 95% of patients with Alagille syndrome. The most common type of defect is pulmonary artery stenosis, although other types of defects also occur. Many of these defects do not have clinical significance to the patient. However, complex and severe heart defects occur and are some of the more common causes of mortality in patients with Alagille syndrome.

Eye manifestations

One important diagnostic feature of Alagille syndrome is a particular eye finding called posterior embryotoxon. This is an anterior chamber defect of the eye caused by a prominent, centrally positioned Schwalbe ring. This feature

can be seen through a split lamp examination and does not affect vision. Since 56% to 90% of patients have this or other changes in the eye, including retinal pigmentary changes, an eye examination can aid in diagnosis.

Skeletal manifestations

A particular finding called a butterfly vertebra is associated with Alagille syndrome. The term refers to the appearance of the space around the vertebrae due to clefting or disruption of formation of a vertebra. There are usually no physical problems associated with this radiological finding. The frequency of butterfly vertebrae in this syndrome is uncertain, with estimates ranging from 33% to 93% in different studies. Other skeletal malformations are also noted in these patients, such as spina bifida occulta and hemivertebrae. Therefore, radiological examination of the spine may aid in diagnosis.

Facial manifestations

The occurrence of particular facial features has been noted in 70%–95% of patients with Alagille syndrome. The facial features include a prominent forehead, deep-set and widely spaced eyes, a pointed chin, and a straight nose with a bulbous tip. These features are more subjective, but they are some of the most consistent features of the diagnosis.

Other manifestations

Problems with the structure and function of the kidneys have been noted with an occurrence of 40% to 70% of patients. Symptoms are usually mild, but renal disease has caused mortality in severe cases. Mild delays in gross motor function have been noted in 16% of children, most of whom had severe organ disease. Intracranial bleeding has also been noted with increased frequency and is associated with mortality in this syndrome.

Diagnosis

The diagnosis of Alagille syndrome is based on clinical features and can be made by the presence of liver disease plus two of the other major features. An ultrasound of the liver can rule out other causes of liver disease, and a liver biopsy can determine whether there is a reduction in the number of bile ducts. However, this finding occurs in other conditions as well as Alagille syndrome, and the timing of the biopsy is important. Older patients are more likely to have fewer bile ducts than those under five years of age. An echocardiogram for heart defects, a radiological examination of the spine, blood tests for renal function, an ophthalmologic examination, and an examination of facial features are important diagnostic tools. A careful family history is also important in diagnosis. When a first- or second-degree relative has already been

QUESTIONS TO ASK YOUR DOCTOR

- How often should liver function tests be performed?
- Would you like to obtain a medical history from other family members?
- What is the likelihood of requiring a liver transplant?
- If a liver transplant is needed, would family members be considered as potential donors?

diagnosed with Alagille syndrome, the presence of even one feature of the condition may constitute a diagnosis.

Once a diagnosis has been made in an individual, the parents should undergo an evaluation for subtle features of the condition. If a parent is diagnosed, then evaluation for appropriate extended family members would be offered. A correct diagnosis is important, because there are other syndromes that exhibit similar liver disease, heart defects, and eye findings. These syndromes are inherited in different ways, so the recurrence risk for offspring and other family members may be different.

Two different types of genetic testing are used: fluorescence in situ hybridization (FISH), which detects the small percentage of patients who have a deletion of the entire gene, and sequencing, which looks at changes within the gene. If a genetic change is identified in the family, prenatal testing would be available through chorionic villus sampling or amniocentesis. However, the interpretation of this testing is difficult, because the presence of a gene change does not allow one to predict the severity of the condition or which medical problems may occur.

Treatment and management

Liver transplantation is needed in 15% to 20% of patients. Other treatments depend on which of the other features of the condition are present and the degree of severity. Repair of heart defects is another surgical treatment that is needed in some cases.

Clinical trials (experimental new drug treatments and procedures for a disease or disorder) may be available to people with Alagille syndrome. Participation is voluntary and at no cost to the participant. All clinical trials receiving U.S. government funding and some supported by private industry, are posted at <https://www.clinicaltrials.gov>.

Prognosis

Prognosis for Alagille syndrome is quite variable and depends on the degree of liver, heart, and kidney disease and the presence of intracranial bleeding. Overall, survival rates are 72% to 85%. The survival rate of those undergoing liver transplantation is 60% to 80%. There is currently no method to determine which patients will reach end-stage liver disease.

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ORGANIZATIONS

- Alagille Syndrome Alliance, P.O. Box 22, Collierville, TN 38027, (901) 286-8869, alagille@alagille.org, <https://www.alagille.org>
- Genetic and Rare Disease Information Center, P.O. Box 8126, Gaithersburg, MD 20898-8126, (888) 205-2311, <https://rarediseases.info.nih.gov>

Sonja Rene Eubanks
Revised by Tish Davidson, AM

Albinism

Definition

Albinism is a collection of inherited conditions affecting melanin production that result in a lack of pigment in the hair, skin, and/or eyes. The conditions are broadly classified as either ocular albinism (OA), which primarily affects the eyes, or oculocutaneous albinism

(OCA), which affects the eyes, hair, and skin. Vision problems are associated with all types of albinism.

Description

Albinism results from one of several different inherited genetic defects in the body’s ability to produce or distribute melanin. Melanin is a photoprotective pigment that absorbs ultraviolet (UV) light from the sun to protect the skin from damage. Sun exposure normally increases melanin in the skin to produce a tan. Many people with albinism do not have melanin in their skin, so they burn in the sun. They may eventually develop skin cancer if they do not adequately protect themselves from sunlight. Some children with albinism may develop some pigmentation as they grow older. Some people with albinism have freckles or large blotches of pigmentation but are still unable to tan.

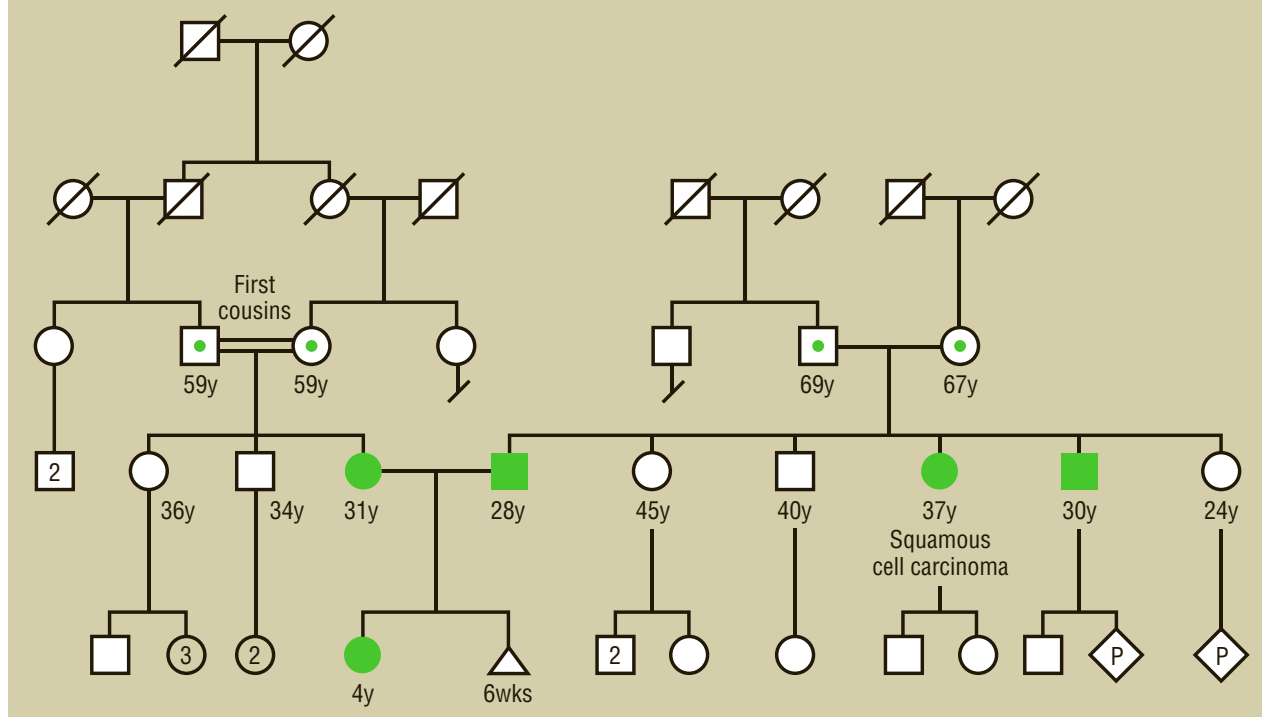
Because melanin gives color to the skin, hair, and iris of the eye, people with albinism typically have pale skin, white or pale yellow hair, and light blue or gray eyes. Lack of pigment in the iris can cause the eyes to appear pink or violet in some types of light, because light is reflected from the reddish part of the retina in the back of the eye. However, some people with albinism have hazel or brown eyes. Many people with albinism have vision problems, since parts of the retina and nerve connections between the retina and the brain do not develop correctly in the absence of melanin. Their eyes also are often very sensitive to light.

Genetic profile

Melanin production by the body is a complex process, involving multiple genes. Defects in these different genes cause different types of albinism. Although albinism is usually inherited, and the risk factor is a family history of the disorder, most children with albinism are born to parents with normal skin, hair, and eye color. This is because most types of albinism are autosomal recessive disorders. Autosomal means that the causative gene is located on one of the 22 chromosome pairs other than the X or Y sex chromosomes. Recessive means that two copies of a defective gene—one inherited from the mother and one from the father—are required for the appearance of symptoms. People who inherit one normal gene and one gene for albinism have no symptoms, because the normal gene provides for normal melanin production and distribution. However, such people are “carriers,” with a 50% chance of passing on the defective gene to each of their offspring. If both parents are carriers, there is a 25% chance of passing on both copies of a defective gene to each of their offspring, who will then have albinism. Therefore, albinism is more common in

Albinism

(i.e. Oculocutaneous Albinism)
Autosomal Recessive



Albinism: pedigree analysis chart (Gale)

smaller populations in which people intermarry. Although the different types of albinism may share many symptoms, they are distinguished by their specific genetic defect.

Ocular albinism

OA primarily affects the eyes, although individuals with OA may have lighter skin, hair, and eye color than other family members. OA1 or XLOA, sometimes called Nettlehip-Falls ocular albinism, is the most common type of OA. It is caused by mutations (changes) in the *GPR143* gene, which is located on the X chromosome. Therefore, unlike other types of albinism, it is a sex-linked recessive trait with inheritance that differs from the genetic profile described above. Males have only a single X chromosome, inherited from their mothers. A woman who has a defective *GPR143* gene on one of her two X chromosomes is a carrier. Although not herself affected by albinism, because of the normal gene on her other X chromosome, each of her offspring has a 50% chance of inheriting the defective gene. Her male offspring who inherit the gene will have albinism. Males with XLOA will transmit their *GPR143* mutation to all of

their daughters but to none of their sons, who inherit their Y chromosome instead.

With XLOA, melanosomes—the granules that produce melanin—do not develop correctly. The skin symptoms of XLOA are minor. Skin and eye colors are usually within the normal range. However, there is no coloring to the retina, and males with XLOA are born with persistent visual impairment.

Oculocutaneous albinism

OCA is the most severe form of albinism. There are four types of OCA, which are caused by mutations in one of four different genes. The types of OCA may be further classified into subtypes, depending on the specific mutations in the genes.

- OCA1 is caused by mutations in the *TYR* gene that code for the enzyme tyrosinase, which is required to convert the amino acid tyrosine into melanin. OCA1 is characterized by white hair, very light skin, and light-colored eyes. OCA1A is the most severe form, resulting in a total absence of pigment in skin, hair,

and eyes, extreme susceptibility to sunburn, and vision problems.

- OCA2 is caused by mutations in the *OCA2* gene and is less severe than OCA1. People with OCA2 commonly have creamy white skin and light blond to brown hair.
- OCA3 is caused by mutations in the *TYRP1* gene and causes milder vision abnormalities than other types of OCA. OCA3 includes rufous oculocutaneous albinism, which typically affects dark-skinned people.
- OCA4 is caused by mutations in the *SLC45A2* gene and has symptoms similar to OCA2.

Other albinism types

Certain other genetic disorders can cause albinism along with other symptoms or pathologies. Hermansky-Pudlak syndrome (HPS) is a rare type of albinism in most parts of the world but is common among people from Puerto Rico. The amount of pigmentation varies greatly. The skin can be creamy white, yellow, or brown. Hair may be white, pale yellow, or brown, but is always lighter than in the rest of the population. Eye color ranges from blue to brown. HPS is associated with bleeding and bruising problems, visual abnormalities, and other pathologies, such as lung and bowel diseases.

- HPS type 1 (HPS1) is caused by mutations in the *HPS1* gene.
- HPS2 is caused by mutations in the *AP3B1* gene.
- HPS3 is caused by mutations in the *HPS3* gene.
- HPS4 is caused by mutations in the *HPS4* gene.
- Other genes associated with HPS are *HPS5*, *HPS6*, *AP3B1*, *BLOC1S3*, *BLOC1S6*, and *DTNBP1*.

Certain rare complex disorders can cause localized or partial albinism:

- Chediak-Higashi syndrome causes patches of colorless skin throughout the body. It is caused by defective *LYST* genes that cause abnormal melanosomes.
- Tuberous sclerosis causes small areas of colorless skin.
- Shah-Waardenburg syndrome may involve a lock of hair on the forehead or no coloring to one or both irises. ABCD syndrome is an acronym for albinism, black locks of hair, cell migration disorder of the gut neurocytes (Hirschsprung disease), and deafness. Both Shah-Waardengurg and ABCD syndromes are autosomal recessive inherited disorders caused by mutations in the *EDNRB* gene that encodes the endothelin B receptor.
- Piebaldism is characterized by patches of white hair or lighter-colored skin blotches. Unlike other types of albinism, it is an autosomal dominant trait, meaning that symptoms are apparent in the presence of only one



Albino child in Sierra Leone, Africa. (Feije Riemersma/Alamy)

defective gene. That gene is either the *KIT* protooncogene or the *SNAI2* gene interfering with the development of melanocytes (the cells that produce melanin).

Demographics

Albinism affects people of all races and nationalities, but different types are more prevalent in certain populations. Some form of albinism affects 1 in 17,000 people in the United States. About one person in 70 carries a single defective gene for albinism but has no symptoms of the condition. The most common form of OA—ocular albinism type 1 (OA1) or X-linked ocular albinism (XLOA)—affects at least 1 in 50,000–60,000 males, but is extremely rare in females.

Worldwide, OCA affects 1 in 20,000 people. OCA types 1 and 2 (OCA1 and OCA2) are more common than types 3 and 4 (OCA3 and OCA4). The prevalence of OCA1 and OCA2 is about 1 in 38,000–40,000 in most populations. OCA2 is more prevalent in African Americans, some Native American groups, and in people from sub-Saharan Africa. OCA2 is estimated to affect 1 in 1,500–3,900 Africans and up to 1 in 10,000 African Americans. OCA3 occurs primarily in people from southern Africa. OCA4 affects about 1 in 100,000 in most populations but is more common among Japanese and Koreans. The persecution of people with albinism is a longstanding tragedy in some African countries.

Signs and symptoms

Eye problems

Lack of melanin causes abnormal development in the eye. For example, the iris, which normally acts as a filter, may let too much light into the eye. Communication

between the retina (the surface inside the eye that absorbs light) and the brain may also be altered. These abnormalities can cause visual impairments such as a lack of depth perception, sensitivity to light (photophobia), nearsightedness, farsightedness, or astigmatism (a curvature in the lens that makes it difficult to focus on objects). Other common effects include nystagmus (constant, involuntary eye movements) and strabismus (wandering eye or crossed eyes). Strabismus can interfere with depth perception. Some people with albinism have functional blindness.

Skin conditions

Albinism can cause absence of color to the hair, skin, or irises. Some people have skin and hair that is lighter than normal or patches of colorless skin.

Other rare symptoms

Rare forms of albinism may cause deafness or decrease the body's ability to fight infection. HPS can cause a variety of medical problems. For example, it may interfere with normal platelet function. Platelets are a component of blood required for clotting. People with this complication may have frequent nosebleeds, bleeding gums, easy bruising, or slow wound healing. Women may have heavy menstrual bleeding and excessive bleeding during childbirth. HPS can lead to a condition called granulomatous colitis, which causes abdominal cramps, intestinal bleeding, and diarrhea. Scarring of the lungs (fibrosis) can cause restrictive lung disease leading to fatigue and breathing problems. People with HPS may also have kidney disease.

Diagnosis

Albinism may be diagnosed by a careful examination of the hair, skin, and eyes, in combination with a family history of the disorder. In the past, doctors examined a sample of hair root with a procedure known as a hairbulb pigmentation test. They also tested hair for the presence of tyrosine to identify the type of albinism. However, these procedures have been replaced by genetic testing to determine the type of albinism. People can also be tested to determine if they are carriers of albinism genes. Amniocentesis at 16–18 weeks gestation can be used for prenatal testing when the disease-causing mutation(s) in the family are known. Chorionic villus sampling (CVS), which can be performed in the first trimester of pregnancy, examines the cells of the placental chorionic villi for genetic analysis; the villi are normal growths found in the placenta that have the same genetic material as the fetal cells. Also, clotting tests, platelet counts, and platelet examination may be used in the diagnosis of HPS.

KEY TERMS

Autosomal recessive—A gene located on a chromosome other than the X or Y sex chromosomes and carrying a trait that is not expressed unless the second copy of the same gene inherited from the other parent is also recessive or mutated.

Carrier—Having one abnormal gene for a trait, such as albinism, and one normal gene for the trait (a heterozygote), without signs or symptoms of the disorder but the possibility of passing the abnormal gene on to offspring.

Hermansky-Pudlak syndrome (HPS)—A rare form of albinism that can include other problems, such as blood clotting, and lung and bowel disorders; there are four types of HPS caused by defects in four different genes.

Iris—The colored ring between the cornea and lens of the eye that controls the amount of light entering through the pupil.

Melanin—A pigment produced in the body that gives color to the skin, hair, and eyes.

Melanosomes—Granules that produce melanin inside specialized cells called melanocytes.

Nystagmus—Involuntary rapid eye movements.

Ocular albinism (OA)—Forms of albinism that primarily affect the eyes.

Oculocutaneous albinism (OCA)—Forms of albinism that can affect the hair, skin, and eyes; there are several inherited forms of OCA that are caused by defects in different genes.

Retina—The light-sensitive membrane at the back of the eye that includes photosensitive rod and cone cells that convert the image from the lens into electrical impulses sent to the brain by the optic nerve.

Strabismus—Crossed eyes; improper eye alignment that interferes with binocular vision.

Tyrosine (Tyr)—The amino-acid precursor of melanin.

X-linked ocular albinism (XLOA)—OA1; the most common type of ocular albinism, which primarily affects vision in males.

An ophthalmologist may perform electroretinography to detect vision problems related to albinism. A visual evoked potentials test can also be useful. Ophthalmologists may be able to identify female carriers of the gene for XLOA by reduced pigment in their retinas.

QUESTIONS TO ASK YOUR DOCTOR

- What type of albinism does my child have?
- How did my child inherit albinism?
- Who in the family should have genetic testing for albinism genes?
- What information will we get from genetic testing?
- What treatments are available for my child's eye condition?
- What types of sun protection are needed?

Treatment and management

There is no treatment for replacing melanin. Eye problems resulting from albinism can be treated but not cured. Treatments vary, depending on the specifics and severity of the disorder, with the goal of relieving symptoms. Children with albinism may need extra support from family or a counselor. Many families find support groups helpful.

People with albinism must avoid sunlight or use sunscreen with sun protection factor (SPF) of 20 or higher. They need to wear protective clothing, hats or visors, and UV-protected sunglasses when outside. They should watch carefully for any changes in birthmarks or moles that could become cancerous.

Although bifocals and other corrective lenses are helpful for some people, these may not be able to compensate for severe development defects of the retina. Surgery may improve the appearance of people with strabismus. Eye muscle surgery may help reduce involuntary eye movements associated with nystagmus. However, surgery may not significantly improve vision. Before undergoing surgery, some doctors have children wear an eye patch in an attempt to strengthen the weaker eye. Children may require special educational accommodations, such as large-print textbooks.

People with HPS and bleeding disorders should notify their doctors and dentists. They should avoid aspirin, which can further reduce blood clotting. Some physicians recommend wearing a medical alert bracelet. People with HPS should not smoke to avoid exacerbating lung disease.

Prognosis

Most people with albinism adapt readily to their condition and live healthy, productive lives. Some activities

may be limited because of the inability to tolerate sunlight. People with severe vision impairment may not be able to drive. Albinism does not directly affect lifespan. It may increase the risk of skin cancer. Furthermore, lung disease or bleeding problems can shorten the lives of people with HPS.

Since albinism is inherited, and the genes have been identified, people with a family history of albinism should consider genetic counseling and possibly testing.

Resources

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ORGANIZATIONS

- American Foundation for the Blind, 2 Penn Plaza, Suite 1102, New York, NY 10121, (212) 502-7600, (800) 232-5463 (AFB-LINE), (888) 545-8331, <http://www.afb.org>

Hermansky-Pudlak Syndrome Network, One South Road,
Oyster Bay, NY 11771-1905, (800) 789-9HPS, (516)
624-0640, info@hpsnetwork.org, http://www.hpsnetwork.org

NOAH, National Organization for Albinism and Hypopigmentation, PO Box 959, East Hampstead, NH 03826-0959,
(603) 887-2310, (800) 473-2310, (800) 648-2310,
webmaster@albinism.org, http://www.albinism.org

Melissa Knopper, PhD,
Judith Sims,
Carol Turkington
and Margaret Alic

Albright syndrome see **McCune-Albright Syndrome**

Alcoholism

Definition

Alcoholism is an alcohol use disorder characterized by chronic physical, psychological, and behavioral issues caused by the frequent and excessive use of alcoholic beverages. Intervening factors include emotional and physical dependence on alcohol; increased tolerance over time to the effects of alcohol; and withdrawal symptoms if the person stops drinking. Alcoholism is sometimes referred to as alcohol dependence. According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), 14.5 million adults ages 18 years and older in the United States had an alcohol use disorder in 2019.

Description

Alcoholism is a complex behavioral problem as well as a medical disorder. It often involves the criminal justice system as well as the fields of medicine and other helping professions. Its emergence in an individual's life is affected by a number of variables ranging from age, weight, sex, and ethnic background to a family history of alcoholism, peer group use of alcohol, occupation, religious preference, and many other categories. Moreover, persons diagnosed with alcoholism may demonstrate considerable variety in their drinking patterns, their age at the onset of the disorder, and the speed of its progression. It is very important for people who are alcoholics to accept treatment, especially in the face of a recent study that revealed the numbers of deaths from alcohol increased significantly between 1999 and 2017. In a study by Aaron M. White and colleagues, the researchers used death certificates to analyze causes of death. They listed deaths as alcohol-related if an alcohol-induced cause was either an underlying cause or one of multiple causes

of death. The researchers found that alcohol-related deaths doubled from 35,914 in 1999 to 72,558 in 2017. They also found that nearly 3% of about 2.8 million deaths in the United States were alcohol-related. About half of these deaths involved liver diseases or overdoses from alcohol and/or other drugs. The highest rates of alcohol deaths were found among men ages 45 to 74 and non-Hispanic American Indians or Alaska Natives. The greatest annual increase, however, was found among non-Hispanic white females.

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), distinguished between alcohol dependence and alcohol abuse, largely on the basis of the compulsive element in dependence that is not present in abuse. However, the newer fifth edition, DSM-5, integrates the two disorders into a single diagnosis called alcohol use disorder (AUD), with mild, moderate, and severe sub-classifications. Alcoholism is a severe alcohol use disorder. Some psychiatrists differentiate between so-called primary alcoholism, in which the patient has no other major psychiatric diagnosis, and secondary alcoholism, in which the problem drinking is the patient's preferred way of medicating symptoms of another psychiatric disorder, such as depression, schizophrenia, post-traumatic stress disorder, or one of the dissociative disorders. Experts in other branches of medicine tend to emphasize patterns of, and attitudes toward, drinking in order to distinguish between the non-problematic use of alcohol and alcohol abuse or dependence. Classification is typically based on the following five categories:

- **Social drinkers.** Individuals who use alcohol in minimal to moderate amounts to enhance meals or other social activities. They do not drink alone.
- **Situational drinkers.** These people rarely or never drink except during periods of stress. They are far more likely to drink alone than social drinkers.
- **Problem drinkers.** These individuals drink heavily, even when they are not under overwhelming stress. Their drinking causes some problems in their lives (e.g., DUI arrests), but they are capable of responding to warnings or advice from others.
- **Binge drinkers.** This type of drinker uses alcohol in an out-of-control fashion at regular intervals. The binges may be planned in advance. This pattern has long been a problem on many college campuses.
- **Alcoholic drinkers.** These are drinkers who have no control of any kind over their intake, and they find that their lives are unmanageable.

Other factors have complicated definitions of alcoholism in the United States, including the increasing tendency to combine alcohol with other drugs of abuse,



Alcohol use disorder. (Shutterstock/solar22)

sometimes called cross-addiction, and the rising rates of alcohol abuse and dependence among adolescents.

Risk factors

According to the NIAAA, the risk for developing alcoholism seems to run in families. Genetics and lifestyle behaviors are both factors. The NIAAA says that genetics is responsible for about 60% of alcohol use disorders. Another causal factor is the early use of alcohol, and the NIAAA says that among individuals ages 26 years and older, people who started drinking before age 15 are greater than five times more likely to have an alcohol use disorder in adulthood, compared to individuals who did not start drinking until age 21 or older. Some mental health conditions also increase the risk for alcohol problems, according to the NIAA, particularly depression, post-traumatic stress disorder, and attention deficit hyperactivity disorder (ADHD). In addition, individuals who suffered childhood traumas are at risk for alcoholism in adulthood. Socializing patterns, the

amount of stress in a person's life, and the availability of alcohol are all factors that may increase the risk for alcoholism. In general, more men than women are alcohol dependent. Alcohol problems are highest in the 18-to-29 age group and lowest among adults aged 65 years and older.

Demographics

The World Health Organization (WHO) estimates that in 2018, three million people worldwide died because of their harmful use of alcohol, or about 4% of all deaths globally. In addition, the WHO reported that the use of alcohol in a harmful manner was a factor in more than 200 injury and disease conditions. In the United States, a major epidemiologic study on more than 36,000 subjects by Bridget F. Grant and colleagues revealed that the 12-month prevalence of alcohol use disorder was 14%, and the lifetime prevalence was 29%. The highest prevalence was seen in white males and Native Americans, as well as those at the lowest income

levels. The NIAAA reports that most people are never treated for their alcohol issues.

Alcohol use by persons under age 21 is an important public health concern. According to the NIAAA, in 2019, 14.1 million adults ages 18 years and older (about 6% of that age group) had an alcohol use disorder. Drinking is also an issue among adolescents; for example, in 2019, 414,000 adolescents ages 12 to 17 years old (about 2% of that age group) had an alcohol use disorder. In the United States, alcohol is the most commonly used and abused drug among youth. Although drinking under the age of 21 is against the law, people ages 12 to 20 years drank nearly 9% of all the alcohol consumed in the United States in 2016, based on research by Raimee H. Eck and colleagues.

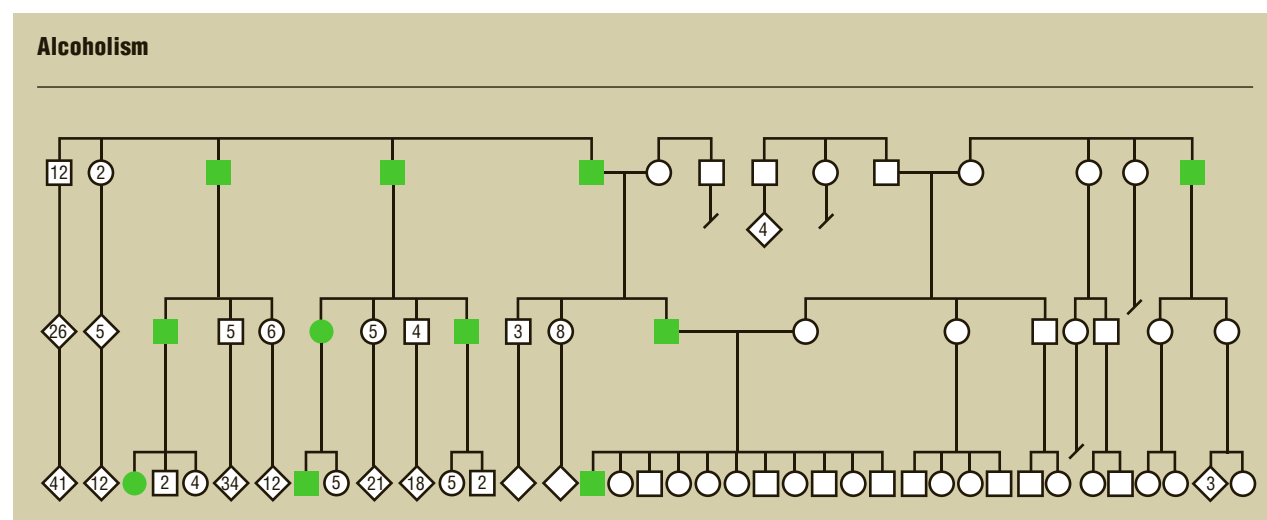
Some women are alcoholics, and many women in the United States consume alcohol. In fact, in some cases, alcohol problems are greater in women than in men. According to the Centers for Disease Control and Prevention (CDC), nearly half of all adult females in the United States reported drinking alcohol in the past 30 days. In addition, about 13% of adult women are binge drinkers, consuming five drinks per binge on four occasions each month. Nearly a third (32%) of female high-school students consumed alcohol in 2019, which was greater than the rate among male high-school students (26%). Further, binge drinking was more common among female teenagers (15%) than male teenagers (13%).

One major concern is that many women drink alcohol during pregnancy. An estimated 20% of pregnant American women had at least one drink during the first trimester of their pregnancy in the period 2015 through

2018, according to Lucinda J. England, MD and colleagues. Further, about 5% of pregnant women reported consuming alcohol in their second or third trimester of pregnancy. This research was based on information provided by more than 3,000 pregnant women ages 12 to 44. This news is disturbing, because physicians urge pregnant women to consume no alcohol during pregnancy. Alcohol consumption during pregnancy puts their babies at risk for fetal alcohol spectrum disorders (FASDs).

Studies of female alcoholics indicate that women are at higher risk than men for serious health problems related to alcoholism. Because women tend to metabolize alcohol more slowly and have a lower percentage of body water and a higher percentage of body fat than men, they develop higher blood alcohol levels than men at a given amount of alcohol per pound of body weight.

At the other end of the age distribution, alcoholism among the elderly appears to be under-recognized. One-third of older alcoholic persons develop a problem with alcohol in later life, while the other two-thirds grow older with the medical and psychosocial consequences of early-onset alcoholism. Confusion and other signs of intoxication in an elderly person are often misinterpreted as side effects of other medications or dementia. In addition, the effects of alcohol may be increased in elderly patients because of physiological changes associated with aging. The elderly are at higher risk than younger people for becoming dependent on alcohol, because their bodies do not absorb it as efficiently; for example, a 90-year-old who drinks the same amount of alcohol as a 20-year-old (of the same sex) will have a blood alcohol level 50% higher.



(Gale)

Signs and symptoms

The symptoms of alcohol intoxication often include talkativeness and a positive mood while the drinker's blood alcohol level is rising, with depression and mental impairment occurring when it is falling. Blood alcohol concentration (BAC) produces the following symptoms of central nervous system (CNS) depression at specific levels:

- 50 mg/dL: feelings of calm or mild drowsiness
- 50 to 150 mg/dL: loss of physical coordination. The legal BAC for drivers in most states is 100 mg/dL or lower.
- 150 to 200 mg/dL: loss of mental faculties
- 300 to 400 mg/dL: unconsciousness
- Over 400 mg/dL: may be fatal.

The symptoms of long-term heavy consumption of alcohol may take a variety of different forms. In spite of a long history of use for “medicinal” purposes, alcohol is increasingly recognized to be toxic to the human body. It is basically a CNS depressant that is absorbed into the bloodstream, primarily from the small intestine. Regular consumption of large amounts of alcohol can cause irreversible damage to a number of the body's organ systems, including the cardiovascular system, the digestive tract, the central nervous system, and the peripheral nervous system. Heavy drinkers are at high risk of developing stomach or duodenal ulcers, cirrhosis of the liver, and cancers of the digestive tract. Many alcoholics do not eat properly and often develop nutritional-deficiency diseases as well as organ damage.

In addition to the physical symptoms, most alcoholics have a history of psychiatric, occupational, financial, legal, or interpersonal problems. Alcohol misuse is the single most important predictor of violence between domestic partners as well as intergenerational violence within families. Alcohol is also involved in deaths caused by drunken driving. The National Highway Traffic Safety Administration (NHTSA) reported that 10,142 people died as the result of alcohol-impaired collisions in 2019. All states have passed stricter laws against alcohol-impaired driving. These laws include such provisions as immediate license suspension for the first DWI arrest and lowering the legal blood alcohol limit to 0.08 g/dL for adults and 0.02 g/dL for drivers under age 21. Penalties for repeated DWI citations include prison sentences; house arrest with electronic monitoring; license plates that identify offending drivers; automobile confiscation; and putting a special ignition interlock on the offender's car.



Studies of female alcoholics indicate that women are at higher risk than men for serious health problems related to alcoholism. (VGstockstudio/Shutterstock)

Diagnosis

The diagnosis of alcoholism is usually based on the patient's drinking history, a thorough physical examination, laboratory findings, and the results of psychodiagnostic assessment.

Examination

A physician who suspects that patients are abusing or are dependent on alcohol should give them a complete physical examination with appropriate laboratory tests, paying particular attention to liver function and the nervous system. Physical findings that suggest alcoholism include head injuries after age 18; broken bones after age 18; other evidence of blackouts, frequent accidents, or falls; puffy eyelids; a flushed face; alcohol odor on the breath; shaky hands; slurred speech or tongue tremor; rapid involuntary eye movements (nystagmus); enlargement of the liver (hepatomegaly); hypertension; insomnia; and problems with impotence (in males). Severe memory loss may point to advanced alcoholic damage to the CNS.

Tests

Several laboratory tests can be used to diagnose alcohol abuse and evaluate the presence of medical problems related to drinking. These tests include:

- Complete blood cell count (CBC). This test indicates the presence of anemia, which is common in alcoholics. In addition, the mean corpuscular volume (MCV) is usually

high in heavy drinkers. An MCV higher than 100 fL suggests alcohol abuse.

- Liver function tests. Tests for serum glutamine oxaloacetic transaminase (SGOT) and alkaline phosphatase can indicate alcohol-related injury to the liver. A high level (30 units) of gamma-glutamyltransferase (GGT) is a useful marker, because it is found in 70% of heavy drinkers.
- Blood alcohol levels.
- Carbohydrate deficient transferrin (CDT) tests. This test should not be used as a screener, but it is useful in monitoring alcohol consumption in heavy drinkers (those who consume 60 grams of alcohol per day). When CDT is present, it indicates regular daily consumption of alcohol.

The results of these tests may not be accurate if the patient is abusing or dependent on other substances.

Procedures

Since some of the physical signs and symptoms of alcoholism can be produced by other drugs or disorders, screening tests can also help to determine the existence of a drinking problem. There are several assessment instruments for alcoholism that can be either self-administered or administered by a clinician. The so-called CAGE test is a brief screener consisting of four questions:

- Have you ever felt the need to *cut down* on drinking?
- Have you ever felt *annoyed* by criticism of your drinking?
- Have you ever felt *guilty* about your drinking?
- Have you ever taken a morning *eye opener*?

One “yes” answer to the questions above should raise a suspicion of alcohol abuse; two “yes” answers are considered a positive screen.

Other brief screeners include the Alcohol Use Disorder Identification Test, or AUDIT, which also highlights some of the physical symptoms of alcohol abuse that doctors look for during a physical examination of the patient. The Michigan Alcoholism Screening Test, or MAST, is considered the diagnostic standard. It consists of 25 questions; a score of five or higher is considered to indicate alcohol dependency. A newer screener, the Substance Abuse Subtle Screening Inventory, or SASSI, was introduced in 1988. It can be given in either group or individual settings in a paper-and-pencil or computerized format. The SASSI is available in an adolescent as well as an adult version from the SASSI Institute.

Some brief screeners may be inappropriate for widespread use in some subpopulations because of ethnic and sex bias. The CAGE questionnaire has often yielded inaccurate results when administered to African American

men and Mexican American women. The AUDIT does not appear to be affected by ethnic or gender biases. Another study of the use of alcohol screening questionnaires in women found that the AUDIT was preferable to the CAGE questionnaire for both African American and Caucasian women.

Treatment and management

Because alcoholism is a complex disorder with social and occupational as well as medical implications, treatment plans usually include a mix of several different approaches. The following key issues are usually considered in determining which treatment option is appropriate:

- Severity of the problem and evidence to suggest other mental health problems (e.g., depression, suicide attempts).
- staff credentials of those treating the child or teen, and what forms of therapy (e.g., family, group, medications) are to be used
- Nature of family involvement.
- How education is to be continued during treatment.
- If an in-patient program is necessary, what length it should be.
- What aftercare is to be provided following discharge.
- What portion of treatment is to be covered by health insurance, and what needs to be paid out of pocket.

Traditional

Most alcoholics are treated with a variety of psychosocial approaches, including regular attendance at Alcoholics Anonymous (AA) meetings, group therapy, marital or family therapy, social skills training, relapse prevention, and stress management techniques. Insight-oriented individual psychotherapy by itself is ineffective with the majority of alcoholics. Some individuals need to be hospitalized to detoxify from alcohol in a safe manner

The most effective psychosocial treatments of alcohol dependence incorporate a cognitive-behavioral approach. Relapse prevention utilizes cognitive-behavioral approaches to identifying high-risk situations for each patient and restructuring his or her perceptions of the effects of alcohol as well as of the relapse process. Network therapy, which combines individual cognitive-behavioral psychotherapy with the involvement of the patient’s family and peers as a group support network, is a newer approach to alcohol dependence.

Drugs

Most drugs that are used to treat alcoholism fall into one of two groups: those that restrain the desire to drink by producing painful physical symptoms if the patient does drink, and those that appear to reduce the craving for

alcohol directly. Several medications in the second category were originally developed to treat addiction to opioid substances (e.g., heroin and morphine). Although medications have been proven effective, the NIAAA reports that only 4% of individuals with alcohol use disorder took one of these medications in 2019.

ALCOHOL-SENSITIZING MEDICATIONS. The most commonly used alcohol-sensitizing agent is disulfiram (Antabuse), which has been used since the 1950s to deter alcoholics from drinking by the threat of a very unpleasant physical reaction if they do consume alcohol. The severity of the disulfiram/ethanol reaction, or DER, depends on the amount of alcohol and disulfiram in the blood. The symptoms of the reaction include facial flushing, rapid heartbeat, palpitations, difficult breathing, lowered blood pressure, headaches, nausea, and vomiting.

A DER results when the drinker consumes alcohol, because disulfiram inhibits the functioning of an enzyme called aldehyde dehydrogenase. This enzyme is needed to convert acetaldehyde, which is produced when the body begins to oxidize the alcohol. Without the aldehyde dehydrogenase, the patient's blood level of acetaldehyde rises, causing the symptoms associated with DER.

Another alcohol-sensitizing agent is calcium carbimide, which is marketed under the brand name Temposil. Calcium carbimide produces physiological reactions with alcohol similar to those produced by disulfiram, but the onset of action is far more rapid, and the duration of action is much shorter.

ANTI-CRAVING MEDICATIONS. Another medication approved for the treatment of alcoholism is naltrexone, which appears to reduce the craving for alcohol. An injectable, long-acting form of naltrexone (Vivitrol) is also available.

Acamprosate is another anti-craving drug used to treat alcoholism in the United States. Acamprosate appears to reduce the frequency of drinking, but its effects on enhancing abstinence from alcohol are no greater than those of naltrexone. This drug does not appear to enhance the effectiveness of naltrexone if the drugs are given in combination.

Other medications are available to treat the symptoms of alcohol withdrawal, such as shakiness, nausea, and sweating that occur after someone with alcohol dependence stops drinking.

Alternative

Many clinical trials for the treatment or prevention of alcoholism are currently sponsored by the National Institutes of Health (NIH) and other agencies. In 2021, NIH reported 651 studies on alcohol use disorders.

QUESTIONS TO ASK YOUR DOCTOR

- Can alcoholism be treated without medications?
- How can I best understand the factors that led to my alcoholism?
- Can I recover?
- Are lifestyle changes required?
- Are there associated conditions that also require treatment?

A few examples include:

- The role of neuroactive steroids in stress, alcohol craving, and alcohol use in alcohol use disorders. (NCT03872128)
- Selective attention in alcohol use disorder. (NCT03816527)
- Pregabalin trial for the treatment of alcohol use disorder. (NCT04322305)
- The effect of rTMS to the prefrontal cortex in alcohol use disorder. (NCT03809286)

Clinical trial information is constantly updated by NIH, and the most recent information on alcoholism trials can be found at: <http://clinicaltrials.gov/ct2/results?term=alcoholism>.

Prognosis

The prognosis for recovery from alcoholism varies widely. The usual course of the disorder is one of episodes of intoxication beginning in adolescence or young adulthood, with full-blown dependence by the mid-20s to mid-30s. The most common pattern is one of periodic attempts at abstinence, alternating with relapses into uncontrolled drinking. On the other hand, it is thought that as many as 20% of persons diagnosed as alcohol-dependent achieve long-term sobriety even without medical treatment. It is difficult to compare the outcomes of the various treatment approaches to alcoholism, in part because their definitions of “success” vary. Some researchers count only total abstinence from alcohol as a successful outcome, while others regard curtailed drinking and better social adjustment as indicators of success. The role of genetic factors in the prognosis is still disputed. Available evidence suggests that such factors as the presence of a supportive partner or close friend in the alcoholic's life, or religious commitment, can outweigh genetic vulnerability to the disorder.

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ORGANIZATIONS

Al-Anon/Alateen, 1600 Corporate Landing Parkway, Virginia Beach, VA 23454-5617, (757) 563-1600, (757) 563-1655, wso@al-anon.org, <http://www.al-anon.alateen.org>

Alcoholics Anonymous World Services, Inc, 475 Riverside Drive at West 120th Street, New York, NY 10115, (212) 870-3400, <http://www.aa.org>

National Council on Alcoholism and Drug Dependence (NCADD), 217 Broadway, Suite 712, New York, NY 10017, (212) 269-7797, (212) 269-7510, national@ncadd.org, <http://ncadd.org>

National Institute on Alcohol Abuse and Alcoholism (NIAAA), 5635 Fishers Lane, Room 2015, Bethesda, MD 20892-9304, (301) 443-2860, (888)-696-4222 (888-MY-NIAAA), <http://www.niaaa.nih.gov>

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Revised by Christine Adamec

Aldrich syndrome see **Wiskott-Aldrich Syndrome**

Alexander disease

Definition

Alexander disease is a rare genetic disease that may strike infants, children, or adults. Individuals with this disorder have abnormal nerve cells, specifically those known as glial cells. Depending on the severity of the disorder, individuals may experience progressive intellectual disability, seizures, and speech problems, among other symptoms. Additionally, they may have only very mild symptoms or none at all. Alexander disease is usually fatal.

Alternate names associated with the disease include dysmyelogenic leukodystrophy, dysmyelogenic leukodystrophy-megalobare, or dysmyelogenic leukodystrophy with megalobarencephaly; fibrinoid degeneration of astrocytes or fibrinoid leukodystrophy; hyaline panneuropathy, megalencephaly with hyaline inclusion, or megalencephaly with hyaline panneuropathy; or leukodystrophy with Rosenthal fibers.

Description

Alexander disease results from a genetic defect that affects the nervous system. This defect usually develops as a new mutation in the GFAP (glial fibrillary acidic protein) gene. Although in rare cases, individuals can inherit it when one of their parents also has the disease. Mutations affect the GFAP gene that carries the blueprint for making glial fibrillary acidic protein. This protein provides support and strength to certain cells, known as astroglial cells or astrocytes, that are important to the brain and the spinal cord.

The full range of astrocyte function is unknown, but in general, they form a structural and functional interface between nerve cells and other cells so that these cells can communicate. They also monitor the spinal cord and brain for damage due to injury or illness. Astrocytes may also participate in the function of cells, known as oligodendrocytes, which play a role in making and

Symptoms of Alexander disease

In infants	In children	In adults
Speech problems Feeding difficulties Delayed development Difficulty walking Progressively increasing muscle spasms Enlarged brain (megalencephaly) Water on the brain, often accompanied by an enlarged head Seizures, sometimes severe Mental retardation that becomes severe over time	Speech problems Feeding difficulties often due to problems swallowing Impaired coordination Difficulty walking Muscle spasms, particularly affecting the legs Weakness Inability to cough Abnormal curvature of the spine (kyphoscoliosis) Declining mental abilities, in some cases	Speech problems Difficulty swallowing Impaired coordination Sleep problems

Symptoms of Alexander disease (Gale)

maintaining the protein myelin. Myelin covers, protects, and insulates nerve fibers. In addition, astrocytes may also help to maintain the blood-brain barrier, a mechanism that acts as a sentry for the brain and only allows certain substances in the circulating blood to pass into the brain.

When individuals have the genetic mutation in the *GFAP* gene associated with Alexander disease, glial fibrillary acidic protein does not work as it should. This can, in turn, have an impact on astrocyte function, which can then affect myelin. Without enough properly working myelin, problems in the nervous system develop, and numerous symptoms can result.

Different types of Alexander disease exist and are based on the age of symptom onset. They are:

- Neonatal Alexander disease affects newborns and is characterized by seizures, hydrocephalus (water on the brain), and severe motor and intellectual disability. Death usually occurs within two years.
- Infantile Alexander disease is characterized by symptoms that appear in the first two years of life. It is the most common form of this disease. Initial symptoms include a progressive loss of developmental milestones, enlarged head with a large forehead, seizures and other neurological signs. The survival of children with this form of Alexander disease ranges from weeks to several years of age.
- Juvenile Alexander disease presents the first symptoms between the ages of 4 and 10 years with the average age of onset at 9.5 years. Symptoms can include ataxia, a gradual loss of intellectual function, seizures and occasionally, but not always, an enlarged head. The survival of individuals with this form of Alexander disease generally ranges from the teens to the twenty and thirties.
- Adult-onset Alexander disease has symptoms that may emerge in the late teens or later, but sometimes not

appearing until the person reaches an advanced age. The symptoms of the adult form are the most variable, and there have been some individuals described that are asymptomatic despite having characteristic findings on MRI or by DNA testing.

Genetic profile

Alexander disease is a rare condition that is caused by a mutation (pathogenic variant) in a gene, specifically the *GFAP* gene. It can be passed down from parent to child in autosomal dominant manner, which means that individuals can inherit it if one of their parents has the mutated gene. In most cases, however, the mutation (pathogenic variant) is a new one that develops in affected individuals and is not inherited from a parent. Symptoms range from mild (sometimes unnoticeable) to severe.

Located on chromosome 17, the *GFAP* gene carries the blueprint for making glial fibrillary acidic protein. Scientists have identified several dozen mutations (pathogenic variants) of this gene that lead to Alexander disease. The mutations often result from the addition or the deletion of some of the protein's normal complement of amino acids (the building blocks of proteins). When too many or too few amino acids are present, the protein's structure changes. Frequently in individuals with Alexander disease, the following sequence occurs:

- Altered glial fibrillary acidic protein builds up in the astrocytes.
- The accumulation of glial fibrillary acidic protein causes unusual fibers to form. These fibers are known as Rosenthal fibers and are not believed to occur in healthy individuals.
- Rosenthal fibers hinder the function of the astrocytes.
- The impaired astrocytes cause poor maintenance of myelin.

- The myelin deficiency is the root of Alexander disease symptoms.

Because Alexander disease can be an autosomal dominant disorder, adults with the mutated gene has a 50% chance of passing it to each child they may have. As noted, however, affected individuals usually develop new mutations in the gene. Therefore, most individuals who develop the disease have no family history of it.

Demographics

Alexander disease does not appear to occur more frequently in any ethnic group. In 2015, approximately 550 individuals had been diagnosed with this disease, but its overall prevalence is unknown.

Signs and symptoms

Individuals with Alexander disease may experience their first symptoms as infants, juveniles, or adults. Symptoms for the infantile form of the disease often include at least several of the following:

- Intellectual disability that becomes severe over time
- Progressively worse muscle spasms that often involve legs and arms (spastic quadriparesis)
- Feeding difficulties
- Delayed development
- Seizures, sometimes severe
- Enlarged brain (megalocephaly)
- Hydrocephalus or water on the brain, often accompanied by an enlarged head
- Speech problems
- Difficulty in walking, sometimes unable to walk

Symptoms for the juvenile form of the disease include the following:

- Speech problems
- Feeding difficulties often due to problems swallowing
- Weakness
- Inability to cough
- Difficulty in walking
- Impaired coordination
- Muscle spasms, particularly affecting the legs
- Abnormal curvature of the spine (kyphoscoliosis)
- Declining mental abilities in some cases

Symptoms for the adult-onset form of the disease may be much like those for the juvenile form, although they are typically milder and sometimes nonexistent. Generally, however, symptoms include the following:

- Speech problems

KEY TERMS

Astrocytes—Glial cells that occur in the brain and spinal cord.

Blood-brain barrier—A mechanism that acts as a sentry for the brain and only allows certain substances in the circulating blood to pass into the brain.

Glial cells—Supportive cells for nerve cells in the brain and spinal cord.

Hydrocephalus—Also known as “water on the brain,” the abnormal accumulation of cerebrospinal fluid in brain cavities.

Kyphoscoliosis—Abnormal curvature of the spine.

Megalocephaly—Enlarged brain.

Myelin—A fatty substance that covers, protects, and insulates nerve fibers.

Oligodendrocyte—A cell in the central nervous system that insulates the parts of nerve cells called axons.

Rosenthal fibers—Abnormal and irregularly shaped structures that form in astrocytes.

Spastic quadriparesis—Muscle spasms involve both the legs and the arms.

- Difficulty swallowing
- Impaired coordination
- Sleep problems

Diagnosis

Diagnosis is based on the constellation of symptoms in the affected individual. MRI findings and molecular genetic testing of the *GFAP* gene are used to confirm the diagnosis. MRI has proven to be a useful tool for diagnosing AD. The results often show high signal intensity of white matter in the frontal area and basal ganglia.

DNA sequencing of the *GFAP* gene is the most productive form of DNA testing for GFAP mutations and detects greater than 98% of mutations (pathogenic variants) in the *GFAP* gene. DNA sequencing is the molecular determination of the precise sequence of nucleotides in a sample of DNA. By looking at the coding regions (exons) of the *GFAP* gene and the junctions between these coding regions, mutations or changes in the sequence of nucleotides can be found. If no mutations are detected by sequencing the *GFAP* gene, then deletion/duplication testing which looks for copy number

QUESTIONS TO ASK YOUR DOCTOR

- Given that my child has been diagnosed with Alexander disease, is it possible that I, too, have the disease?
- Is there anything I can do to slow the decline in mental abilities in my child?
- I have been diagnosed with adult-onset Alexander disease. Based on the symptoms I have had, what can I expect in the coming years?
- Are any experimental treatments being researched to help promote myelin formation?

variants is performed. As of 2015, no deletions or duplications had been found in the *GFAP* gene.

If DNA sequencing does not detect a mutation (pathogenic variant) in a person who clinically appears to have Alexander disease, then other DNA testing techniques may be used. Multigene panels testing identifies groups of genes, *GFAP* gene and other genes, that cause diseases that have symptoms similar to Alexander disease.

Genomic testing with whole exome sequencing (WES) and whole genome sequencing (WGS) may also be performed. WES and WGS are performed by sequencing an entire genome, which is an individual's complete set of DNA, composed of approximately 22,000 genes. Whole exome sequencing is the sequencing of all of the coding portions of an individual's genome (known as the exome). Whole genome sequencing (WGS) is the sequencing of an individual's entire genome in both coding and non-coding regions. Both techniques are expensive and results can be difficult to interpret.

Procedures

The doctor may order an MRI (magnetic resonance imaging) or CT (computed tomography) scan to look for myelin, brainstem, or other abnormalities.

Treatment and management

No cure exists for Alexander disease, although doctors may be able to treat some of the symptoms.

Traditional

Treatments are available for some of the symptoms of this disease. For instance, individuals with feeding problems may require a nasogastric tube (feeding tube) in order to get the nutrition they need. For patients with

hydrocephalus, the doctor may recommend surgery to alleviate the fluid accumulation on the brain. Anti-epileptic drugs may be necessary to control seizure activity. Antibiotics are used to treat co-existing infections.

Individuals with Alexander disease should be assessed for learning disabilities and cognitive issues. Physical and occupational therapy may also be of value depending on their symptoms. In addition, they should have regular visits with a multidisciplinary team to assess and monitor symptoms development.

Drugs

The doctor may prescribe certain drugs to treat specific symptoms of this disease. These will vary from one patient to another.

Prognosis

Regardless of the form of the disease, symptoms typically progressively worsen as time goes by. In the infantile forms particularly, disease progression may be rapid, and affected individuals may die within a few years of the onset of the first symptoms.

The juvenile form of the disease usually progresses more slowly than the infantile form. While some patients with juvenile Alexander disease live into adulthood, many die young, often between 15 months and 12 years of the onset of symptoms.

Symptoms of the adult-onset form of the disease are generally milder than other forms of the disease, although this is not always the case. In some instances, the symptoms may be so mild as to be unnoticeable.

Prevention

There is no way to prevent Alexander disease.

Adults who have the disease should consider undergoing genetic counseling before deciding to have a child so that they fully understand the risks. Similarly, siblings of an individual with Alexander disease may want to consult a genetic counselor for family planning purposes. Pre-conception, prenatal, or preimplantation genetic diagnosis may be helpful in certain cases.

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ORGANIZATIONS

The Arc of the United States, 1825 K St. NW, Suite 100, Washington, DC 20006, (202) 534-3700, (800) 433-5255, info@the-arc.org, <http://www.thearc.org>

United Leukodystrophy Foundation, 224 N. Second St., Suite 2, DeKalb, IL 60115, (800) 728-5483, office@ulf.org, <http://www.ulf.org/index.html>

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Alkaptonuria

Definition

Alkaptonuria is a rare, inherited disorder characterized by urine that turns dark when exposed to air, dark pigmentation of the cartilage and other tissues, and arthritis.

Description

Alkaptonuria (AKU) (sometimes spelled alcaptonuria) is a disorder in which a substance called homogentisic acid (HGA) accumulates in cells and connective tissues throughout the body. Large amounts of HGA also are excreted in the urine. In a process known as ochronosis, deposits of HGA form dark pigments in the skin, joints, and other tissues of the body. Over the long term, ochronosis leads to ochronotic arthritis, which is a painful inflammation and stiffening of the joints. AKU is also known as homogentisic acid oxidase deficiency, ochronosis, alkaptonuria ochronosis, or ochronotic arthritis.

History

The black urine that characterizes AKU has been recognized throughout history. It sometimes was considered to be a bad omen. The dark pigmentation of ochronosis has been identified in an Egyptian mummy from 1500 BCE.

AKU was one of the first inherited disorders to be identified as a deficiency in a single enzyme in one pathway of the body's metabolism. In 1902, Sir Archibald Garrod, after consultation with the famous geneticist William Bateson, proposed that the inheritance of AKU could best be described by Gregor Mendel's theory of the inheritance of recessive characteristics. These are inherited traits expressed in some of the offspring of parents who both carry the trait. The parents may or may not express the trait. In 1908, Garrod coined the term "inborn error of metabolism" to describe AKU and three other metabolic disorders. Furthermore, he suggested that AKU was due to a deficiency in a specific enzyme, a protein that catalyzes one step of a metabolic pathway.

Homogentisic acid

During normal metabolism, the 20 common amino acids, that are the building blocks of enzymes and other proteins, are broken down into simpler substances. This process provides energy for the body. The amino acids phenylalanine and tyrosine are converted to simpler substances in a series of eight steps. Each step in this pathway occurs through the action of a different enzyme. The first step in the pathway converts phenylalanine to tyrosine. The inherited disorder known as phenylketonuria results from a deficiency in the enzyme that carries out this first step.

AKU results from a deficiency in an enzyme called homogentisate 1,2-dioxygenase (HGD). This enzyme also is called homogentisic acid oxidase. It is responsible for the fourth step in the breakdown of phenylalanine and tyrosine, the conversion of HGA to 4-maleylacetoacetic acid. When there is a deficiency in active HGD, as in AKU, HGA cannot be broken down further. It accumulates in cells and tissues throughout the body, and large amounts of HGA are excreted in the urine.

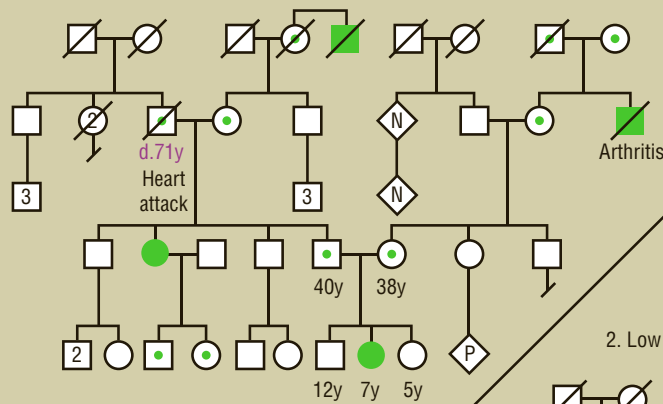
Oxygen causes HGA molecules to combine with each other to form a very large molecule called a polymer. This polymer is a dark pigment similar to melanin, the pigment responsible for skin color. This pigment is formed in the tissues of the body, as well as in urine exposed to the oxygen in air. Oxygen can also convert HGA into a toxic substance called benzoquinone acetic acid.

HGA is excreted very quickly. In general, levels of HGA are kept quite low in individuals with AKU.

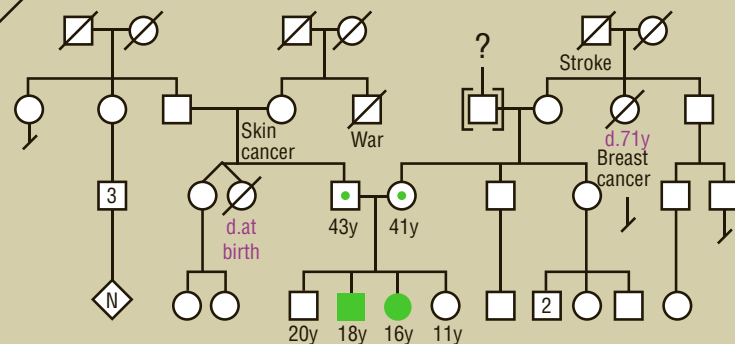
Alkaptonuria

Autosomal Recessive

1. High carrier frequency in Czechoslovakia



2. Low carrier frequency in other countries



Alkaptonuria: pedigree analysis chart (Gale)

Nevertheless, over time, large quantities of HGA, either as individual molecules or as a polymer, are deposited in the cartilage (the flexible tissue of the joints and other bony structures) and in other connective tissues of the body.

Granules of HGA pigment collect around collagen. This is the protein that makes up the fibers of connective tissues. Collagen is the most abundant protein in the body. It is a major structural component of cartilage, bone, tendons, ligaments, and blood vessels. Collagen also forms an important structural layer beneath the skin, and it holds together the cells of various tissues. The accumulation of HGA in connective tissues interferes with the body's ability to make new collagen. As a result, collagen fibers throughout the body are weakened. In particular, HGA weakens the collagen fibers in the cartilage of the joints.

Ochronosis

Initially, an ochre or yellowish-colored HGA pigment is deposited in the tissues of individuals with AKU. Over a period of years, the cartilage, bones, and skin begin to turn

a slate-blue or blue-black color. This pigmentation, or ochronosis, of the tissues eventually leads to a serious form of arthritis. Furthermore, as the HGA polymer accumulates, inflammation occurs. This causes calcium to be deposited in the joints in a process called calcification.

Genetic profile

AKU is an autosomal recessive disorder. It is autosomal because the gene encoding the HGD enzyme is located on chromosome 3, rather than on either of the X or Y sex chromosomes. AKU is a recessive trait because it only occurs when an individual has two copies of the defective gene, one inherited from each parent. The two defective HGD genes do not need to carry the same mutations. If the two mutations are identical, the individual is a homozygote. If the two mutations are different, the affected individual is called a compound heterozygote.

In individuals with a single defective *HGD* gene, at least 50% of the HGD enzyme has normal activity. These individuals have no symptoms of AKU. However, they are carriers of AKU and can pass the gene on to their offspring.

All of the offspring of two parents with AKU will inherit the disorder. All of the offspring of one parent with AKU and one parent with a single defective *HGD* gene will inherit at least one defective *HGD* gene. These offspring have a 50% chance of inheriting two defective genes and developing AKU. The offspring of one parent with AKU and one parent with normal *HGD* genes will inherit a defective gene from the affected parent, but will not develop AKU. The offspring of parents who both carry one defective *HGD* gene have a 50% chance of inheriting one defective *HGD* gene. They have an additional 25% chance of inheriting two such genes and developing AKU. Finally, the children of one parent with a single defective *HGD* gene and one parent with normal *HGD* genes have a 50% chance of inheriting the defective gene, but will not develop AKU.

A large number of different mutations have been identified in the *HGD* gene. These changes reduce or destroy the activity of the HGD enzyme. Mutational hot spots have also been identified in the gene. These are regions of the gene in which mutations are particularly likely to occur.

Demographics

As a recessive disorder, AKU requires two copies of the defective gene, one inherited from each parent. Thus, AKU is much more common in the offspring of couples who are related to each other, such as first or second cousins. As an autosomal disorder, AKU occurs equally among males and females. However, in general, the symptoms of arthritis appear at an earlier age in males and tend to be more severe than in females. The reason for this difference is not known.

AKU occurs with equal frequency among various races; however, the frequency varies substantially among different populations. It is most common in geographically isolated populations. The worldwide prevalence of AKU is estimated at between 1 in 100,000 and 1 in 250,000 individuals. However, some estimates are as low as 1 in 1,000,000 individuals and, in the United States, AKU frequency is estimated to be only 1 in 4,000,000.

AKU occurs with particularly high frequency in the Dominican Republic, Slovakia, and the Czech Republic. The frequency has been reported to be as high as 1 in 19,000 live births in Slovakia. The frequency of AKU is particularly low in Finland. Certain mutations occur only in *HGD* genes from Slovakia. Two specific mutations occur in 50% of all Slovaks with AKU. Other mutations in *HGD* appear to be unique to the Finnish population.

Signs and symptoms

Early symptoms

Often, the first sign of AKU is the dark staining of an infant's diapers from the HGA in the urine. However, a significant number of AKU-affected individuals do not have blackened urine, particularly if their urine is acidic. Other than darkened urine, AKU generally has no symptoms throughout childhood and early adulthood. Nevertheless, pigment is being deposited in the tissues throughout the early years. Occasionally, black ear wax and pigmentation under the arms may develop before the age of ten.

Ochronosis

Ochronosis, the pigmentation of the cartilage, usually does not become apparent until the fourth decade of life. Small rings or patches of slate-blue, gray, or black discoloration of the white, outer membranes of the eyeballs are one of the first visible symptoms. This usually begins when affected individuals are in their 30s. Thickening and discoloration of the cartilage of the ear usually begins in the following decade. This is indicative of the widespread staining of cartilage and other tissues. The ear cartilage may become stiff, irregularly shaped, and calcified (hardened with deposits of calcium).

Discoloration of the skin is due to the depositing of ochronotic pigment granules in the inner layer of the skin and around the sweat glands. The outer ear and nose may darken with a bluish tint. Pigmentation also may be visible on the eyelids, forehead, and armpits. Where the skin is exposed to the sun, and in the regions of the sweat glands, the skin may become speckled with blue-black discoloration. Sweat may stain clothes brown. Fingernails may become bluish.

The ochronotic effects of AKU on the cartilage and tendons are most visible on parts of the body where the connective tissues are closest to the skin. Pigmentation may be visible in the genital regions, the larynx (voice box), and the middle ear. Dark-stained tendons can be seen when the hand is made into a fist.

Arthritis

The symptoms of ochronotic arthritis are similar to those of other types of arthritis. However, the large, weight-bearing joints usually are the most affected in ochronotic arthritis. These include the joints of the hips, knees, and shoulders, and between the vertebrae of the spine. The joints become stiff and difficult to move. This arthritis develops at an unusually early age. In unaffected individuals, similar arthritis usually does not develop before age 55. Men with AKU develop arthritis in their

30s and 40s. Women with AKU usually develop arthritis in their 50s.

AKU can lead to osteoarthritis, a degenerative joint disease, and ochronotic arthropathy, which is characterized by the swelling and enlargement of the bones. Ankylosis, the adhesion of bones in the joints, also may occur. The pigment deposits may cause the cartilage to become brittle and susceptible to fragmenting. Individuals with AKU may be at risk for bone fractures.

Calcium deposits can lead to painful attacks similar to those of gout. This calcification may occur in the ear cartilage and in the lumbar disks of the lower back. The disks between vertebrae may become narrowed and eventually may collapse.

Organ damage

The coronary artery of the heart can become diseased as a result of AKU. The aortic valve of the heart may harden and narrow from calcification. Similar problems may develop with the mitral or left atrioventricular valve of the heart (mitral valvulitis). Deposits of pigment can lead to the formation of hard spots of cholesterol and fat (atherosclerotic plaques) in the arteries. This can put a person at risk for a heart attack.

Complications from the deficiency of the HGD enzyme arise primarily in the kidneys and the liver. HGD normally is most active in the kidneys, liver, small intestine, colon, and prostate. The calcification of the genital and urinary tract may lead to blockages in as many as 60% of individuals with ochronosis. Kidney stones and other kidney diseases may develop. Stones in the urine may occur in middle to late adulthood. Increasingly though, this condition is seen in children with AKU under the age of 15 and even as young as two. In men, pigment deposits may lead to stones in the prostate.

The teeth, the brain and spinal cord, and the endocrine system that produces hormones also may be affected by ochronosis. Breathing may become restricted due to the effects of ochronosis on the joints where the ribs attach to the spine. Deposits of pigment on the ear bones and on the membrane of the inner ear may lead to tinnitus, or ringing of the ears, and hearing problems.

Diagnosis

Visual diagnosis

AKU is often detected in early childhood because of the characteristic dark-staining of the urine. In adults, diagnosis usually is made on the basis of joint pain and skin discoloration. Most individuals with AKU

KEY TERMS

Alkaline—Having a basic pH; not acidic.

Amino acid—Organic compounds that form the building blocks of protein. There are 20 types of amino acids (eight are “essential amino acids” which the body cannot make and must therefore be obtained from food).

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Benzoquinone acetic acid—Toxic compound that is formed when oxygen reacts with homogentisic acid.

Calcification—A process in which tissue becomes hardened due to calcium deposits.

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Compound heterozygote—Having two different mutated versions of a gene.

Homogentisate 1,2-dioxygenase (HGD)—Homogentisic acid oxidase, the fourth enzyme in the metabolic pathway for the breakdown of phenylalanine.

Homogentisic acid (HGA)—2,5-Dihydroxyphenylacetic acid, the third intermediate in the metabolic pathway for the breakdown of phenylalanine.

Homozygote—Having two identical copies of a gene or chromosome.

Melanin—Pigments normally produced by the body that give color to the skin and hair.

Mendel, Gregor—Austrian monk who discovered the basic principles of heredity.

Ochronosis—A condition marked by pigment deposits in cartilage, ligaments, and tendons.

Phenylalanine—An essential amino acid that must be obtained from food since the human body cannot manufacture it.

Polymer—A very large molecule, formed from many smaller, identical molecules.

Tyrosine—An aromatic amino acid that is made from phenylalanine.

have pigment visible in the whites of their eyes by their early 40s.

A family history of AKU helps with the diagnosis. Since many individuals with AKU have no symptoms, siblings of affected individuals should be tested for the disorder.

Identification of HGA

An individual with AKU may excrete as much as 4–8 g of HGA per day in the urine. There are several simple methods to test for HGA in the urine: the addition of sodium hydroxide (an alkali) to the urine will turn it dark; urine with HGA turns black when reacted with iron chloride; and alkaline urine containing HGA blackens photographic paper. In the laboratory, HGA can be identified in the urine using a technique called gas chromatography-mass spectroscopy. This technique separates and identifies the components of a mixture.

There are a number of methods for identifying HGA in the blood and tissues. These include procedures for separating HGA from other components of the blood and instruments that can detect the characteristic color of HGA. With AKU, the concentration of HGA in the blood is approximately 40 micromolar, or 40 micromoles of per liter.

Microscopic examination

With AKU, there usually is visible black staining of cartilage in various body regions, particularly the larynx, trachea (windpipe), and cartilage junctions. Heavy deposits of pigment also occur in the bronchi (the air passages to the lungs). Pigment on the inside and outside of the cells of these tissues can be seen with a microscope.

A skin biopsy, the removal of a small piece of skin, may be used to obtain tissue for examination. The tissue is stained with dyes to reveal the yellowish-brown pigment deposits on the outside of skin cells. Pigment deposits also occur in cells of the endothelium (the thin layer of cells that line blood vessels and other tissues), in the sweat glands, and in the membranes below the skin. These pigments will not fade, even after three days in a solution of bleach.

Skeletal x-rays

X-ray examination is used to detect calcification of the joints. Since many individuals with AKU do not have dark-staining urine, x-ray evidence of osteoarthritis may indicate a need to test for the presence of HGA in the urine. However, osteoarthritis usually affects the smaller joints; whereas ochronosis most often affects the large joints of the hips and shoulders. Spinal x-rays may show dense calcification, degeneration, and fusion of the disks of the vertebrae, particularly in the lumbar region of the lower back. Chest x-rays are used to assess damage to the valves of the heart.

Other procedures

Physicians may order computerized tomography (CT) scans of the brain and chest or magnetic resonance

imaging (MRI) of affected joints. An electrocardiogram (ECG or EKG) may reveal signs of heart complications resulting from AKU. Kidney problems may be diagnosed by ultrasound, the use of sound waves to obtain images of an organ. Lung function tests and hearing tests may be performed to assess additional complications.

Acquired ochronosis

In addition to being a complication of AKU, ochronosis can be acquired. In the past, ochronosis developed from the repeated use of carbolic acid dressings for treating chronic skin ulcers. The prolonged use of the drug quinacrine (atabrine) can cause ochronosis, with pigmentation occurring in many of the same sites as with AKU. Ochronosis can also result from the use of bleaching creams containing hydroquinone. Certain other substances, including phenol, trinitrophenol, quinines, and benzene, can cause ochronosis. However, these forms of ochronosis do not lead to joint disease and, unlike ochronosis from AKU, are reversible.

Treatment and management

The binding of HGA to collagen fibers is irreversible. Treatment of AKU is directed at reducing the deposition of pigment and thereby minimizing arthritis and heart problems in later life.

Vitamin C

Often, high doses (about 1 gm per day) of ascorbic acid (vitamin C) are administered to older children and adults with AKU. Ascorbic acid appears to slow the formation of the HGA polymer and decrease the binding of the polymer to connective tissues. Vitamin C reduces the amount of toxic benzoquinone acetic acid in the urine. However, the amount of HGA in the urine does not decrease. Furthermore, vitamin C does not appear to interrupt the progress of the disease.

Dietary restrictions

Sometimes individuals with AKU are placed on low-protein diets. This limits the intake of phenylalanine and tyrosine from proteins. If the body has lower amounts of phenylalanine and tyrosine to break down, less HGA will be formed. However, both of these amino acids are necessary for making proteins in the body. Furthermore, phenylalanine is an essential amino acid that must be obtained from food, since the human body cannot produce it. Adult males require approximately 2 gm per day of phenylalanine. Phenylalanine also is present in some artificial sweeteners.

Restricting protein intake to no more than the daily protein requirement may be beneficial for children with

QUESTIONS TO ASK YOUR DOCTOR

- What are possible side effects of long-term vitamin C therapy?
- Can you provide a low protein diet regime?
- How do the benefits of long-term use of painkillers compare with the risks?
- What is the expected outcome of joint replacement surgery?

AKU. Such diets appear to substantially reduce the amount of benzoquinone acetic acid in the urine. In children under the age of 12, low-protein diets significantly reduce the amount of HGA in the urine, as well. However, these diets seem to have little effect on older children and young adults with AKU, and low-protein diets are difficult to maintain. When low-protein diets are prescribed, the levels of amino acids in the blood must be monitored, to assure that there is no deficiency in phenylalanine.

Ochronosis

Most treatment of AKU is directed at the diseased joints. The treatment for ochronosis is the same as for other forms of degenerative arthritis. Treatments include painkillers, physical therapy, rehabilitation, orthopedic supports, and rest. Chiropractic manipulations and exercise regimens also are utilized.

Treatment of ochronotic arthritis eventually may require hip and/or knee joint replacements with artificial materials. In older individuals, fusion of the lumbar discs of the lower spine may be necessary. Aortic valve replacement may be necessary to treat heart disease.

Future drug treatment

The National Institutes of Health are undertaking clinical research studies to better understand the clinical, biochemical, and molecular aspects of AKU. These studies are in preparation for clinical trials of a new drug, nitisinone, to treat AKU. A 2005 study showed that nitisinone was effective in reducing HGA levels in individuals with AKU. Other studies are being conducted.

Prognosis

There is no cure for AKU. Essentially all individuals with AKU eventually experience arthritic symptoms, particularly arthritis of the hips, knees, and spine. The bone and joint disease may become debilitating by the sixth to eighth decades of life. Furthermore, cardiovascular

involvement and ochronotic skin abnormalities are to be expected with AKU.

Despite these difficulties, individuals with AKU have normal life expectancies. Although there is an increased risk of heart attack in later life, most individuals with AKU die of causes unrelated to the disorder.

Resources

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WEBSITES

"Alkaptonuria." MedlinePlus. August 18, 2020. <https://medlineplus.gov/genetics/condition/alkaptonuria> (accessed May 21, 2021).

ORGANIZATIONS

Alkaptonuria Society (AKU), 66 Devonshire Rd., Cambridge, UK CB1 2BL, +44 (0) 1223 322897, <http://www.akusociety.org>

National Heart, Lung, and Blood Institute, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbiinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov>

National Institute of Child Health and Human Development (NICHD), Patient Recruitment and Public Liaison Office, Building 61, 10 Cloister Court, Bethesda, MD 20892-4754, (800) 411-1222, prpl@mail.cc.nih.gov, <https://www.nichd.nih.gov/Pages/index.aspx>

Margaret Alic, PhD

Alpha thalassemia

Definition

Thalassemia describes a group of genetic blood disorders characterized by absent or reduced production of hemoglobin, the oxygen-carrying protein inside the red blood cells. There are two basic groups of thalassemia disorders: alpha thalassemias and beta thalassemias. These conditions cause varying degrees of anemia, which can range from mild to life-threatening.

Description

Normal adult hemoglobin consists of four protein chains: two alpha and two beta globins. Each chain

carries a group called a heme, a ring-like molecule that contains the iron that binds the oxygen. Thalassemias are classified according to the globin that is affected, hence the names *alpha* and *beta* thalassemia. Although both classes of thalassemia affect the same protein, the alpha and beta thalassemias are distinct diseases that affect the body in different ways.

Types of alpha thalassemia

People whose hemoglobin does not produce enough alpha globin have alpha thalassemia. The condition is the result of changes in the genes that code for making alpha chains in hemoglobin. There are four types of alpha thalassemia:

- Hemoglobin H disease (HbH): This thalassemia causes severe anemia and serious health problems such as an enlarged spleen, and bone deformities.
- Alpha thalassemia major: this is the most severe type of alpha thalassemia. It is also called hydrops fetalis or Hb Bart syndrome. Most individuals affected by this condition die before or shortly after birth.
- Alpha thalassemia minor: individuals affected by this thalassemia have smaller red blood cells known as microcytes, and display mild anemia. It is often misdiagnosed as iron deficiency anemia.
- Alpha thalassemia, silent carrier: this thalassemia is difficult to detect because it usually does not cause symptoms, hence its name.

Genetic profile

Humans normally make several types of hemoglobin. An individual's stage in development determines whether he or she makes primarily embryonic, fetal, or adult hemoglobins. Normal adult hemoglobin (HbA) is a tetrameric protein consisting of four chains: two alpha

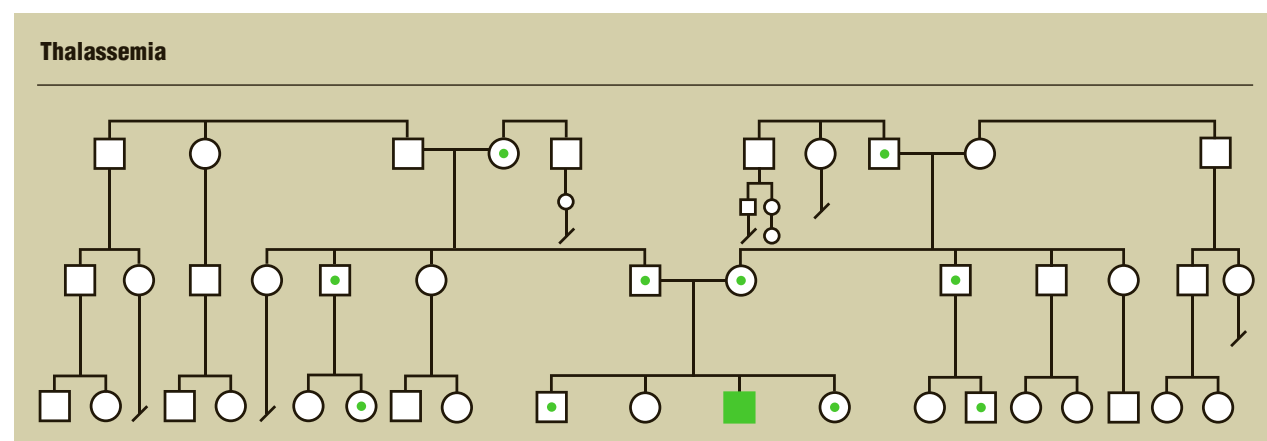
globins and two beta globins, each chain also containing a heme molecule. It is the major hemoglobin component of red blood cells (95%). In addition, red blood cells contain other minor hemoglobin forms: hemoglobin A2 (HbA2) consisting of two alpha chains and two delta chains (~3%) and hemoglobin F (HbF), consisting of two alpha chains and two gamma chains (~2%). If a person cannot produce enough of either alpha or beta globins, the red blood cells do not form normally and cannot carry oxygen properly, resulting in anemia.

All thalassemias are caused by deletions or modifications in the genes that control globin production. These genes are located on chromosome 16 (alpha globin genes) and chromosome 11 (beta, gamma, and delta genes). Mutations modify the amount of alpha globin relative to that of the other globins being produced, leading to an abnormal hemoglobin ratio and decreased hemoglobin production. The globin that is produced in normal amounts over the other globin accumulates and forms aggregates that damage the red blood cell membrane.

The thalassemias are inherited in an autosomal recessive pattern, meaning that a genetic change must be inherited from both the mother and the father. The severity of the disease is influenced by the exact thalassemia mutations inherited, as well as other genetic and environmental factors. There are rare exceptions, notably with beta thalassemia, in which globin gene mutations exhibit a dominant pattern of inheritance in which only one gene needs to be altered in order to see disease expression.

Alpha thalassemia

In alpha thalassemia, beta globins are produced in excess over the alpha globins, which leads to the formation of beta globin tetramers that also accumulate and interfere with erythropoiesis. Most individuals have four normal copies of the alpha globin genes, two copies



Thalassemia: pedigree analysis chart (Gale)

on the short arm of chromosome 16. There are two alpha globin genes in humans, *HBA1* and *HBA2*, located in what is known as the alpha locus at chromosome 16p13.3.

These genes make the alpha globin component of HbA. Alpha globin is also a component of HbF and HbA2. Defects in the alpha globin genes are usually deletions of the genes rather than mutations, resulting in the absence of alpha globin. The signs and symptoms of alpha thalassemia tend to be more severe when the disease results from mutations in the alpha-globin genes than when it is caused by deletions of these genes. Because there are four genes (instead of the usual two) to consider when looking at alpha globin gene inheritance, there are several alpha globin types that are possible.

Absence of one alpha globin gene leads to a condition known as silent alpha thalassemia trait or alpha thalassemia minima. This condition causes no health problems and can be detected only by special genetic testing. Alpha thalassemia trait, also known as alpha thalassemia minor, occurs when two alpha globin genes are missing. This condition can occur in two ways. The genes may be deleted from the same chromosome, causing the ‘cis’ type of alpha thalassemia trait. Alternately, they may be deleted from different chromosomes, causing the ‘trans’ type of alpha thalassemia trait. In both instances, there are no associated health problems, although the trait status may be detected by more routine blood screening.

Hemoglobin H (HbH) disease results from the deletion of three alpha globin genes, such that there is only one functioning gene. Typically, this condition can occur when one parent carries the silent alpha thalassemia trait and the other parent carries the ‘cis’ type of the alpha thalassemia trait. In this situation, there is a 25% chance for hemoglobin H disease in each of such a couple’s children.

Hemoglobin H disease-like symptoms can also be a part of a unique condition called alpha thalassemia intellectual disability syndrome 16 (ATR-16). Alpha thalassemia intellectual disability syndrome results from the deletion of a significant amount of chromosome 16, affecting the alpha globin genes. This condition is usually not inherited but occurs sporadically in affected individuals. Affected individuals have mild hemoglobin H disease, mild-to-moderate intellectual disability, and characteristic facial features. This syndrome can also occur as a sex-linked form (ATR-X) in which a mutation is inherited in a particular gene on the X chromosome; it affects only males. The ATR-X syndrome is more common than the ATR-16 syndrome. This gene influences alpha globin production, as well as various other developmental processes. Individuals affected with this form of the syndrome tend to have more severe intellectual

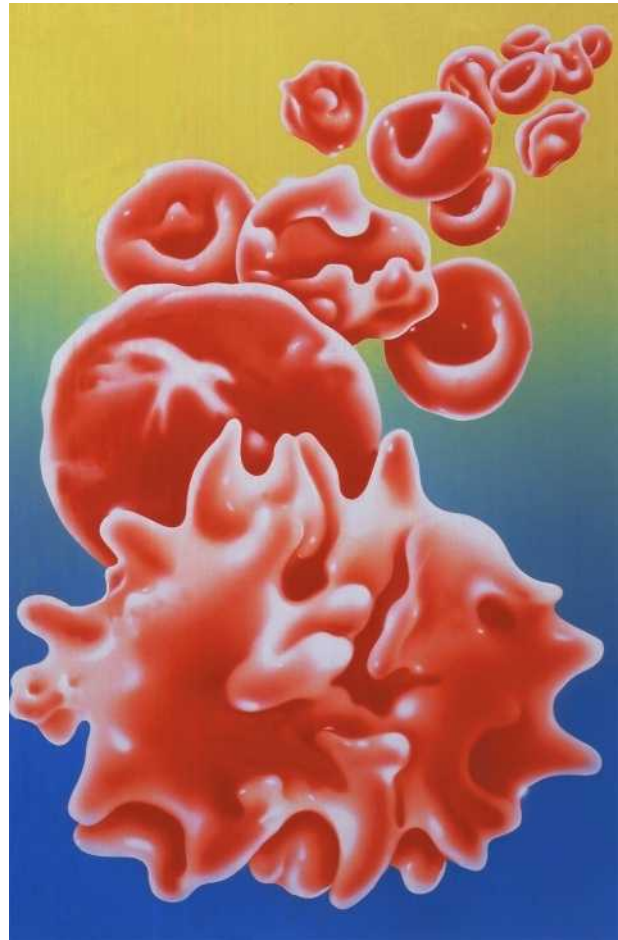


Illustration of normal and malformed blood cells affected by alpha thalassemia. (joshya/Shutterstock)

disability, delayed development, nearly absent speech, characteristic facial features, and genitourinary abnormalities.

Alpha thalassemia major results from the deletion of all four alpha globin genes, such that there are no functioning alpha globin genes. This condition can occur when both parents carry the ‘cis’ type of the alpha thalassemia trait. In this situation, there is a 25% chance for alpha thalassemia major in each of a couple’s children.

Demographics

The thalassemias are among the most common single-gene diseases worldwide, with more than 100,000 babies worldwide born each year with severe forms of thalassemia, resulting in some 15 million people having thalassemic disorders. It is estimated that there are 270 million carriers of mutant globin genes that can potentially cause severe forms of thalassemia. Both alpha and beta thalassemia have been described in individuals of almost every ancestry, but the

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Bilirubin—A yellow pigment that is the end result of hemoglobin breakdown. This pigment is metabolized in the liver and excreted from the body through the bile. Bloodstream levels are normally low; however, extensive red cell destruction leads to excessive bilirubin formation and jaundice.

Bone marrow—A spongy tissue located in the hollow centers of certain bones, such as the skull and hip bones. Bone marrow is the site of blood cell generation.

Bone marrow transplantation—A medical procedure used to treat some diseases that arise from defective blood cell formation in the bone marrow. Healthy bone marrow is extracted from a donor to replace the marrow in an ailing individual. Proteins on the surface of bone marrow cells must be identical or very closely matched between a donor and the recipient.

Desferoxamine—The oldest of three drugs used in iron chelation therapy. It aids in counteracting the

life-threatening buildup of iron in the body associated with long-term blood transfusions.

Ferritin—An intracellular protein that stores iron and releases it in a controlled manner. Ferritin in blood plasma is an indirect marker of the total amount of iron stored in the body.

Globins—A family of protein chains found in hemoglobin. Normal adult hemoglobin has two alpha globin chains and two beta globin chains.

Heme—The iron-containing molecule in hemoglobin that serves as the site for oxygen binding. Each of the four hemoglobin chains has one heme molecule.

Hemoglobin—Tetrameric protein in the blood that carries oxygen to the cells and carries carbon dioxide away from the cells. Hemoglobin consists of four chains, each containing a heme molecule.

Hemoglobin A (HbA)—Normal adult hemoglobin; it consists of two alpha globins and two beta globins.

Hemoglobin electrophoresis—A laboratory test that separates molecules based on their size, shape, or electrical charge.

Hemoglobin F (HbF)—Fetal hemoglobin; it consists of two alpha and two gamma globins. HbF is

conditions are more common among certain ethnic groups. Unaffected carriers of all types of thalassemia traits do not experience health problems. In fact, the thalassemia trait protects against malaria, a disease caused by bloodborne parasites transmitted through mosquito bites. According to a widely accepted theory, most genetic mutations that cause thalassemia occurred multiple generations ago. Coincidentally, these mutations increased the likelihood that carriers would survive malaria infection. Survivors passed the mutation onto their offspring, and the trait became established throughout areas where malaria is common. As populations migrated, so did the thalassemia traits.

The frequency of hemoglobin H disease and alpha thalassemia major depends on the type of alpha thalassemia trait. The populations in which alpha thalassemia diseases are most common include Southeast Asians and Chinese (particularly Southern Chinese). Alpha thalassemia also occurs frequently in people from Mediterranean countries, North Africa, the Middle East, India, and Central Asia.

Determining prevalence figures for alpha thalassemia is even more difficult due to increased limitations in

diagnostic testing. All types of alpha thalassemia disease are most common among people of Southeast Asian and Chinese descent, for reasons that become clearer with an understanding of the underlying genetics of alpha thalassemia. For example, one study of 500 pregnant women in Northern Thailand estimated a frequency of one in 500 pregnancies affected by alpha thalassemia major.

The frequency of alpha thalassemia disease is significantly lower in the United States owing primarily to immigration patterns. The incidence of alpha thalassemia is low among Caucasians in the United States. However, it is estimated that about 15% of African Americans are silent carriers of alpha thalassemia and 3% have alpha thalassemia trait. However, at least one state, California, has observed growing hemoglobin H disease incidence rates that are high enough to justify universal newborn screening for the condition.

Signs and symptoms

Hemoglobin H disease

Absence of three alpha globin genes causes an imbalance of alpha and beta globin proteins in the red

produced by the fetus in utero and until about 48 weeks after birth. At this stage, the production of HbA rapidly increases while that of HbF drops off.

Hepatomegaly—An abnormally enlarged liver.

HLA type—The unique set of proteins called human leukocyte antigens. These proteins are present on each individual's cells. They allow the immune system to recognize 'self' from 'non-self'. HLA type is particularly important in organ and tissue transplantation.

Hydrops fetalis—A condition in which excess fluid builds up in a fetus's body prior to birth.

Hydroxyurea—A drug that has been shown to induce production of fetal hemoglobin. HbF has a pair of gamma-globin molecules instead of the beta-globins of HbA. Higher-than-normal levels of HbF can alleviate some of the symptoms of thalassemia.

Iron deficiency anemia—A decrease in the number of red cells in the blood caused by too little iron in the diet, poor absorption of iron by the body, or loss of blood.

Iron overload—A side effect of frequent blood transfusions in which the body accumulates

abnormally high levels of iron. Iron deposits can form in organs, particularly the heart, and cause life-threatening damage.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Microcyte—An abnormally small red blood cell.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Placenta—The organ responsible for oxygen and nutrition exchange between a pregnant mother and her developing baby.

Red blood cells (RBCs)—Hemoglobin-containing blood cells that transport oxygen from the lungs to tissues. In the tissues, the red blood cells exchange their oxygen for carbon dioxide, which is brought back to the lungs to be exhaled.

Screening—Process through which carriers of a trait may be identified within a population.

Splenomegaly—Enlargement of the spleen.

Tetramer—Protein that consists of four amino acid chains.

blood cells. The excess beta globin proteins tend to come together to form hemoglobin H, which is unable to release oxygen to the tissues. In addition, hemoglobin H tends to precipitate out in the cells, causing damage to the red blood cell membrane. When affected individuals are exposed to certain drugs and chemicals known to make the membrane more fragile, the cells are thought to become vulnerable to breakdown in large numbers, a complication called hemolytic anemia. Fever and infection are also considered to be triggers of hemolytic anemia in hemoglobin H disease. This process can result in fatigue, paleness, and a yellow discoloration of the skin and whites of eyes called jaundice. Other complications of HbH disease include ulcers on the legs, gallstones, short limbs, and compression fractures of the spine.

Usually, the anemia is mild enough not to require treatment. Severe anemia events may require blood transfusion, however, and are usually accompanied by such other symptoms as dark feces or urine and abdominal or back pain. These events are uncommon in hemoglobin H disease, although they occur more frequently in a more serious type of hemoglobin H disease called hemoglobin H/Constant Spring disease. Individuals affected with this

type of hemoglobin H disease are also more likely to have enlarged spleen and other spleen problems.

Alpha thalassemia major (Hb Bart syndrome)

Because alpha globin is a necessary component of all major hemoglobins and some minor hemoglobins, absence of all functioning alpha globin genes leads to serious medical consequences that begin even before birth. Affected fetuses develop severe anemia as early as the first trimester of pregnancy. The placenta, heart, liver, spleen, and adrenal glands may all become enlarged. Fluid can begin collecting throughout the body as early as the start of the second trimester, causing damage to developing tissues and organs. Growth retardation is also common. Affected fetuses usually miscarry or die shortly after birth. In addition, women carrying affected fetuses are at increased risk of developing complications of pregnancy and delivery. Up to 80% of such women develop toxemia, a disturbance of metabolism that can potentially lead to convulsions and coma. Other maternal complications include premature delivery and increased rates of cesarean section, as well as hemorrhage after delivery.

Diagnosis

Thalassemia may be suspected if an individual shows signs that are suggestive of the disease. In all cases, however, laboratory diagnosis is essential to confirm the exact diagnosis and to allow for the provision of accurate genetic counseling about recurrence risks and testing options for parents and affected individuals. Screening is likewise recommended to determine trait status for individuals of high-risk ethnic groups.

The following tests are used to screen for thalassemia disease and/or trait:

- Complete blood count
- Hemoglobin electrophoresis with quantitative hemoglobin A2 and hemoglobin F
- Free erythrocyte-protoporphyrin (or ferritin or other studies of serum iron levels)

A complete blood count will identify low levels of hemoglobin, microcytes (abnormally small red blood cells), and other red blood cell abnormalities that are characteristic of a thalassemia diagnosis. Since thalassemia trait can sometimes be difficult to distinguish from iron deficiency, tests to evaluate iron levels are important. A hemoglobin electrophoresis is a test that can help identify the types and quantities of hemoglobin made by an individual. This test uses an electric field applied across a slab of gel-like material. Hemoglobins migrate through this gel at various rates and to specific locations, depending on their size, shape, and electrical charge. Isoelectric focusing and high-performance liquid chromatography (HPLC) use similar processes to separate hemoglobins and can be used instead of hemoglobin electrophoresis to determine the types and quantities of hemoglobin present. Hemoglobin electrophoresis results are usually within the normal range for all types of alpha thalassemia. However, hemoglobin A2 levels and sometimes hemoglobin F levels are elevated when beta thalassemia disease or trait is present. Hemoglobin electrophoresis can also detect structurally abnormal hemoglobins that may be coinherited with a thalassemia trait to cause thalassemia disease (i.e., hemoglobin E) or other types of hemoglobin disease (i.e., sickle hemoglobin). Sometimes DNA testing is needed in addition to the screening tests. This test can be performed to help confirm the diagnosis and establish the exact genetic type of thalassemia.

Diagnosis of thalassemia can occur under various circumstances and at various ages. Several states offer thalassemia screening as part of the usual battery of blood tests done for newborns. This screening allows for early identification and treatment. Thalassemia can be identified before birth through the use of prenatal diagnosis. Chorionic villus sampling (CVS) can be offered as early

QUESTIONS TO ASK YOUR DOCTOR

- How can you determine whether the symptoms I notice in my child are those of thalassemia?
- What is the difference between alpha thalassemia and beta thalassemia?
- Can alpha thalassemia be treated, and, if so, what medications and procedures will my child need?
- What is the prognosis for my child if the condition is diagnosed as alpha thalassemia?

as 10 weeks of pregnancy and involves removing a sample of the placenta made by the baby and testing the cells. Amniocentesis is generally offered between 15 and 22 weeks of pregnancy, but can sometimes be offered earlier. Two to three tablespoons of the fluid surrounding the baby is removed. This fluid contains fetal cells that can be tested.

Pregnant women and couples may choose prenatal testing in order to prepare for the birth of a baby that may have thalassemia. Alternately, knowing the diagnosis during pregnancy allows for the option of pregnancy termination. Preimplantation genetic diagnosis (PGD) is a relatively new technique that involves in-vitro fertilization followed by genetic testing of one cell from each developing embryo. Only the embryos unaffected by thalassemia disease are transferred back into the uterus. PGD is currently available on a research basis only and is relatively expensive.

Imaging studies are not useful in diagnosing alpha thalassemia in adults but are often helpful in evaluating patients for such complications as splenomegaly, gallstones, or hepatomegaly. Ultrasound, however, can be used to evaluate the cardiovascular function and hemodynamic status of fetuses suspected of having alpha thalassemia major.

Treatment and management

Hemoglobin H disease

Hemoglobin H disease (HbH) is a relatively mild form of thalassemia that may go unrecognized. It is not generally considered a condition that will reduce one's life expectancy. Education is an important part of managing the health of an individual with hemoglobin H disease. It is important to be able to recognize the signs of severe anemia that require medical attention. It is also important to be aware of the medications, chemicals, and other

exposures to avoid due to the theoretical risk they pose of causing a severe anemia event.

When severe anemia occurs, it is treated with blood transfusion therapy. For individuals with hemoglobin H disease, this is rarely required. For those with the hemoglobin H/Constant Spring form of the disease, the need for transfusions may be intermittent or ongoing. A reasonable estimate would be on a monthly basis and requiring deferoxamine (Desferal) treatment, which is given intravenously. Deferasirox (Exjade), a newer chelating agent, is now preferred to deferoxamine because it is orally administered. Individuals with this more severe form of the disease may also have an increased chance of requiring a splenectomy (surgical removal of an enlarged and/or overactive spleen).

Pregnant women with HbH disease should be carefully monitored because they are at increased risk of severe anemia, preeclampsia, congestive heart failure, and miscarriage.

Alpha thalassemia major (Hb Bart syndrome)

Because alpha thalassemia major is most often a condition that is fatal in the prenatal or newborn period, treatment has previously been focused on identifying affected pregnancies in order to provide appropriate management to reduce potential maternal complications. Pregnancy termination provides one form of management. Increased prenatal surveillance and early treatment of maternal complications is an approach that is appropriate for mothers who wish to continue their pregnancy with the knowledge that the baby will most likely not survive.

In recent years, there have been a handful of infants with this condition who have survived long-term. Most of these infants received experimental treatment including transfusions before birth, early delivery, and even bone marrow transplantation before birth, although the latter procedure has not yet been successful. A still newer therapy is in utero hematopoietic stem cell transplantation (IUHCTx). For those infants that survive to delivery, there seems to be an increased risk of developmental problems and physical effects, particularly heart and genital malformations. Otherwise, their medical outlook is similar to a child with beta thalassemia major, with the important exception that ongoing lifelong blood transfusions begin right at birth.

Clinical trials

Clinical trials on alpha thalassemia are currently sponsored by the National Institutes of Health (NIH) and other agencies. Most are studies of hydroxyurea or chelating agents (currently approved or investigational).

However, some are longitudinal studies of patients with milder forms of alpha thalassemia. Clinical trial information is constantly updated by NIH and the most recent information on thalassemia trials can be found at: <http://clinicaltrials.gov/search/>

Prognosis

The prognosis for individuals who are silent alpha thalassemia carriers and those with alpha thalassemia trait is excellent. Persons with HbH disease, however, often have shortened lifespans although most survive into adulthood. Patients with HbH disease are at risk of severe anemia and have a lifelong requirement for transfusions.

The prognosis of patients with the most serious types of thalassemia has improved drastically in the last several years following recent medical advances in transfusion, chemotherapy, and transplantation therapy. Advances continue and promise to improve the life expectancy and quality of life further for affected individuals.

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AABB [formerly American Association of Blood Banks], 4550 Montgomery Avenue, Suite 700, North Tower, Bethesda, MD 20814, (301) 907-6977, aabb@aabb.org, <http://www.aabb.org/Pages/default.aspx>

American Society of Hematology (ASH), 2021 L Street NW, Suite 900, Washington, DC 20036, (202) 776-0544, (202) 776-0545, <http://www.hematology.org>

Cooley's Anemia Foundation Inc, 330 Seventh Avenue, #200, New York, NY 10001, (212) 279-8090, <http://www.thalassemia.org/about-the-foundation/contact><http://www.cooleysanemia.org>

Iron Disorders Institute, P.O. Box 4891, Greenville, SC 29608, info@irondisorders.org, <http://www.irondisorders.org>

Thalassemia Foundation of Canada, 10 Holland Drive, Bolton, ON Canada L7E 1G6, (416) 242-THAL (8425), info@thalassemia.ca, <http://www.thalassemia.ca>

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Alpha-1 antitrypsin deficiency

Definition

Alpha-1 antitrypsin deficiency (AATD) is one of the most common inherited diseases in Caucasians of European descent. AATD is caused by low amounts of, and abnormalities in, alpha-1 antitrypsin protein (AAT). People with AATD are more likely to have lung and liver problems. Lung problems are more common in people with AATD who are smokers.

Description

The alpha-1 antitrypsin protein (AAT) is a protease inhibitor, made mostly in the liver. It inactivates other proteins called proteases. This is an important function, as proteases themselves disable proteins. In the human body, the levels of proteases and their inhibitors need to be balanced so that proteases can perform their functions but not over-perform, which can lead to problems.

A protease called neutrophil elastase is the most important target of AAT. It protects the lungs against bacteria and other foreign particles. However, too much neutrophil elastase can destroy lung tissue. AAT ensures that there is not too much neutrophil elastase.

People with AATD have low amounts of, and abnormalities in, AAT, which means that they do not have enough AAT protein or that it does not work as well, resulting in increased amounts of proteases like Neutrophil elastase. This condition, in turn, can cause damage to the lung and liver and other less-common symptoms. Buildup of the abnormal AAT can also cause liver damage.

Genetic profile

The *SERPINA1* gene (serpin peptidase inhibitor, clade A [alpha-1 antiproteinase, antitrypsin] member 1), located on chromosome 14, is responsible for the production of AAT. Variations (mutations) in the *SERPINA1* gene can lead to lower amounts or abnormal alpha-1 antitrypsin protein (AAT) being produced by the body. To date, over 120 variations (mutations) of the *SERPINA1* gene that influence the AAT being produced have been identified.

AATD is inherited in an autosomal codominant pattern, which means two different versions (alleles) of the *SERPINA1* gene can be active in an individual with both versions (alleles) contributing to the amount and type of AAT being produced.

The most common allele of the *SERPINA1* gene is called M, and it produces a normal amount and type of AAT. Most people have two copies of the M allele (MM), and they produce normal amounts and a normal type of AAT. Other alleles of the *SERPINA1* gene produce reduced amounts and/or abnormal AAT and cause AATD. The most common of these alleles are the (Z) and (S) alleles. Individuals with two Z alleles usually have the most severe AATD. Even those who have one Z allele and one normal allele M (ZM) may have an increased risk of developing symptoms of AATD. People with SS have somewhat lower levels of AAT but don't typically have symptoms. Individuals with SZ, on the other hand, are at increased risk for symptoms but less so than those with ZZ. The F allele is rarer. Individuals with this allele have near-normal levels of AAT, but the protein doesn't work properly. People with the F allele seem to have an increased risk of lung problems but not liver problems. The I allele is also rare and similar to the S allele. More than 95% of all severely AAT-deficient individuals have either the ZZ or SZ genotype.

Demographics

AATD is most common in Caucasians, especially those of Northern European descent. It is less common in populations of Asian, African, and American Indian descent. Approximately one in 2,500 Caucasians has two Z genes. These individuals account for 1% of all emphysema patients. Because people with one *SERPINA1* Z allele and one other deleterious *SERPINA1* allele may also have symptoms, the number of people at risk to have AATD associated lung disease is greater than one in 2,500. Approximately one in 20 Caucasians has one Z allele and one normal M allele. The number of Caucasians with one S allele and one normal allele is even higher. Approximately one in 1,000 Caucasians of Northern European descent has two S alleles. The National

Institutes of Health estimate that 161 million people have an S or Z allele.

Signs and symptoms

The first symptoms in adults with AATD are often shortness of breath with mild activity and problems exercising caused by a lung disease called chronic obstructive pulmonary disease (COPD). Some people with AATD get an early-onset, rapidly progressive type of COPD, called emphysema. Emphysema is caused by damage to the lungs; it begins with breathlessness during exertion and progresses to shortness of breath at all times. People with AATD can also have frequent lung infections, tiredness, rapid heartbeat, vision problems, and weight loss. Adults with AATD are at increased risk for asthma, liver disease and liver cancer, and, more rarely, tender bumps under the skin called panniculitis. Some children with AATD have liver disease. The chance that someone will have symptoms, the age of onset, and the severity of symptoms depend on the alleles that they have and their environmental exposures.

Lung disease

Approximately 60% to 70% of the people with two Z alleles (ZZ) develop chronic lung disease. Shortness of breath with exertion may begin before age 40 and progress rapidly to incapacitating emphysema. Life expectancy may be reduced by 10 to 15 years and is reduced further for people with two Z alleles who smoke. Some individuals with two Z alleles never develop chronic lung disease, however. Individuals with MZ alleles and SZ alleles appear to be at slightly increased risk for lung problems. The chances appear to be less than for those with two major alleles (ZZ). The age of onset of symptoms and the severity seem to be less in MZ and ZS individuals.

Environmental exposures significantly affect whether a person will develop symptoms. Smoking puts individuals with AATD at much greater risk of developing emphysema. The Z allele protein functions 1,000 times less efficiently in smokers. People with AATD who are not exposed to harmful environmental factors are less likely to develop emphysema. If people with two Z alleles stop smoking before they develop lung disease, their life expectancy increases, and the risk of lung disease decreases. Respiratory infections can also cause a risk of lung damage, because they increase the level of harmful neutrophil elastase in the lungs. Infections should, therefore, be treated promptly.

Liver disease

The risks of liver disease and liver cancer are increased in individuals with AATD. The highest risk is

KEY TERMS

Alleles—Different versions or alternative forms of a gene. We inherit two alleles for most genes.

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Bronchiectasis—Permanent enlargement of parts of the airways of the lung.

Emphysema—A chronic lung disease that begins with breathlessness during exertion and progresses to shortness of breath at all times, caused by destructive changes in the lungs.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein. A gene is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Granulomatosis with Polyangitis—Permanent enlargement of parts of the airways of the lung.

Necrotizing Panniculitis—Raised bumps under the skin that develop into ulcers.

Proteins—Important building blocks of the body, composed of amino acids. Proteins are involved in the formation of bodily structures and the regulation of basic bodily functions.

for individuals with ZZ alleles. The liver disease appears to be caused by buildup of abnormal AAT in the liver. Infants and children with AATD may have abnormal liver function and inflammation. The abnormal liver function they develop is called cholestasis, a condition in which the liver stops secreting a digestive fluid called bile. A buildup of bile causes cholestatic jaundice (yellowing of the skin). These abnormalities sometimes progress to liver disease and liver failure, which is fatal without a liver transplant. In other children, liver function returns to normal. Adults with AATD, who had liver abnormalities as children, may be at increased risk to develop liver disease or liver cancer.

Researchers do not know exactly why some people with AATD develop liver disease while others do not. The chance that someone with AATD will develop liver disease is influenced by environmental factors and also the alleles that they have. For example, people with two ZZ alleles have a higher risk than someone with MZ or ZS alleles. The chance that someone with AATD and two Z alleles will develop significant liver disease is approximately one out of 10 (10%), and the chance that they will develop liver cancer

is approximately 2 out of 100 (2%). The risk of developing liver disease is also increased if an individual is male or diabetic or has a hepatic virus infection. People with AATD who have family members with liver disease or liver cancer are also at increased risk. An individual with repeated increased levels of liver enzymes is at increased risk for liver disease. AATD is the most common genetic cause of liver disease in infants and children.

Diagnosis

Testing should be considered in newborns with cholestatic jaundice, swollen abdomen, and poor feeding. In later childhood or adulthood, fatigue, poor appetite, swelling of the abdomen and legs, or abnormal liver tests may suggest the need for testing. Testing for AATD should also be done on any person with:

- chronic obstructive pulmonary disease
- unexplained chronic liver disease
- necrotizing panniculitis (raised bumps that develop into ulcers)
- granulomatosis with polyangiitis (inflammation of the blood vessels in the nose, sinuses, throat, lungs, and kidneys).
- unexplained bronchiectasis (permanent enlargement of parts of the airways of the lung)
- parents, siblings, children, or extended family members of individuals with an abnormal *SERPINA1* allele.

Some organizations recommend that individuals with asthma also be tested for AATD.

Testing for symptomatic individuals should include measurement of AAT in the blood and also testing for genetic variants. Measurement of protein levels alone is not sufficient, because the AAT level can fluctuate with inflammation or pregnancy, and in children. Levels of AAT in ZM and ZS individuals can be normal even though those people may be at risk for lung and liver disease. Although less common, PI typing to see whether the AAT is abnormal can also be done.

People without symptoms, who have family members with an abnormal *SERPINA1* allele, should undergo genetic testing. Genetic testing can test specifically for the most common allele variants (Z and S and sometimes F and I) or can look for any variations in the gene. Prenatal genetic diagnosis is available. It is recommended that the parents be tested first to see which alleles they have, to ensure accurate interpretation of results.

Lung disease in people with AATD is diagnosed by the same methods that are used to diagnose lung disease in those who do not have AATD. These studies include breathing tests such as total lung capacity and

pulmonary function tests. Total lung capacity, also called spirometry, is measured with a device called a spirometer. Pulmonary function tests measure oxygen/carbon dioxide exchange by determining the amount of air exhaled, the time to exhale, and the efficiency of oxygen transport. X-rays and other studies may also be performed. The initial evaluation should include complete lung function testing, which should be followed by at least yearly spirometry. A CT scan of the chest should be considered for people who have just been diagnosed and who have symptoms or abnormal pulmonary function testing.

Liver disease in children and adults with AATD is diagnosed by the same methods that are used to diagnose liver disease in people who do not have AATD. Liver function studies include tests measuring two liver proteins called serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT). SGOT is sometimes called aspartate transaminase (AST), and SGPT is sometimes called alanine aminotransferase (ALT). Studies may also look for deposits within the cells of the liver, called inclusions. Monitoring for liver disease should be done at least yearly and may include physical examination, including focused exam for signs of liver disease, liver ultrasound, and laboratory monitoring of AST, ALT, GGT, albumin, bilirubin, INR, and platelets.

Once the diagnosis of AATD has been made, it is important to share this information with relatives related by blood, especially parents, siblings, and children. These relatives may also have AATD and may want to have genetic testing. If they know that they have AATD before they develop lung disease, they can take preventative measures such as avoiding exposure to smoke and other lung toxins.

Treatment and management

Although AATD cannot be cured, proper management may prevent many of its serious consequences. People with AATD should not smoke cigarettes and should not be exposed to smoke or other lung irritants. Respiratory infections should be treated promptly, because they increase the level of harmful neutrophil elastase in the lungs. Some doctors recommend avoiding alcohol and oxidants; keeping hepatitis A and B, pneumococcal, and influenza vaccinations up to date; and preventing hepatitis C exposure.

Lung disease

The treatment of lung diseases caused by AATD is similar to the treatment of emphysema and lung disease from other causes. Short-acting bronchodilators may be

QUESTIONS TO ASK YOUR DOCTOR

- What other testing should I have done?
- How often should I undergo liver studies?
- What are the symptoms of liver disease?
- What *SERPINA1* gene variants do I have?
- What new treatments are available?

used to help maximize lung function, but these medications do not slow disease progression. Inhaled steroids may also help to control symptoms.

Protein augmentation

Treatment is available if individuals with AATD develop lung disease. One of the main treatments involves infusion of AAT protein concentrates, which are pooled, purified, human plasma protein replacement for the missing AAT. They may halt or slow progression of respiratory problems. Generally, the protein concentrate is infused into a vein weekly. Treatment with the replacement protein may not be effective if tissue damage to the lungs is severe. This is often called augmentation therapy. It is safe, and people who receive it have few adverse reactions. Results from the NIH patient registry and a comparison of Danish and German registries have been published. Both analyses suggest that augmentation therapy has beneficial effects. However, some researchers are not convinced that it is an effective treatment. Although the AAT concentrate is purified and screened for both HIV and hepatitis viruses, doctors recommend that patients undergoing this treatment receive immunization against hepatitis viruses.

Treatments in development

People with AATD have reason to be hopeful that effective treatments may be available soon. Researchers are studying an inhaled form of AAT concentrate and other biotechnology based treatments such as aerosols that deliver the normal gene to lung tissue.

Liver disease treatments

People with AATD and severe liver disease can be treated with a liver transplant. AATD with liver disease is a common reason for liver transplant in children. If the new liver is from a donor with normal AAT, it will have normal, functional protein after the transplant. Augmentation therapy (replacing the protein in the blood) does not effectively treat liver disease. Gene therapy for liver disease is not currently available.

Prognosis

Individuals with AATD who have never smoked nor been exposed to other respiratory irritants have the best prognosis. They might never develop lung disease, but if they do, the age of onset is usually later than that of smokers by 10 or more years. Prognosis is improved if people with AATD stop smoking before the onset of lung disease.

Lung disease in people with AATD typically progresses rapidly. Affected individuals may progress from decreased respiration during exertion to incapacitation within five years. Smoking cessation and prompt treatment are critical. Prompt treatment with replacement protein improves prognosis. Some scientists recommend delaying treatment until the affected person has quit smoking.

Prognosis of infants with liver disease is poor. However, if a donor is found, and the transplant is successful, the new liver has the *SERPINA1* alleles of the donor. In such cases, the prognosis related to AATD is very good.

A great deal of research is done on the prevention and cure of AATD. In 1997, 12 countries with registries of AATD patients formed an international registry, which has helped researchers to complete studies involving large numbers of patients. These studies are absolutely necessary to answer research questions, especially treatment questions. Pharmaceutical companies are also studying new treatment options.

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ORGANIZATIONS

- Alpha-1 Foundation, 3300 Ponce de Leon Boulevard, Coral Gables, FL 33134, (305) 567-9888, (877) 2-CURE-A1 or (877) 228-7321, (305) 567-1317, info@alpha-1foundation.org, <http://www.alpha1portal.org>
- American Liver Foundation, 39 Broadway, Suite 2700, New York, NY 10006, (212) 668-1000, (212) 483-8179, <http://www.liverfoundation.org>
- American Lung Association, 55 W. Wacker Drive, Suite 1150, Chicago, IL 60601, (800)-LUNGUSA, (202) 452-1805, <http://www.lung.org>

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Alpha-thalassemia X-linked intellectual disability syndrome

Definition

Alpha-thalassemia X-linked intellectual disability syndrome is a rare, inherited condition that usually only affects boys and is characterized by severe intellectual disability, characteristic facial features, and mild anemia.

Description

Alpha-thalassemia X-linked intellectual disability syndrome is also known as ATRX syndrome, X-linked intellectual disability hypotonic facies syndrome, and alpha-thalassemia/intellectual disability, X-linked. This condition is characterized by intellectual disability, severe developmental delay, unique head and facial features, skeletal abnormalities, poor muscle tone, and genital abnormalities. People with ATRX syndrome often have a form of mild anemia, called alpha thalassemia, resulting from a defect in the production of hemoglobin.

The distinguishing features of this rare disorder include severe intellectual disability and a distinctive facial appearance. Children with the syndrome also have clinical problems such as deformed joints or limbs, small kidneys, or abnormalities with how their bladders and other parts of the urinary tract form. Additionally, many children are born with a hole in their heart, as well as abnormalities in their gastrointestinal systems, such as bowel obstructions or problems with swallowing.

Genetic profile

Alpha-thalassemia X-linked intellectual disability syndrome is caused by pathogenic variants (mutations) in the *ATRX* gene, which is located on the X chromosome. More than 125 variants of the *ATRX* gene have been found in people who have alpha-thalassemia X-linked intellectual disability syndrome. Males only have one X chromosome, which they always inherit from their mother. Thus, males who inherit a variant in the *ATRX* gene are always affected with the disorder. Females who inherit a variant in the *ATRX* gene are carriers of the disorder. Carriers have one functional *ATRX* gene and one *ATRX* that has a variant. Female carriers rarely have signs of the condition, since they have one functional copy of the *ATRX* gene. Their mutated copy of the gene is usually inactivated in most cells. Some rare females have symptoms, because their mutated copy of the *ATRX* gene is not preferentially inactivated. Carrier females without preferential inactivation may also be at increased risk for bone cancer.

If a male is affected with alpha-thalassemia X-linked intellectual disability syndrome, it is impossible for him to reproduce because of genital abnormalities, such as testes that don't descend and other problems. Male children of female carriers of an *ATRX* variant have a 50% chance of inheriting the variant. Carrier females who bear children have a 25% of having a male who is affected with alpha-thalassemia X-linked intellectual disability syndrome, since there is a 50% chance that a child will be male (50% × 50%). Maternal aunts of a male with an *ATRX* variant may be carriers.

Sometimes the *ATRX* variant is a new (*de novo*) variant in the affected individual. In those cases, his mother is not a carrier. It is not known how often a *de novo* variant occurs in *ATRX*. The possibility of a *de novo* variant is unlikely if there are two or more affected brothers in the family. Testing for X-inactivation can sometimes help detect carrier mothers. If there are no other affected individuals in the family, and if the mother's X-inactivation studies are normal, then the variant is probably *de novo*, and the mother is unlikely to be a carrier. In that case, the recurrence risk to siblings is very small.

KEY TERMS

Amniocentesis—A prenatal test in which a hollow needle is inserted through the abdominal wall and into the uterus of a pregnant woman to obtain amniotic fluid containing cells from the fetus. These cells can be examined to determine the sex of the fetus or to look for genetic diseases.

Anemia—A condition in which the blood has too few red blood cells. As a result, tissues and organs do not get a sufficient amount of oxygen.

Chorionic villus sampling (CVS)—Biopsy of the placenta through the abdominal wall or by way of the vagina and uterine cervix to obtain fetal cells for the prenatal diagnosis of a genetic disorder.

Hemoglobin—A component of red blood cells that transports oxygen from the lungs to the tissues of the body.

Microcytic, hypochromic anemia—An anemia marked by too little hemoglobin and small red blood cells.

In other cases, a female may have germline mosaicism and appear not to be a carrier but have a child with an ATRX variant. In that case, the ATRX variant would be present only in the egg cells of the mother. Her blood cells would be normal, and therefore, X-inactivation studies and genetic testing would be normal. Since the ATRX variant is present in her egg cells, she will have an increased chance of passing the variant on to her offspring. The exact risk to offspring is hard to predict, since the number of affected eggs is unknown. Germline mosaicism cannot be tested for but would be suspected in a female who appears not to be a carrier but has multiple affected children. Males and females with germline variants may be at increased risk for bone cancer.

Demographics

The prevalence of alpha-thalassemia X-linked intellectual disability syndrome is not precisely known. More than 200 affected people have been identified worldwide. There are no reports of the condition being more common in specific ethnic groups or geographical regions, although more than 70 cases have been identified in Japan.

Signs and symptoms

There are distinctive features that accompany alpha-thalassemia X-linked intellectual disability syndrome. The most noticeable clinical signs are the severe

developmental delay and intellectual disability that is almost always present. From very early in life, affected individuals are delayed in meeting developmental milestones. Some fail to walk independently, and many do not learn to speak coherently. Poor muscle tone (hypotonia), which is also very common in this condition, plays a role in the developmental delay.

There are unique head and facial features associated with alpha-thalassemia X-linked intellectual disability syndrome. Affected individuals often have a small head (microcephaly); widely spaced eyes (telecanthus); a flat mid-facial area (mid-face hypoplasia); small and low-set ears; a small, triangular nose; a tented upper lip; and a full, everted lower lip with a protruding tongue. About two-thirds of affected individuals have short stature. In some patients, growth retardation is present throughout life, and in other cases, it begins around puberty. Other minor skeletal abnormalities have been observed as well, such as joint contractures, abnormalities of the fingers and toes, foot deformations, and scoliosis. Genitalia of affected individuals are often abnormal and underdeveloped. These abnormalities may be as negligible as undescended testes or as substantial as ambiguous genitalia appearing to be female in nature. In many cases, patients do not progress through a normal puberty, presumably due to inadequate amounts of the male hormone testosterone.

Patients with alpha-thalassemia X-linked intellectual disability syndrome can have abnormal digestion. Feeding problems are fairly common as well, such as swallowing difficulties, regurgitation of food, and/or vomiting. Constipation becomes an issue in some patients. These difficulties often resolve with age. Seizures occur in approximately one-third of cases. Cleft palate, deafness, cardiac defects, and renal/urinary abnormalities are less common but have been reported.

About 75% of the time, blood tests in affected individuals show a mild form of anemia, also known as alpha thalassemia, which results from a defect in the production of an important component of hemoglobin. However, this mild anemia does not appear to have any adverse consequences in patients with the disorder.

Diagnosis

Alpha-thalassemia X-linked intellectual disability syndrome can be suspected clinically in an individual who has intellectual disability; hypotonia; characteristic physical features such as craniofacial, skeletal, or genital abnormalities; and a family history consistent with X-linked recessive inheritance. Usually, the most obvious signs of the disorder are developmental delay, severely impaired cognitive function, and the characteristic facial

features. Magnetic resonance imaging (MRI) exams may show abnormalities in the white matter portion of the affected child's brain.

A clinical diagnosis is usually followed by genetic testing for variants in the *ATRX* gene. Genetic testing will detect variants in approximately 90% of individuals with alpha-thalassemia X-linked intellectual disability syndrome. This testing is usually done by looking for small variants and pieces missing and added in the entire *ATRX* gene. Since the clinical symptoms of alpha-thalassemia X-linked intellectual disability syndrome can overlap with other syndromes, sometimes genetic testing will include other genes. Once a variant is detected, testing can be done on the mother and other at-risk females.

If genetic testing uncovers a variant of unknown significance, then epigenetic signature analysis may be done to help confirm a diagnosis. This test looks for characteristic changes in the production of the protein produced by the *ATRX* gene that are usually found in affected individuals.

In some cases, blood abnormalities can be detected by various laboratory tests. For example, molecules called hemoglobin H (HbH) inclusions may be seen in the red blood cells of affected individuals. The presence of HbH is associated with alpha thalassemia. HbH inclusions are less helpful in identifying female carriers and are only seen in approximately 25% of women who carry an *ATRX* variant. Microcytic, hypochromic anemia can be detected by a blood test and may be a sign of alpha thalassemia X-linked intellectual disability syndrome. However, the absence of either of these blood abnormalities does not rule out this condition—many affected individuals will not demonstrate these abnormalities.

Another option for detecting female carriers of the *ATRX* gene is X-chromosome inactivation studies. In a typical female, each cell has two X chromosomes (X1 and X2), and one of them will be inactivated. This inactivation is a random process, meaning that there is a 50% chance that either one is affected. If one were to look at a significant number of cells, X1 would be inactivated in approximately the same number of cells as X2. This process is skewed in females who are carriers of the *ATRX* gene variant, because the X chromosome that carries the *ATRX* variant will be preferentially inactivated. A laboratory test can detect this skewed X inactivation. However, this characteristic is not always present in carriers of *ATRX* variants. It also can be present for other reasons. Thus, it is not diagnostic and must be interpreted in the context of the clinical findings and family history. X chromosome inactivation studies can be especially useful if molecular testing is not available or is uninformative in a family.

Prenatal testing is available for pregnancies that are at risk for alpha-thalassemia X-linked intellectual disability syndrome. For pregnancies in which the mother is a definite carrier of the *ATRX* variant, fetal sex is determined via cells obtained from amniocentesis or chorionic villus sampling (CVS). If the fetus is male, DNA from the fetal cells can be analyzed for the *ATRX* variant that has been found in the family. For pregnancies in which the mother has tested negative for the *ATRX* variant but has previously birthed an affected child, prenatal diagnosis should still be offered to all male fetuses, due to the possibility of germline mosaicism.

Treatment and management

Very few of the abnormalities that result from alpha-thalassemia X-linked intellectual disability syndrome are life-threatening. The anemia that often accompanies this condition is mild and does not require any treatment. In order to improve quality of life, a thorough clinical evaluation is recommended after the initial diagnosis. A growth evaluation of height, weight, and head circumference is recommended, as is a developmental assessment of motor, speech, cognitive skills. Early speech, physical, and occupational therapies, and special education are usually recommended. A neurological evaluation should include analysis of muscle tone and reflexes, and EEG and MRI if seizures are present. A genital exam can help assess whether surgery is necessary. A pediatric cardiologist can check for a hole in the heart that might require surgery. The eyes should be checked to make sure that they are not cross-eyed and that there are no other eye defects or vision problems.

The child should also have an evaluation of their feeding and gastrointestinal health. They should be evaluated for swallowing difficulties, aspiration risk, nutrition, reflux, vomiting, and bowel blockages. Feeding problems may need to be managed with tube feeding in the early months. In rare cases, a permanent feeding tube passed through the abdominal wall into the stomach can be used. An operation known as fundoplication may be necessary to correct problems with vomiting.

An assessment of the musculoskeletal system is also important. It will look at gross and fine motor skills to see whether physical and occupational therapy or adaptive devices like wheelchairs are needed. It will also look for problems with the spine, clubfoot, and problems moving the joints, which may require surgery or other therapies.

Prognosis

There is limited information on the prognosis for Alpha-thalassemia X-linked intellectual disability syndrome. The lifespan can be normal, but some children will die at an early age. One of the main causes of early death in this condition is pneumonia, which can

result from food entering the lungs due to vomiting and regurgitation problems.

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ORGANIZATIONS

Madisons Foundation, P.O. Box 241956, Los Angeles, CA 90024, (310) 264-0826, (310) 264-4766, getinfo@madisonsfoundation.org, <http://www.madisonsfoundation.org>

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Alport syndrome

Definition

Alport syndrome, also called familial nephritis, is an inheritable form of kidney disease. There are multiple distinct forms of kidney disease that are genetic disorders. The main inheritable types are Alport syndrome, autosomal recessive polycystic kidney disease, and autosomal dominant polycystic kidney disease. These are all forms

of kidney disease in which the nephrons, the basic functional units of the kidney, are diseased or damaged.

Description

Kidneys perform many important bodily functions. Having at least one kidney is necessary for life. Kidneys filter waste and extra fluid from the blood, keep a healthy blood level of electrolytes and minerals, help to maintain healthy blood pressure, and release hormones that are important for bodily functions. Normally, there are two fist-sized kidneys present, one on each side of the spinal column of the back just below the rib cage. Each kidney contains microscopic filter lobules called nephrons that transfer bodily waste products from the bloodstream to the urinary system. Healthy nephrons are critical for maintaining bodily functions, and the buildup of waste products can be life-threatening.

Alport syndrome is a genetic disease in which there is significant damage to the nephrons of the kidney. The disease is characterized by the onset of bloody urine in early childhood, which later leads to renal failure. The onset is typically in males before six years of age. After years of recurrent or persistent bloody urine, the kidneys begin to malfunction. Renal dysfunction typically occurs in the third or fourth decade of life, but occasionally before 20 years of age. Alport syndrome also involves progressive hearing loss and eye complications.

Genetic profile

The Mendelian genetic model demonstrates that an individual inherits two functional copies (alleles) of every non-sex linked gene. One copy is paternally inherited and the other is maternally inherited. When genes follow the Mendelian inheritance pattern, both the paternal and maternal copies are functionally expressed, regardless of which parent they came from.

There are different modes of inheritance for genetic disorders. An autosomal dominant mode of inheritance means that if one gene in the pair has a mutation, an individual will become affected with the disease. Since a parent only passes one copy of each gene on to their offspring, there is a 50%, or one in two, chance that a person who has autosomal dominant disorder will pass it on to each of their offspring. Males and females are equally likely to be affected in this mode of inheritance.

Autosomal recessive diseases are caused by the inheritance of two defective copies of a gene. Each parent may contribute one copy of autosomal genes to their offspring. In autosomal recessive inheritance, only if both copies are mutated does disease occur. If only one

defective copy is present, the disease does not occur, but the mutated gene can still be passed on to subsequent generations. If both parents are carrying a mutated gene, then each offspring has a 25% chance of inheriting the disease. Populations with a high frequency of healthy individuals carrying defective genes will also have higher prevalence of offspring with the disease.

The sex-linked chromosomes are denoted XX in females and XY in males. A female receives an X chromosome from each parent. A male receives the X chromosome maternally and the Y chromosome paternally. Some genetic disorders display X-linked recessive inheritance. In this mode of inheritance, mothers carrying defective X-linked genes can pass one copy to each offspring. However, because female offspring also receive a normal X-linked gene from the father, female offspring typically do not develop the disease. However, since male offspring receive their only X chromosome from the mother, if their mother carries the mutated X gene, the males can develop the disease.

Alport syndrome is a genetic disorder that can be inherited in different ways. The mode of inheritance is X-linked in 80% of cases, autosomal recessive in 15% of cases, and autosomal dominant in 5% of cases. Alport syndrome frequently affects the ears and eyes in addition to the kidneys. The inherited defect involves the basement membranes of the affected organs, as a result of mutations in type IV collagen genes. The basement membrane is a sheet-like structure made up of type IV collagen that supports the kidney cells. Type IV collagen is made up of six segments, called chains, designated A1 through A6. Each chain is encoded for by a distinct gene. These genes are distributed in pairs on three chromosomes. The A1 and A2 chains are encoded by the genes *COL4A1* and *COL4A2* on chromosome 13; the A3 and A4 chains are encoded by *COL4A3* and *COL4A4* on chromosome 2; and the A5 and A6 chains are encoded by *COL4A5* and *COL4A6* on the X chromosome. Alport syndrome involves mutations in the *COL4A3*, *COL4A4*, or *COL4A5* genes. All of the A chains encoded for by these genes are present in the basement membranes of the glomerulus (portion of the kidney that filters the blood), cochlea (portion of the ear involved with hearing), and the eye. Consequently, there are abnormalities in the basement membranes causing the symptoms associated with Alport syndrome.

Demographics

Estimates of the incidence of Alport syndrome vary and range from 1 in 5,000 to 10,000 to 50,000 individuals. It is believed to be under diagnosed. There is no distinction between ethnic populations. The X-linked form of Alport syndrome is the most common and predominantly

affects males. Further, there appears to be a relationship between the type and location of the mutation and the severity of disease. Females who carry the X-linked form of the condition typically have blood in their urine that does not cause symptoms. However, occasionally, other associated findings and severe renal disease may be present. The autosomal recessive and dominant forms of Alport syndrome are less common and affect both sexes equally.

Signs and symptoms

Alport syndrome usually has an onset of persistent microscopic bloody urine (hematuria). The amount of blood in the urine is too small to be detected visually, but can be detected in a laboratory test. For X-linked Alport syndrome, males typically present in early childhood with blood in their urine. The hematuria may last for many years and all males develop abnormal levels of protein in the urine (proteinuria), eventually resulting in renal dysfunction between 20 and 40 years of age. In autosomal recessive Alport syndrome, both males and females present in late childhood with hematuria and typically develop end stage renal disease in their 30s. End-stage renal disease occurs later in the autosomal dominant form of Alport syndrome.

Hearing loss is variable. It typically presents by or during adolescence and is progressive. However, in some families, hearing loss may present late in life. As with renal disease, hearing loss typically presents later with the autosomal dominant form of Alport syndrome.

Other associated complications may include abnormalities of the eye. These occur in about 1 in 3 individuals with X-linked and autosomal recessive Alport syndrome. The findings are rare in the autosomal dominant form. Anterior protrusion of the lens capsule and underlying cortex (lenticonus) is highly suggestive of Alport syndrome. Additionally, individuals may have dot and fleck retinopathy, corneal erosion, and a macular hole.

Diagnosis

Alport syndrome is diagnosed through multiple tests, including urinalysis, blood testing, family history, hearing and vision evaluation, kidney ultrasound, kidney and skin biopsies, and genetic testing. Urinalysis in individuals with Alport syndrome can identify microscopic or visible hematuria. The presence of high protein levels in the urine (proteinuria) is indicative of kidney disease. Proteinuria eventually develops in males with X-linked Alport syndrome, and in both sexes with the autosomal recessive form of the disease. Proteinuria usually becomes worse as kidney disease progresses. Blood tests

KEY TERMS

Amniotic fluid—The protective fluid surrounding a fetus in the womb.

Anemia—Condition in which there are low levels of red blood cells.

Asymptomatic—Without symptoms.

Computerized axial tomography (CAT) scan—An imaging technique that visualizes organs or tissues.

Cornea—The transparent, curved, fibrous coat of the front of the eye.

Creatinine—A normal component of blood kept in low levels in urine by functioning kidneys.

Dialysis—Filtering of blood to remove waste products that the kidneys would normally remove if they were present and functioning.

DNA—Deoxyribonucleic acid, inheritable material that constitutes the building blocks of life.

Locus (plural: loci)—Position occupied by a gene on a chromosome.

Mendelian genetics—A set of parameters describing the traditional method of the transmission of genes from one generation to the next.

Neonate—A newborn infant up to six weeks of age.

Nephron—Basic functional filtration unit of the kidney.

Oligohydramnios—An abnormally small amount of amniotic fluid.

Platelet—An important component of blood that forms clots to close wounds.

Pulmonary hypoplasia—Underdevelopment of the lungs.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

are also performed to look for standard protein markers of kidney dysfunction. If kidney disease has progressed, there may also be high cholesterol in the blood. Some cases of autosomal dominant Alport syndrome also have defects in platelets of the blood.

All children with a medical history that suggests Alport syndrome are tested for high-frequency hearing loss. To confirm a diagnosis of high-frequency hearing loss, a special tool called an audiometer is used. Eye complications can be diagnosed through an ophthalmologic examination.

Ultrasound imaging studies of the kidneys may be normal in the early stages of Alport disease. In the later stages of the disease, the kidneys may progressively decrease in size. A renal biopsy is performed to confirm the diagnosis. Physicians search for abnormalities in collagen indicative of Alport syndrome. The gene mutations that cause collagen abnormalities in the kidneys in Alport syndrome also cause similar collagen abnormalities in skin. For this reason, a skin biopsy may also be used. Skin biopsies are preferred if the patient has end-stage renal disease, in which case a renal biopsy may be unsafe. Genetic analysis is the only method by which to diagnose asymptomatic carrier females that carry an X-linked Alport syndrome gene. Genetic analysis is also the only method by which to make a prenatal diagnosis. It can also be used to make a definitive diagnosis when clinical findings or analysis of renal biopsy specimens is unclear.

Treatment and management

There is no treatment for Alport syndrome. The main therapeutic goal is to identify treatments that slow down or delay the onset of kidney disease. Several studies in mice have demonstrated that certain medications can slow down the loss of kidney function. These include angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Individuals with Alport syndrome who have taken angiotensin-converting enzyme (ACE) inhibitors while their kidney function was normal have been shown to develop kidney failure later. For end stage renal disease, the options are dialysis or a kidney transplant.

Other therapy treats the complications that arise as a result of Alport syndrome. Therapy includes erythropoietin for chronic anemia, medications that affect phosphate and vitamin D levels to combat bone loss, bicarbonate to correct acidic blood conditions, and antihypertensive therapy. Hearing aids may be used and individuals with corneal erosions may need to wear protective eyewear. Individuals should also avoid medications that are harmful to the kidneys, such as non-steroidal anti-inflammatory medications containing aspirin, ibuprofen and naproxen, as well as decongestants.

Prognosis

The prognosis for males with X-linked Alport syndrome and for all patients with autosomal recessive disease is poor. Most patients develop hypertension and end-stage renal disease. Deafness and visual loss may also be components of the poor prognosis. Many patients with a family history of juvenile-onset Alport syndrome or early-onset deafness usually develop end-stage renal disease by 20–30 years of age. In contrast, the prognosis for females with X-linked Alport syndrome is generally

good, with most having normal lifespans and clinically mild renal disease.

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ORGANIZATIONS

- Alport Syndrome Foundation, P.O. Box 4130, Scottsdale, AZ 85261-4130, (480) 800-3510, info@alportsyndrome.org, <http://alportsyndrome.org>
- National Institute of Diabetes and Digestive and Kidney Urologic Diseases, (800) 860-8747, <https://www.niddk.nih.gov/about-niddk/research-areas/urologic-diseases>

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Alström syndrome

Definition

Alström syndrome is a very rare inherited human disorder that adversely affects several body organs and systems, including the eyes, ears, and heart.

Description

Alström syndrome is characterized by a progressive loss of vision and hearing, dilated cardiomyopathy (which is a type of heart disease that results in an enlarged and weakened heart muscle), obesity, type 2 diabetes mellitus, and short stature. Alström syndrome may also adversely affect the liver, kidneys, bladder, and lungs. Some persons with Alström syndrome have a skin condition, acanthosis nigricans, that causes body folds and creases of the skin to be thick, dark, and velvety. Carl-Henry Alström, a Swedish doctor, first described the syndrome in 1959.

The conditions associated with Alström syndrome may begin in infancy or early childhood, but some do not develop until later in life. There is considerable variability in degree and type of clinical conditions associated with individuals with Alström syndrome, even among affected siblings.

Persons with Alström syndrome have a similar level of intelligence as their family members. However, they may have learning difficulties due to vision and hearing losses that result in delayed early developmental milestones, academic difficulties, and problems with language skills. About 50% of persons with the syndrome exhibit such developmental delays.

Genetic profile

Alström syndrome is an inherited autosomal recessive disorder; that is, two copies of an abnormal non-sex-related gene, one inherited from each parent, must be present in order for the syndrome to develop. Alström syndrome can be inherited by both males and females with equal probability. A child born to parents who both carry an autosomal recessive gene mutation has a one-in-four chance of inheriting the malfunctioning genes from both parents and developing the syndrome. The child has a one-in-two chance of inheriting one abnormal gene and becoming a carrier. The parents, who each carry one copy of the inherited gene, do not show signs or symptoms of the syndrome.

The mutated gene responsible for Alström syndrome is *ALMS1*, which is located on chromosome 2. This gene is responsible for making a protein whose function is not well known. However, there is evidence that the protein is involved in hearing, vision, weight control regulation, and functioning of the heart, kidney, lungs, and liver. The *ALMS1* gene may also be involved in the regulation of insulin production by the pancreas, which controls blood sugar levels.

Studies of the *ALMS1* gene have shown that more than 80 mutations have been identified in persons with

Alström syndrome. Most of the mutations result in an abnormally small version of the ALMS1 protein that does not function properly. For example, a lack of normal ALMS1 function in the brain could result in the person overeating, or a loss of the normal ALMS1 protein in the pancreas could cause insulin resistance, resulting in obesity and diabetes, two common conditions associated with Alström syndrome.

Demographics

Alström syndrome is extremely rare, having been reported as affecting only about 800 people in 47 countries. It is more common in the Netherlands and Sweden than it is in the United States. Alström syndrome is sometimes confused with Bardet-Biedl syndrome, which has similar symptoms, although it typically develops later in life.

Signs and symptoms

Parents may first recognize symptoms of Alström syndrome by changes in their infant's eyesight between birth and fifteen months of age. The infant may exhibit sensitivity to light (photophobia) and a rapid movement of the eyes (nystagmus), which are caused by a slow degeneration of the cones of the retina. The cones are the photoreceptors that are used for seeing in well-lit environments. As Alström syndrome progresses, the rods in the eyes, which are responsible for capturing light in dimly lit environments, deteriorate. This retinal degeneration is called cone-rod dystrophy.

Up to 70% of persons with Alström syndrome begin to lose hearing in childhood (usually before they are 10 years of age) or as adults due to loss of nerve functioning in the auditory system, resulting in auditory information not being transferred to the brain. About half of all children with Alström syndrome have developmental delays.

Infants and toddlers with Alström syndrome, although born with normal birth weight, are usually overweight. However, by adulthood, weights of individuals with the syndrome may be in the high-normal to normal weight range. Individuals with Alström syndrome often have distinctive facial characteristics, including deep-set eyes with a rounded face, premature frontal balding, and thin hair, and they may have wide, thick, flat feet and short, stubby fingers and toes.

Type 2 diabetes mellitus may develop in individuals with Alström syndrome during the childhood or teenage years due to the development of insulin resistance. Insulin resistance is a condition in which the body's cells do not use insulin properly. Insulin, which is produced by the pancreas, helps cells use blood glucose for energy.

Complications from diabetes include amputation of limbs, blindness, heart disease, and kidney failure.

Diabetes insipidus may also develop in individuals with Alström syndrome. This is a condition characterized by frequent and heavy urination, excessive thirst, and an overall feeling of weakness. It may be caused by a defect in the pituitary gland or in the kidney. In this type of diabetes, there is no elevated blood sugar. Effects include interference with eating, appetite, weight gain, and growth. There may also be vomiting, diarrhea, and fever. Adequate intake of water is necessary to prevent dehydration and potassium loss.

An enlarged heart muscle associated with dilated cardiomyopathy can present in infancy or later during adolescence. Fluid and blood can accumulate in the lungs, resulting in shortness of breath. Fluids may also build up in the feet, ankles, and legs, causing congestive heart failure, in which case the heart is unable to maintain an adequate circulation of blood throughout the body. Up to 60% of persons with Alström syndrome develop heart failure as a result of dilated cardiomyopathy at some stage of their lives. Persons with Alström syndrome may also have elevated levels of cholesterol and triglycerides in their blood, which can also result in heart problems and stroke.

When children affected by Alström syndrome are in their late teens, they often start to exhibit problems with their kidneys and liver. Steatosis, or fatty liver, may develop due to excessive amounts of triglycerides and other fats accumulating inside the liver cells. There may also be elevated levels of enzymes in the liver. Effects on the liver may result in the development of portal hypertension, a condition in which the normal flow of blood through the liver is slowed or blocked by scarring or other damage. Progressive and chronic kidney disease may also develop. By adulthood (during the second to fourth decade of life), the liver and kidneys may start to fail and cause severe problems in those affected.

Additional conditions that may be associated with Alström syndrome include scoliosis (curvature of the spine) or kyphosis (a curving of the spine that causes a bowing of the back, leading to a hunchback or slouching posture), digestive and respiratory problems, high blood pressure, enlarged spleen, alopecia (loss of hair from the head or body) or hirsutism (excessive hairiness), low levels of growth hormone, advanced bone age, and an underactive thyroid. Persons with Alström syndrome may suffer from muscle dystonia, which causes involuntary movements and prolonged muscle contraction, resulting in twisting body motions, tremors, and abnormal posture; hyperuricemia (abnormally high levels of uric acid in the blood); frequent urinary tract infections;

kidney disease (advancing over time to kidney failure); digestive problems such as gastrointestinal reflux; and respiratory difficulties, such as chronic obstructive pulmonary disease (COPD), a progressive lung disease process characterized by wheezing, a chronic cough, and difficulties in breathing. Males with Alström syndrome may exhibit male hypogonadism, which is partial or complete failure of the genitalia to develop, while females with the syndrome may experience irregular menstrual patterns.

Diagnosis

Diagnosis of Alström syndrome is accomplished by clinical diagnosis, including blood tests, urine tests for presence of uric acid, eye exams for retinal degeneration, and hearing testing. Symptoms of diabetes, such as increased thirst or urination, also are used to diagnose the disease. Alström syndrome is usually not diagnosed in infancy, but is detected later by medical personnel as more symptoms develop through time. The syndrome is often not recognized until diabetes mellitus develops in the second or third decade of life. The diagnosis of Alström syndrome should be considered in infants if they exhibit cone-rod dystrophy, if their weight is above the 90th percentile, or if there is cardiomyopathy present.

Genetic diagnosis is not usually used, as testing is expensive.

Treatment and management

Alström syndrome has no specific treatment or cure. However, regular medical care is essential to manage all of the possible symptoms and conditions associated with the syndrome. Symptoms of the disorder must be treated as necessary, for example, with diabetes medications, hearing aids, or thyroid hormone replacement hormones, depending on the specific symptoms experienced by each individual patient.

Cardiac problems may require heart medications to remove excess fluids from body tissues, surgical intervention, or even heart transplantation.

Children experiencing cone-rod dystrophy can be aided with the use of enlarged-print reading materials, tinted glasses (with corrective prescriptions as needed), and magnifying tools such as monocular telescopes and electronic magnifiers.

Type 2 diabetes mellitus in persons with Alström syndrome may or may not require insulin treatments. A diet low in calories and refined carbohydrates may be sufficient to control the diabetes. High cholesterol and triglycerides may require the use of medications for control. A variety of medications may also be required in order to

KEY TERMS

Bardet-Biedl syndrome—A human genetic disorder that affects many body systems. It is characterized principally by obesity, retinitis pigmentosa (a type of progressive retinal dystrophy), polydactyly (having additional fingers or toes), intellectual disability, hypogonadism (a defect of the gonads that results in underproduction of testosterone), and possibly kidney failure.

Gastrointestinal reflux—A chronic condition in which acid from the stomach flows back into the lower esophagus, causing pain or tissue damage.

Genetic counseling—A short-term educational counseling process for individuals and families who have a genetic disease or who are at risk for such a disease. Genetic counseling provides patients with information about their condition and helps them make informed decisions.

Retina—Light-sensitive nerve tissue in the eye that converts images from the eye's optical system into electrical impulses that are sent along the optic nerve to the brain. The retina forms a thin membrane that lines the rear two-thirds of the eye.

manage symptoms involving kidney failure, liver problems, lung problems, and cardiomyopathy.

Increased exercise is useful for all persons with Alström syndrome. Yearly blood tests are recommended to screen for kidney or liver problems.

There is no known prevention for Alström syndrome. Based on family history and known cases of Alström syndrome in family members and ancestors, parents may seek genetic counseling to determine their risk of having a child with Alström syndrome. They may seek genetic testing to evaluate their *ALMS1* gene status and to determine whether both parents are carriers of Alström syndrome. Based on the results of genetic testing, parents may elect to adopt, become pregnant with egg or sperm from an unaffected known or unknown donor, prevent pregnancy, or terminate an affected fetus. Counseling will also help parents prepare for treatment and care of an affected infant after birth. Siblings of individuals with Alström syndrome may also wish to be tested in order to ascertain their risk of passing on the disorder to offspring.

Unfortunately, most families are not aware that both parents carry the mutated *ALMS1* gene until the birth of an affected child, as children with Alström syndrome are most often born to parents with no family history of the disease.

QUESTIONS TO ASK YOUR DOCTOR

- What symptoms and conditions do we need to watch for in our child?
- What types of medical specialties should we consult for our child's specific condition?
- What organizations and support groups are available?
- Where can we get genetic counseling for possible future pregnancies?

Prognosis

Alström syndrome is progressive, with affected children developing more symptoms as they get older. However, due to variability in the expression of various symptoms and conditions, the prognosis for individuals with the syndrome is also highly variable. However, the lifespan of patients with Alström syndrome rarely exceeds 40 years.

By the late teen years, children affected with Alström syndrome usually have little or no vision. They are also likely to develop deafness and type 2 diabetes. Kidney and liver failure will likely continue to worsen. Persons affected with Alström syndrome may also suffer from coronary heart disease, develop complications from diabetes, and exhibit fatigue and shortness of breath due to poor heart function.

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ORGANIZATIONS

Alström Syndrome International, 14 Whitney Farm Road, Mount Desert, ME 04660, (800) 371-3628, info@alstrom.org, <https://www.alstrom.org>

Alström Syndrome UK, 31 Shearwater Drive, Torquay, Devon UK TQ2 7TL, info@alstrom.org.uk, <http://alstrom.org.uk>

Judith L. Sims, MS

Alzheimer's disease

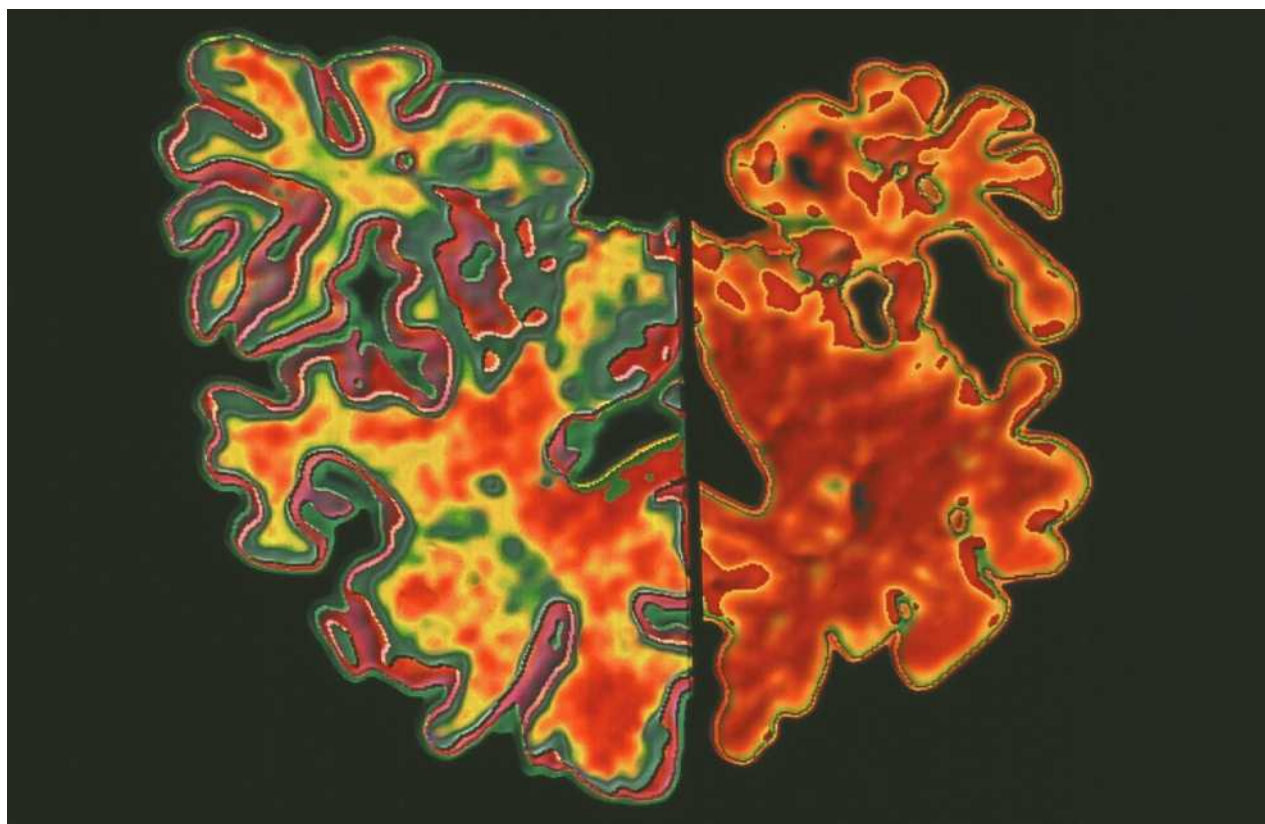
Definition

Alzheimer's disease (AD) is an irreversible, progressive neurological disease caused by the degeneration and death of large numbers of neurons (nerve cells) in several areas of the brain, accompanied by diminished brain size. It is the most common form of dementia—the loss of cognitive functions. AD usually begins with short-term memory loss, followed by the progressive loss of memory and cognitive functioning, deterioration of physical functioning, incapacitation, and death. With growing numbers of people affected by AD, their increasing life expectancy, and the direct and indirect costs of their care, AD is a major public health concern.

Description

AD was first described by Alois Alzheimer (1864–1915), a German psychiatrist and neuroanatomist. While studying slides prepared from the brain of a 51-year-old woman who had died after suffering from dementia for several years, Alzheimer found abnormal clumps—now called beta-amyloid plaques—and bundles of fibers—now called neurofibrillary tangles. Because dementia was associated with the elderly, and Alzheimer's patient had been middle-aged, her disease was named presenile dementia and was thought to be very rare. It was not until the early 1950s that researchers came to realize that these plaques and tangles are the diagnostic signatures of AD—the single most common cause of dementia.

AD plaques are sticky clumps or clusters of dead and dying neurons and other cellular debris surrounding insoluble deposits of beta-amyloid. The latter are fragments of a larger protein called amyloid precursor protein (APP) that has not been properly processed. The plaques are situated among neurons and are believed to interfere with normal communication among neurons, eventually causing the nerve cells to die. The tangles are



Normal brain of a 70-year-old (left) and the brain of a 70-year-old with Alzheimer's disease (right). The right brain is atrophied.
(Jessica Wilson/Science Source)

accumulations of twisted fragments of tau proteins inside neurons. Tau proteins normally bind and stabilize neurons. When they are damaged by the addition of phosphate, in a process called hyperphosphorylation, they form filaments that twist around each other to form neurofibrillary tangles that can no longer stabilize the neurons. Increased beta-amyloid may cause the formation of neurofibrillary tangles. However, it is not known whether the plaques and tangles cause AD or are the result of it. They occur as part of the normal aging process but are far less prevalent in normal brains than in those of AD patients.

Scientists have found other changes in the brains of AD patients. Connections among nerve cells are disrupted, and nerve cells die in areas of the brain that are vital for memory and learning, including the hippocampus. The hippocampus is a structure deep in the brain that is essential for short-term memory. Later in the disease, the cerebral cortex is affected, particularly the areas responsible for language and reasoning. Eventually, many areas of the brain atrophy (i.e., become shrunken and dysfunctional).

Scientists also have observed that some neurons are more susceptible to AD-related changes than others,

producing the tangles of toxic tau proteins while other cells are able to resist these changes for years or even decades. In January 2021, researchers identified the neurons that are most vulnerable to the disease, distinguishing them from neighboring cells that appear to be more resilient. Using a technique called single-nucleus RNA sequencing, they were able to group neurons by patterns of gene activity and found that vulnerable cells expressed a protein called RORB. It is not yet known whether RORB itself causes the cells to be more vulnerable to tau. Scientists hope that further study will reveal how and why these cells accumulate tau proteins earlier than others in order to identify ways to make the cells more resilient, thereby slowing the spread of AD.

Levels of the brain neurotransmitters serotonin, norepinephrine, and acetylcholine are lower in AD. These chemicals transmit signals across the synapses or gaps among nerve cells. Many of the behavioral and psychiatric problems associated with AD are thought to result from low levels of these neurotransmitters. Acetylcholine and norepinephrine are also important for many other bodily processes, including digestion, blood vessel dilation and constriction, and regulation of the heartbeat.

There are other common causes of dementia besides AD, such as alcoholism and the overuse of drugs such as tranquilizers or pain relievers. Common causes of dementia also include multi-infarct vascular dementia, caused by strokes (blood clots in the brain). Vascular dementia can also be caused by diffuse white-matter disease that may result from multiple “mini-strokes.” Parkinson’s disease, which causes abnormalities in movement and functioning, also can cause dementia. Less common causes include thyroid dysfunction or other endocrine abnormalities, chronic infections, trauma or injury to the brain, brain tumors, psychiatric abnormalities, and certain other degenerative disorders. However, AD accounts for 50%–70% of all dementias and about 75% of all dementias in people over age 65.

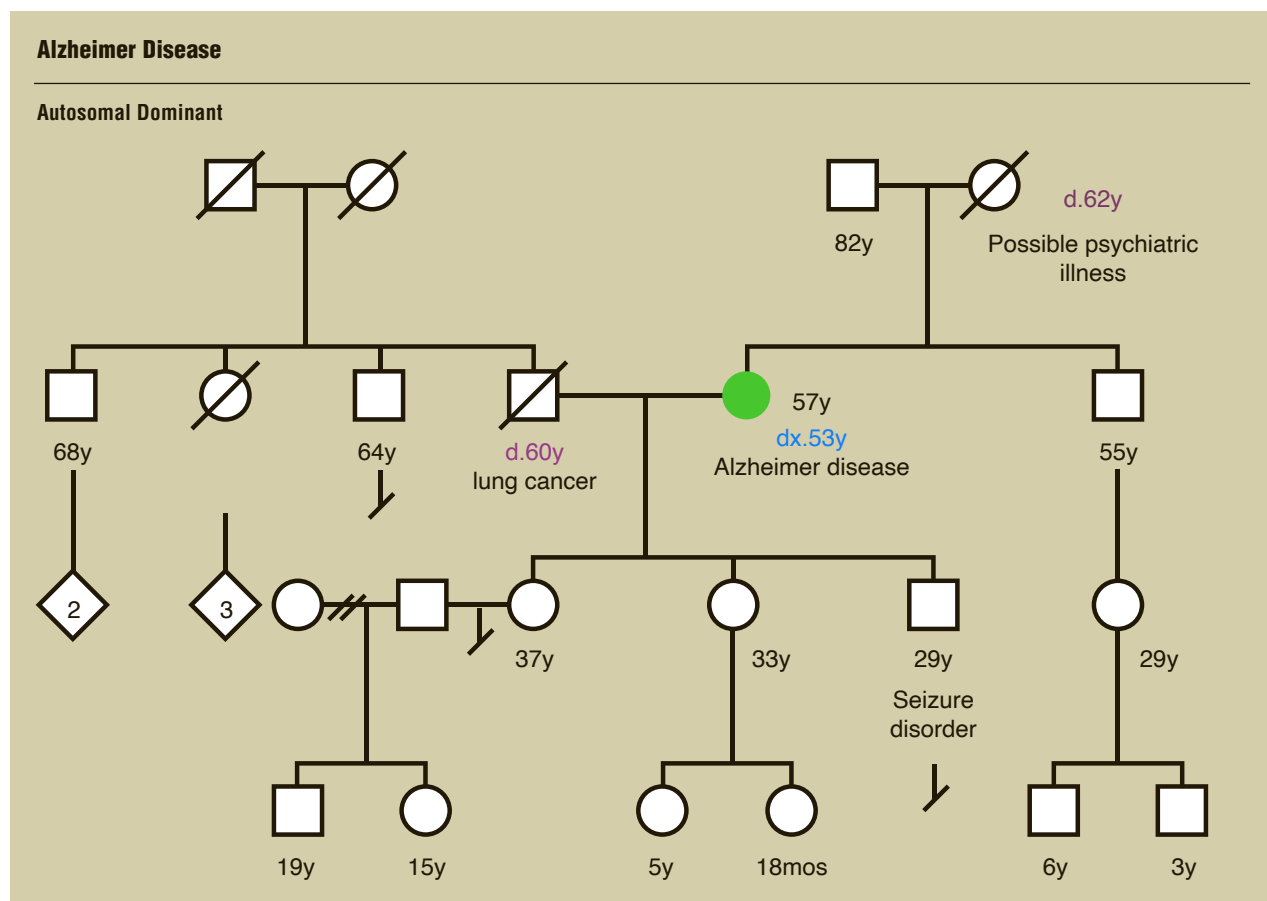
Genetic profile

The causes of most cases of AD are unknown, although they are believed to be due to a combination of genetic and environmental factors. Most cases of AD are late-onset, developing after age 60–65. More than 75% of cases are sporadic—patients have no family history

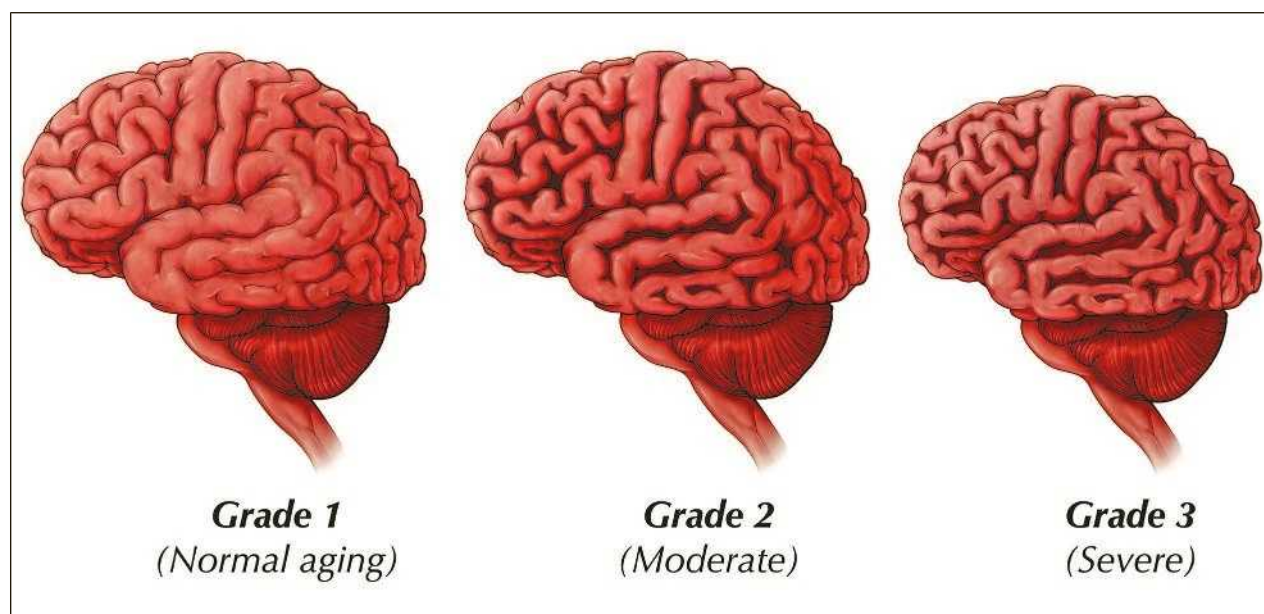
of the disease. About 25% of AD cases are in patients who have family histories of AD. They may have inherited AD susceptibility or risk genes from their parents or may share environmental or lifestyle risk factors with family members. They may also share both genetic and environmental factors. Familial AD may be either early-onset or late-onset.

Early-onset AD

Early-onset AD develops between the ages of 30 and 60 and can be caused by inheriting one of three defective genes. Variant alleles or mutations in any of these three different genes result in the production of abnormal proteins that directly cause familial early-onset AD. Because these genes are located on chromosomes other than the X and Y sex chromosomes, they are called autosomal genes and affect males and females with equal frequency. A defective version of one of these genes, inherited from one parent, causes AD even if a normal version of the same gene is inherited from the other parent. Therefore, the defective gene is described as dominant. AD caused by one of these defective genes is known as



Alzheimer's disease: pedigree analysis chart (Gale)



The stages of Alzheimer's disease. The disease is characterized by the loss of neurons in the brain, leading to gradual atrophy of the cerebral cortex and loss of cognitive function. The illustration shows a series of coronal sections of the brain, depicting the shrinkage of the cerebral cortex and hippocampus, and the development of enlarged ventricles. (Evan Oto/Science Source)

autosomal dominant Alzheimer's disease (ADAD). Each child of a parent with one of these defective genes has a 50% risk of inheriting the gene and AD. If both parents have one copy of the mutant gene, each of their children has a 75% chance of inheriting at least one copy of it. Parents carrying two copies of the mutant gene will pass on the defective gene to all of their offspring.

All three of the abnormal proteins produced by these early-onset AD genes increase the amount of beta-amyloid in the brain.

- Mutations in the *APP* gene, located on chromosome 21, are associated with AD onset between the ages of 55 and 60, which is sometimes called AD1.
- Variations or mutations in the presenilin-1 (*PS-1*) gene on chromosome 14 are the most common cause of early-onset AD, sometimes referred to as AD3. PS-1 may be one of the enzymes that clip APP into beta-amyloid. It also may be important for the functioning of synaptic connections among neurons.
- AD4 is an extremely rare genetic defect in the presenilin-2 (*PS-2*) gene located on chromosome 1. Presenilin 2 is involved in processing APP.

AD-causing mutations in these “deterministic” genes are very rare, accounting for less than 5% of AD cases. They do not appear to be involved in late-onset AD. Since mutations in these genes account for only about 50% of early-onset familial AD, there are presumed to

be other as-yet-unidentified genes associated with early-onset AD.

Early-onset AD is also associated with Down syndrome—a genetic disorder caused by the presence of part or all of an extra chromosome 21. People over age 40 with Down syndrome develop the brain changes characteristic of AD. This is thought to be due to the overproduction of APP caused by the *APP* gene on the extra chromosome 21. Down syndrome-associated AD accounts for less than 1% of all AD cases.

Late-onset AD risk genes

As of 2021, genome-wide association studies have identified more than 30 genes and 200 different variants associated with late-onset AD. It is expected that more will be identified in the future. The presence of specific versions (alleles) of these genes or changes (mutations) in these genes may increase the risk of late-onset AD.

The gene with the strongest influence on AD is the apolipoprotein E (*APOE*) gene located on chromosome 19. Familial late-onset AD associated with the *APOE* gene is sometimes called AD2. The *APOE* gene codes for a protein that helps remove cholesterol from the blood. There are three common versions of *APOE*: *APOE-2*, *APOE-3*, and *APOE-4*. *APOE-2*, which is relatively rare, may provide some protection against AD. *APOE-3*, the most common *APOE* variant, does not appear to affect AD risk. *APOE-4* occurs in 10–15% of the population and in 40–60% of all people with late-

onset AD. People who inherit an *APOE-4* gene from one parent are at increased risk for AD. Those who inherit two copies of *APOE-4*—one from each parent—are at higher risk for AD. *APOE-4* may also cause AD at a younger-than-average age. Nevertheless, many people with one or two copies of *APOE-4* do not develop AD, and many people with AD do not have an *APOE-4* gene.

Other genes with variant alleles that have been associated with AD risk include:

- *AP4E1*, which plays a key role in brain development and functioning
- *AP4M1*, which encodes a subunit of a protein complex involved in intracellular transport of proteins that is thought to have a unique role in neurons
- *APBB3*, which encodes a protein that binds to the AD beta-amyloid precursor protein (APP)
- *BIN1*, which encodes a protein that interacts with tau protein
- *CLU*, which helps regulate clearance of beta-amyloid from the brain
- *CRI*, which encodes a protein that, when deficient, may contribute to chronic inflammation in the brain
- *MS4A4A* and *MS4A6A*, which alter levels of TREM2, a protein thought to help clear amyloid and tau from the brain
- *PICALM*, which is involved in communication among neurons
- *PILRA*, which encodes a protein involved in cell signaling pathways
- *RABEP1*, which encodes a protein involved in transport of the PKD1:PKD2 complex and membrane fusion
- *SORL1*, which is involved in regulating the transport of APP and lipoproteins
- *SPI1*, which encodes a protein that regulates several AD-associated genetic risk factors
- *TP53INP1*, which encodes two proteins that induce cell cycle arrest and cell death
- *TREM2*, which is involved in regulation of the response to inflammation in the brain
- *ZYX*, which encodes Zyxin, a protein located at sites of cell adhesion that regulates signaling in response to DNA damage

Other risk factors

- The most significant risk factor for AD is advancing age. The risk of developing AD begins to rise after age 65 and rises sharply after age 75.
- Head trauma—especially repeated trauma or serious injury with loss of consciousness—is strongly linked to increased AD risk.

- Conditions that damage the heart or blood vessels—including high blood pressure, heart disease, diabetes, and high cholesterol—increase the risk of both AD and vascular dementia.
- Strokes or other blood vessel damage in the brain appear to increase the risk that plaques and tangles will cause AD.
- Dietary fatty acids are associated with the development of AD, although probably only in people with APOE-4. This may be because higher consumption of fats increases cholesterol levels, which may lead to atherosclerosis in people with APOE-4. Atherosclerosis affecting blood vessels in the brain is an independent risk factor for AD.

Genetic testing

Genetic testing is available for early-onset AD genes and *APOE*. Most experts do not recommend *APOE* gene testing. People with APOE-4 do not necessarily develop AD, and people without APOE-4 may develop the disease. Furthermore, there is no preventive treatment for AD. In some cases, genetic testing for early-onset AD may be appropriate. For example, early diagnosis can lead to advanced planning and help to rule out other causes for symptoms.

Demographics

AD is the most common of all degenerative brain disorders. As of 2021, more than 6 million Americans were living with AD—nearly three-quarters of them are aged 75 and older. Deaths from AD more than doubled between 2000 and 2019. If current trends in AD incidence and life expectancy continue, it is estimated that by 2050, 12.7 million Americans aged 65 and over will have AD. Although two-thirds of Americans with AD are female, this is generally attributed to their longer life expectancy. African Americans and Latino Americans have higher rates of both vascular disease and AD than other racial and ethnic groups.

The incidence of AD in other developed countries with aging populations is similar to that in the United States. The risk of AD doubles every five years after age 65, to almost 50% in people over 85. Furthermore, AD is both underdiagnosed and misdiagnosed, at least until its late stages. It is estimated that at least half of affected people are unaware of their disease.

Signs and symptoms

Memory loss and other AD symptoms progress at different rates in different people. Some people may be unaware of their memory loss, a condition referred to as anosognosia. Others are keenly aware of their memory

KEY TERMS

Activities of daily living (ADL)—The skills and practices necessary for functioning in daily life and for participating in one's environment; progressively lost with Alzheimer's disease.

Allele—Any of the alternative versions of a gene that are present in the population.

Amyloid precursor protein (APP)—A protein that forms beta-amyloid in the brain when it is not correctly broken down; mutations in the APP gene can cause early-onset familial Alzheimer's disease.

Apolipoprotein E (APOE)—A protein that transports cholesterol and helps remove it from the bloodstream; the gene encoding one form of this protein, APOE-4, is associated with an increased risk of late-onset Alzheimer's disease.

Atherosclerosis—Thickening and hardening of the inner layer of the arteries due to the accumulation of plaque; a risk factor for Alzheimer's disease.

Autosomal dominant—A gene located on a chromosome other than the X or Y sex chromosomes that is expressed (translated into protein) in preference over a second copy of the same gene.

Beta-amyloid plaques—Senile plaques; dead or dying nerve cells and cell debris surrounding deposits of beta-amyloid protein in the brain; excess plaques are diagnostic of Alzheimer's disease.

Cholinesterase inhibitors—Drugs that may slow the progression of Alzheimer's disease by inhibiting the enzymes that break down the neurotransmitter acetylcholine.

Computed topography (CT)—Scans that use x rays and a computer to form detailed images of a part of the body such as the brain.

Dementia—A group of symptoms associated with chronic progressive impairment of memory, reasoning ability, cognitive functioning, personality

changes, deterioration in personal grooming, and disorientation.

Down syndrome—A genetic disorder characterized by an extra chromosome 21 (trisomy 21), mental retardation, and early-onset Alzheimer's disease.

Early-onset AD—Alzheimer's disease that develops between the ages of 30 and 60.

Familial—An inherited disease affecting multiple family members.

Late-onset AD—Alzheimer's disease that develops after age 65.

Magnetic resonance imaging (MRI)—An imaging technique that uses electromagnetic radiation and a computer to obtain detailed images of soft tissues such as the brain.

Neurofibrillary tangles—Accumulations of twisted tau protein fragments inside nerve cells in the brain that are diagnostic of Alzheimer's disease.

Neuron—Nerve cell.

Neurotransmitters—Chemicals that carry nerve impulses from one nerve cell to another; Alzheimer's disease causes a drop in the production of several important neurotransmitters.

Positron emission tomography; PET—A type of medical imaging that displays the metabolic activity of organs such as the brain.

Presenilin (PS-1 or PS-2)—Proteins involved in processing amyloid precursor protein; mutations in the genes encoding these proteins can cause early-onset familial Alzheimer's disease.

Single photon emission computed tomography; SPECT—An imaging technique for mapping brain function.

Tau—A protein involved in maintaining the internal structure of nerve cells; tau is damaged in Alzheimer's disease and forms neurofibrillary tangles.

loss and may become anxious and frustrated, which are common early-phase manifestations of AD. Eventually, memory loss starts to interfere with daily activities. Patients may also begin to experience disorientation and become confused by changes in their environment.

During the middle phase of AD, patients can easily become confused. Language difficulties develop, and patients experience problems with comprehension, remembering common names, or performing simple

mathematical calculations. Speech may not flow smoothly. Tasks such as dressing and preparing meals become difficult. However, some patients are able to continue routine behaviors and engage in generalized conversation during this phase. A small number of patients experience vision problems, but these are frequently denied and only confirmed after death when an autopsy indicates destruction of visual processing areas in the brain.

Late-stage AD patients require constant supervision. Those who can rise from bed may wander aimlessly and must be monitored at night, because sleeping patterns can become altered. However, muscle stiffening may make walking difficult. Patients are often unable to reason or demonstrate appropriate judgment. They may become uninhibited and confrontational. They may experience delusions—false beliefs despite ample evidence to the contrary—or hallucinations and may not recognize family members.

In the final stage of AD, patients need assistance with the simplest activities of daily living (ADL) such as feeding and dressing. A majority of patients are bedridden. Many are unable to talk and have lost bladder and bowel control. Abnormal jerking movements may occur, often precipitated by noise or touching. Reflexes are frequently exaggerated. Some patients experience whole-body contractions called generalized seizures.

Diagnosis

Although skilled physicians can diagnose probable AD with 90% accuracy, a definitive diagnosis is only possible by examination of brain tissue after death. Beta-amyloid plaques and intraneuronal neurofibrillary tangles normally occur with age but are greatly increased in AD. The pattern of increase is similar regardless of whether the AD is sporadic, familial early-onset, familial late-onset, or Down syndrome-related. In addition, the further the disease has progressed, the smaller the brain at death.

Despite the difficulties of definitive diagnosis, early and accurate diagnosis is important for developing strategies for managing symptoms. Additionally, helping patients and their families plan for treatment, long-term care, and financial concerns should be conducted while the patient can still be involved in decision-making. A diagnosis of AD also may help family members avoid unnecessary anger and feelings of helplessness when dealing with the progression of the disease.

Diagnosis is based on clinical findings of unexplained slowly progressing dementia when other causes have been ruled out. An accurate medical history is essential, including a family history of AD and ages of onset. Although neuroimaging alone cannot diagnose AD, positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), or computed topography (CT) can reveal gross cerebral cortex atrophy (structural changes and shrinkage in the brain). The earliest changes in brain structure can be seen with PET scans. PET and SPECT scans can evaluate patterns of glucose (sugar) metabolism in the brain to differentiate patterns characteristic of AD

from those associated with vascular dementia and Pick's disease. PET scans are more precise than SPECT scans but are more expensive. MRI and CT scans are most useful in the early phase for excluding other brain abnormalities that may be causing dementia. As AD progresses, MRI and CT scans can show changes that indicate brain cell death. MRI is often performed on patients who are having problems with balance or gait and can detect diffuse atrophy in the cerebrum. Along with imaging studies, examination of cerebrospinal fluid has been used to confirm the diagnosis of AD.

In 2020, researchers reported accurate detection of amyloid and tau in the brain using a simple blood test. The test, which detects the presence of phosphorylated tau protein (p-tau181), a hallmark of AD, could be used to predict future AD, even in people without any symptoms at the time of the test. The affordable blood test also could help physicians monitor patients' responses to treatment to slow the progress of the disease.

Treatment and management

Although there is no cure for AD, early diagnosis and prompt intervention can slow its progression and enable patients to function independently for a longer period. Healthcare professionals usually assess a patient's ADL to determine the type of care that is needed. The mainstay of treatment is the establishment of daily routines, good nursing care and/or homecare strategies, and providing physical and emotional support. In the initial stages, counseling by a psychologist or an AD support group is recommended. The home environment must be made as safe as possible, and patients should be closely monitored to determine when they are no longer able to drive safely. Because disorientation is common, it is important to maintain a stable, familiar environment. Illnesses, such as urinary or respiratory infections, must be properly diagnosed and treated. Nutritional intake must be monitored, since patients will eventually become incapable of maintaining an adequate diet, and advancing age itself results in decreased appetite. Neurological and behavioral aspects of AD—including anxiety, agitation, defiant behavior, insomnia, hallucinations, and seizures—are treated on an as-needed basis.

Drugs

Medications may delay some AD symptoms and improve quality of life. Cholinesterase inhibitors—galantamine, rivastigmine, and donepezil—are prescribed for mild-to-moderate AD and may delay some symptoms or prevent them from worsening for a limited time. They may also help control some behavioral symptoms. Acetylcholine is a neurotransmitter that is important for memory and thinking. Cholinesterase inhibitors increase

QUESTIONS TO ASK YOUR DOCTOR

- Should I have genetic testing for Alzheimer's disease risk genes?
- Should my family members undergo genetic testing?
- Are there other tests for Alzheimer's disease?
- What form of Alzheimer's disease do I have?
- Are there treatments to slow the progression of Alzheimer's disease?

the amount of acetylcholine in the brain by preventing its breakdown. As AD progresses, the brain produces less and less acetylcholine, and the drugs become ineffective. Memantine is an N-methyl D-aspartate (NMDA) antagonist that lowers the amount of glutamate in the brain, since excess glutamate can cause brain cell death. Memantine is used to delay the progression of some symptoms of moderate-to-severe AD. It may help patients maintain some ADL, such as toileting, for a bit longer. However, all of these drugs are ineffective in many patients.

As of 2021 there were more than 1,700 active clinical trials of novel diagnostics and treatments for AD. Trials range from drugs targeting the beta amyloid protein and specific neurotransmitters to the use of transcranial ultrasound stimulation to relieve symptoms to studies assessing the effects of exercise, therapeutic diets, and caffeine on cognition.

In June 2021, the U.S. Food and Drug Administration (FDA) approved the drug aducanumab for the treatment of AD, after its own advisory panel had advised against approving the drug because it had found insufficient evidence of the drug's effectiveness. Aducanumab, an anti-amyloid-beta human monoclonal antibody, targets beta-amyloid and is intended to slow the progress of AD. Because it was fast-tracked for approval, Biogen, the drug's manufacturer, must conduct an additional randomized, controlled clinical trial to confirm Aducanumab's benefit. In addition to the controversy about its efficacy, the drug's price tag, \$56,000 per year, raises ethical questions about which patients will have access to it.

Medications can be prescribed to manage behavioral and psychiatric symptoms of AD that can be very stressful for caregivers. However, AD patients are more susceptible to the side effects of medications, especially psychoactive drugs, and they are usually given lower doses. Physicians often recommend first trying to reduce behavioral symptoms with changes to the patient's

environment. Drugs are usually prescribed for specific symptoms:

- typical antipsychotics—usually haloperidol, risperidone, olanzapine, or quetiapine—for anxiety, aggression, delusions, and hallucinations
- short-term anti-anxiety drugs—usually lorazepam or buspirone—for agitation
- a selective serotonin reuptake inhibitor (SSRI)—such as citalopram or sertraline at half the usual adult dosage—for depression, which is common in early-stage AD
- acetaminophen or very-low-dose codeine for pain

Prognosis

There is no cure for AD, and once symptoms develop patients do not recover. Although there is considerable variation in the rate of disease progression, symptoms continue to worsen, usually over a period of years. The goal is to maintain cognitive and physical functioning for as long as possible. Eventually, loss of brain cells and brain damage result in the impairment of autonomic body functions, the failure of various organ systems, coma, and death. Most AD patients die within eight to ten years of diagnosis, although survival can be as short as one year or as long as 20 years. The life expectancy of AD patients is increasing, because the disease is generally being diagnosed at an earlier stage.

Infection is the most common direct cause of death in AD patients. People with AD are often in poor health and may be malnourished, which puts them at increased risk for life-threatening infections such as pneumonia. They are also susceptible to other chronic conditions and diseases. The consequences of cancer, stroke, and heart disease can be more severe in patients with AD than in otherwise healthy people.

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ORGANIZATIONS

Alzheimer's Association, 225 North Michigan Avenue, Floor 17, Chicago, IL 60601-7633, (312) 335-8700, (800) 272-3900, (866) 699-1246, info@alz.org, <http://www.alz.org>

National Institute of Neurological Disorders and Stroke, NIH Neurological Institute, P.O. Box 5801, Bethesda, MD 20824, (301) 496-5751, (800) 496-5751, <http://www.ninds.nih.gov>

National Institute on Aging NIA Information Center, 31 Center Drive, MSC 2292, Bethesda, MD 20892, (800) 222-2225, niaic@nia.nih.gov, <http://www.nia.nih.gov>

Margaret Alic, PhD

Revised by Barbara Wexler, MPH

Ambiguous genitalia

Definition

Ambiguous genitalia is a congenital anomaly in which the genital organs do not appear to be male or female.

Description

Ambiguous genitalia, also called indeterminate sex and intersexuality, is a condition present at birth in which an individual has what appears to be both male and female external sex organs. This diagnosis is usually preliminary, based on an initial physical examination. After further evaluation and diagnostic procedures, specific genital anomalies are usually diagnosed and the underlying syndrome or condition that caused them identified.

When the genitals are abnormal, a genetic screening is usually performed to determine the genetic sex of the infant and to rule out chromosomal abnormalities.

In a genetic female with ambiguous genitalia, the clitoris may be enlarged, having the appearance of a small penis; the labia may be fused, resembling a scrotum; and the opening to the urinary tract may be located anywhere along the clitoris.

In a genetic male with ambiguous genitalia, the penis may be small, measuring less than .78 in. (2 cm); it can be mistaken for an enlarged clitoris. The clitoris often appears enlarged in newborns. The testicles may be undescended, a condition in which they remain inside the body, and they may have a groove or cleft resembling labia. The urinary tract opening may be located anywhere from the tip of the penis to any point along the underside, an anomaly known as hypospadias.

Ambiguous genitalia is not a medically threatening anomaly, but it can be an extremely emotional issue for parents. Often parents must decide in which gender the child will be raised. This is a complex and difficult decision. There are healthcare professionals who can help

inform and support parents. Counselors, doctors, and surgeons should be consulted before this decision is made.

The assignment of gender is not always based solely on the genetic sex of the child. When surgical treatment is necessary, parents may choose to raise a genetic male as a female because it is easier to surgically create functional female genitalia than male genitalia.

Children with ambiguous genitalia generally have one of the following conditions that cause the external genitalia to be abnormal:

- **Congenital adrenal hyperplasia:** This is the most common cause of ambiguous genitalia in infants. It is a condition affecting only females in which the fetus cannot process an enzyme called 21-hydroxylase, causing an inability to process steroids in the body. It is characterized by a genetic female with internal female sex organs and ambiguous or masculine external genitalia.
- **True hermaphroditism:** In this extremely rare condition, an individual has both ovarian and testicular tissue, the internal sex organs of both genders, external genitalia that are ambiguous or of both genders, and abnormalities of the X or Y chromosome.
- **Pseudohermaphroditism:** In this condition, the individual has ambiguous external genitalia, but the internal sex organs of only one gender.
- **Gonadal dysgenesis:** In this condition, an individual has the internal sex organs of a female, external genitalia that have characteristics of both genders but are predominantly female, abnormalities of the X or Y chromosome, and poorly developed ovaries or testicles.
- **Klinefelter syndrome:** This is a chromosomal abnormality in which males have an extra X chromosome. It is characterized by small testicles, infertility, and, in some cases, intellectual disability.

Genetic profile

The development of normal genitalia is a complex sequential process, beginning with the information stored on the X and Y chromosomes. Gonadal development in the fetus is first regulated by genetic information found on the short arm of the Y chromosome. Testis-determining factor (TDF) is a genetic sequence on the 11.3 sub-band of the Y chromosome. In the presence of TDF, testes develop. If TDF is absent, either because of a mutation of the Y chromosome or because the fetus is a female and therefore has no Y chromosome, then ovaries develop.

Testicular tissue produces two hormones essential for the development of normal male external genitalia: testosterone and müllerian-inhibiting substance (MIS). If

these hormones are present, the internal male sex organs develop. These hormones work in two ways. Testosterone promotes development of male genitalia, both external and internal, and MIS prevents the development of female internal sex organs. In the absence of these two hormones, female genitalia develop.

Until these hormones are produced, all external fetal genitalia are identical and resemble female genitalia. In males, around week eight of fetal development, testosterone and another hormone, dihydrotestosterone (DHT), cause the external sex organs to become those of a normal male.

Ambiguous genitalia as a condition is caused by an interruption in some part of this process. Such interruptions may be caused by genetic mutations; exposure to substances in utero, such as steroids; or, in very rare cases, maternal endocrine abnormalities.

The exact genetic or metabolic cause of ambiguous genitalia is determined by the underlying condition that leads to the anomaly. The following are the most common syndromes causing ambiguous genitalia:

- **Congenital adrenal hyperplasia,** the most common cause of abnormal external genital formation, is a defect in the production of the 21-hydroxylation enzyme. This is an autosomal recessive trait thought to be linked to the human leukocyte antigen (HLA) locus on chromosome 6, or more recently to Cytochrome P450 oxidoreductase deficiency.
- **True hermaphroditism** is extremely rare and involves development of both male and female internal and external genitalia. The most common karyotype of an individual with this condition is 46, XX. Researchers suspect that mosaicism is present and that a translocation of one antigen from a Y chromosome to one X chromosome or to an autosome may explain the development of male sex organs. True hermaphroditism does occur in individuals with a 46, XY karyotype. Explaining the development of ovarian tissue in this individual is difficult since two X chromosomes must be present for this to occur. Researchers theorize that there may be an undetected XX cell line within these individuals.
- **Pseudohermaphroditism** is generally caused by a failure in the production or absorption of the hormones testosterone and DHT. There are several different types of this condition, but they all appear to be passed on to the individual via either X-linked or autosomal recessive transmission. The anomalies are caused by a failure to produce sufficient levels of testosterone or a deficiency of enzymes, namely 5-alpha-reductase, necessary for DHT production.

- Individuals with gonadal dysgenesis have an abnormality of the sex chromosomes. Karyotypes often seen in these individuals are 46, XO/XY mosaicism and 46, XO.

Demographics

Ambiguous genitalia is a very rare condition. Researchers estimate that the most common cause, congenital adrenal hyperplasia, may occur in 1 of every 15,000 live births worldwide. Other conditions that affect the formation of external genitalia are even rarer.

Signs and symptoms

Primarily, ambiguous genitalia is a physical condition characterized by an abnormal appearance of the external genitals; however, the internal sex organs are typically malformed as well. There may be partially formed testes, ovaries, or both, or a complete absence of internal sex organs. Typically, individuals with ambiguous genitalia are infertile.

In some cases of pseudohermaphroditism, the genitalia may appear to be slightly abnormal but female at birth, but at puberty, the genitals may become more masculine as testosterone levels rise. What appeared to be an enlarged clitoris may develop into a penis of up to 2.7 in. (7 cm) in length.

The long-term health risks of this condition include an increased risk of tumors. Abnormal testicular tissue is vulnerable to tumor formation. As many as 40% of genetic males with ambiguous genitalia develop tumors within this tissue by the time they reach the age of 50. For this reason, regular screening is important.

Diagnosis

Ambiguous genitalia is usually diagnosed initially during a newborn's physical exam or during subsequent well-baby check-ups. Once it is suspected that the infant has abnormal genitalia, diagnostic tests may be performed to identify the child's genetic gender; the presence of a chromosomal abnormality; the presence, absence, and type of internal sex organs; and the potential for production of sex hormones.

Diagnostic tests that may be performed include the following:

- Chromosomal analysis to determine which sex chromosomes are present and if there are any abnormalities.
- Abdominal ultrasound to assess internal sex organs, if present, and to view the adrenal gland that is enlarged in females with congenital adrenal hyperplasia.
- Tests to assess the levels of male and female hormones present and the child's ability to process them; to determine if the infant can process enzymes; and to

KEY TERMS

Ambiguous—Unclear or open to more than one interpretation.

Autosome—One of the 22 chromosomes that are not involved in determining gender (chromosomes 1 through 22 and not the X or Y chromosome).

Clitoris—A small mass of erectile tissue in the female genitalia.

Congenital anomaly—An abnormality that is present at birth.

Genetic sex—The gender determined by the sex chromosomes. XX is female; XY is male.

Genitalia—The organs of reproduction.

Hypospadias—A birth defect in which the opening to the urinary tract, called the urethra, is located away from the tip of the penis.

Infertile—Incapable of reproduction.

Karyotype—A photographic representation of the full set of chromosomes numbered and arranged in pairs.

Labia—The two parts of the vulva (the external female genitalia).

Mosaicism—A condition in which an individual's cells are not all genetically identical.

Recessive—A genetic trait that is expressed only when present on both members of a pair of genes, one inherited from each parent.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosomal material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

X-linked—A genetic trait that is carried on the X chromosome.

screen for other metabolic conditions that may accompany ambiguous genitalia.

Treatment and management

Treatment of ambiguous genitalia depends on the extent of the abnormalities present, the underlying cause, and associated conditions. Treatment options include hormone replacement therapy (HRT) and surgical correction.

QUESTIONS TO ASK YOUR DOCTOR

- Will my child be able to have children of his or her own?
- Will my child have later psychological problems, particularly in sexual preference or gender identity?
- How many surgeries will my child need?

In some cases, gender assignment may be necessary. This can be a difficult and emotional decision for parents. Complicating the situation is the fact that when surgery is required to reconstruct external genitalia, the genetic sex of the child may not be the primary determining factor. It is far more difficult for surgeons to create functional male genitalia than female. For many years, it was thought that, in children for whom gender assignment surgery was considered the best treatment, a gender assignment should be made in the first few days of life. It was believed that environment or the influence of being raised as a girl or boy was enough to ensure gender identity. Recent data about individuals who were “assigned” a gender different from their genetic gender contradict this theory. Some individuals who were assigned a gender different from their genetic gender as infants and who were raised as the reassigned gender chose to assume the gender identity of their genetic gender as adults. Currently, many doctors believe that gender assignment involving surgical reconstruction of the external genitalia should be delayed until the individual has an established gender identity and can be involved in the decision.

Other factors that must be considered are issues of fertility, the ability of the internal sex organs to produce gender-appropriate sex hormones, the effects of sex hormone exposure on the fetus while in the womb, and the risk of additional health problems that may develop later in life either from HRT or internal sex organs.

Prognosis

If gender assignment is successful, the prognosis for children diagnosed with ambiguous genitalia is excellent. Depending on the underlying diagnosis and associated conditions, some additional medical management may be necessary. In children with congenital adrenal hyperplasia, steroid treatment is necessary for survival. Despite the complications from long-term steroid use, if the condition is properly diagnosed and treated, children with congenital adrenal hyperplasia can have healthy and normal lives.

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ORGANIZATIONS

- Hypospadias & Epispadias Association, P.O. Box 1617, Kyle, TX 10025, <http://heainfo.org>
- National Adrenal Diseases Foundation, P.O. Box 566, Lake Zurich, IL 60047, <http://www.nadf.us>
- Urology Care Foundation, 1000 Corporate Boulevard, Linthicum, MD 21090, (410) 689-3700 or (800) 828-7866, info@urologyhealth.org, <http://www.urologyhealth.org>

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Amelia

Definition

Amelia is an extremely rare birth defect marked by the absence of one or more limbs. The term may be modified to indicate the number of legs or arms missing at birth, such as tetra-amelia for the absence of all four limbs. A related term is meromelia, which is the partial

absence of a limb or limbs. Several older terms are no longer in use in international nomenclature because of their imprecision: phocomelia, peromelia, dysmelia, ectromelia, and hemimelia.

Description

The complete absence of an arm or leg in amelia occurs when the limb formation process is either prevented or interrupted very early in the developing embryo: between 24 and 36 days following fertilization. Nearly 25% of all congenital limb defects are amelia. A single limb is involved about 60% of the time, and symmetrical amelia is uncommon. The likelihood for upper versus lower limb absence varies with the syndrome.

Amelia may be present as an isolated defect, but more than 50% of the time it is associated with major malformations in other organ systems. The malformations most frequently seen with amelia include cleft lip and/or palate, body wall defects, malformed head, and defects of the neural tube, kidneys and diaphragm. Facial clefts may be accompanied by other facial anomalies such as abnormally small jaw, and missing ears or nose. The body wall defects allow internal organs to protrude through the abdomen. Head malformations may be minor to severe with a near absence of the brain. The diaphragm may be herniated or absent, and one or both kidneys may be small or absent.

Other abnormalities associated with amelia include severe defects of the lungs, vertebrae, heart, internal and external genital system, and anus. There is usually a severe growth deficiency, both before and after birth, and mental retardation may be present in survivors. Benign facial tumors made up of clusters of blood vessels (hemangiomas) may be present.

Amelia was traditionally thought to be a sporadic anomaly with little risk of recurrence, or evidence of genetic origins. However, an estimated 20% of amelia cases can now be traced to probable genetic causes. These genetic conditions may be due to recessive or dominant mutations, or involve chromosomal aberrations where entire sections of chromosomes are deleted, duplicated or exchanged. The best defined of these genetic diseases is known as Roberts SC phocomelia or, pseudothalidomide syndrome, caused by an autosomal recessive mutation of unknown location. There is a great variability of expression of the disease, even within families. Classic signs of Roberts SC phocomelia include symmetrical defects of all four limbs including amelia, severe growth deficiency, head and face (craniofacial) abnormalities such as small head and cleft lip or palate, also sparse, silvery blond hair, and facial hemangiomas.

A very small group of genetically based amelia cases is referred to as “autosomal recessive tetra-amelia” which consists of an absence of all four limbs, with small or absent lungs, cleft lip or palate, malformed head and other anomalies. A similar “X-linked tetra-amelia” is highly lethal to the fetus and involves the same set of abnormalities. The abnormal gene for X-linked tetra-amelia is assumed to be located on the X chromosome. Very few cases have been documented for either of these inherited conditions but the defective gene seems to be more prevalent in Arab populations of the Middle East or in small isolated cultures where consanguineous relationships (intermarriage within extended families) is more common. There is disagreement as to whether these conditions represent new syndromes or are severe cases of Roberts SC phocomelia.

Amelia is associated with various other genetic syndromes. It is seen in the autosomal recessive Baller-Gerold syndrome and Holt-Oram syndrome, an autosomal dominant condition that sometimes involves amelia. It has been proposed that many of the new, isolated cases of amelia are due to autosomal dominant mutations where only one copy of an abnormal gene on a non-sex chromosome is powerful enough to cause amelia to be displayed. Absent limbs have also been seen in chromosomal aberrations such as trisomy 8 (three copies of chromosome 8) and a deletion of region 7q22 found on the long arm of chromosome 7.

Sporadic amelia may be the end result of various types of disturbances of limb development in the embryo. These disturbances can be vascular, mechanical, due to teratogens (substances that can cause birth defects) or accompany other disease processes such as diabetes. An example of vascular disturbance would be hemorrhage in the embryo causing lack of blood and oxygen flow to surrounding tissue. The type and number of resulting defects would depend on the location of the hemorrhage and the point of embryo development when the bleed took place. Defects in limbs and the body wall tend to result from this type of disturbance.

Mechanical disruption can be seen following rupture of the amnion (the thin but tough membrane surrounding the embryo) due to infection, direct trauma such as attempted abortion or removal of IUD, or familial predisposition to rupture. Strands of the collapsed amnion and adhesions (fibrous bands, which abnormally connect tissue surfaces) may entangle and amputate developing limbs and cause a variety of other defects including facial clefts.

Various teratogens are well-established causes of amelia. A well-documented historic instance was due to thalidomide use by pregnant women from 1958 to 1963.

Thalidomide was used as a sedative and anti-nausea drug but was found to cause a wide array of limb deficiencies, including amelia. It is estimated to have caused 5,800 cases of malformed fetuses, mostly in Europe, but also in North America and wherever it was available worldwide. The mechanism by which thalidomide causes birth defects is still not known but may involve disruption of nerve processes. Although thalidomide is again in use today to treat certain cancers, infections and arthritis, it should not be used by women of childbearing age.

Alcohol (ethanol) consumption by pregnant women, especially in the first trimester, has been documented by several surveys to cause limb deformities. The abnormalities range from frequent, minor defects such as shortened fingers to the much rarer amelia. It is hypothesized that alcohol interrupts the blood supply to the developing limb resulting in malformation or non-growth. Additional teratogens known to cause amelia include methotrexate, other chemotherapeutic agents and potent vasoconstrictive drugs such as epinephrine and ergotamine.

Maternal diabetes mellitus (non-gestational) has long been associated with congenital anomalies, rarely including amelia. There is a two to threefold risk for congenital abnormalities in children of diabetic mothers and limb defects of various types occur in about one percent of infants of these mothers. It is thought that either abnormal maternal carbohydrate metabolism, or vascular disease resulting in decreased oxygen flow to the fetus, might play a role in causing malformations.

Genetic profile

Amelia is generally considered to be sporadic with scattered cases occurring infrequently. These rare events are presumably influenced by environmental factors, such as teratogenic drugs, maternal factors such as diabetes mellitus, and vascular accidents in the uterus. The role of genetics in causing this condition is still undetermined but two large epidemiological studies estimate that nearly 20% of amelia cases are of genetic origin. Mutations in more than one gene with different modes of transmission can lead to this severe limb deficiency.

Recurrence of amelia within families is the exception. When this occurs, it is most often associated with other malformations in autosomally recessive syndromes such as Roberts SC phocomelia, autosomal recessive amelia and X-linked amelia. Roberts SC phocomelia has a clearly identifiable genetic abnormality that can be seen during chromosome analysis. The abnormality is called either premature centromeric separation (PCS) or heterochromatin repulsion (HR). The darkly staining heterochromatin of the chromosome can be seen puffing and

KEY TERMS

Amnion—Thin, tough membrane surrounding the embryo and containing the amniotic fluid.

Autosomal dominant mutation—An abnormal gene on one of the 22 pairs of non-sex chromosomes that will display the defect when only one copy is inherited.

Autosomal recessive mutation—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Consanguineous—Sharing a common bloodline or ancestor.

Craniofacial—Relating to or involving both the head and the face.

Hemangioma—Benign tumor made up of clusters of newly formed blood vessels.

Homeotic genes—Developmental control genes active in the embryo.

Homozygous—Having two identical copies of a gene or chromosome.

Teratogen—Any drug, chemical, maternal disease, or exposure that can cause physical or functional defects in an exposed embryo or fetus.

X-linked mutation—An abnormal gene transmitted on the X chromosome.

splitting. The PCS test is positive in almost 80% of patients with Roberts SC phocomelia.

Demographics

The rarity of amelia makes the study of it on a population level speculative. A few large-scale studies pooling decades of information from malformation registries in several countries do provide preliminary data. Amelia has an incidence of 11–15 cases per million live births and 790 cases per million stillbirths. The condition is probably under reported due to lack of documentation of some miscarriages, stillbirths, and neonatal deaths.

There is no significant difference between number of males and females affected except in the select, extremely rare cases of X-linked amelia, which are all male. Only men would be affected, since the abnormal gene is inherited on the X chromosome and men only receive one copy of an X chromosome. Since females inherit two copies of the X chromosome, the normal copy of the gene on the second X chromosome can usually mask

the more severe complications that would result if only the abnormal gene was expressed.

The disorder occurs worldwide and there are no geographic clusters except for two. Amelia resulting from the use of thalidomide occurred primarily in Europe and other areas where the drug was available. Autosomal recessive and X-linked amelia has mostly occurred in Arabic and Turkish families. This suggests ethnic differences for an abnormal recessive gene but is based on less than 20 cases. Such a recessive gene is likely to be homozygous (meaning two copies of the abnormal gene need to be inherited for amelia to result), and thus expressed in malformation more often in any culture that tends to be isolated and has more intermarriage from a limited gene pool.

Signs and symptoms

Prior to clinical observation of absent limbs, certain signs in the pregnant mother may indicate a greater likelihood of amelia. Abnormal vaginal bleeding, diabetes mellitus, and toxemia (disturbed metabolism during pregnancy characterized by high blood pressure, swelling and protein in the urine) are all associated with amelia in the fetus. Alpha fetoprotein is a protein normally produced by the liver of the fetus which then circulates in the mother's blood. An increased alpha fetoprotein in the maternal blood may indicate neural tube defects that can accompany limb defects. Besides seeing missing limbs by ultrasound, signs in the fetus accompanying amelia include breech and other non-cephalic presentations at birth (where the baby is not in the normal head-first, face-down delivery position), an increased frequency of only a single artery in the umbilical cord, low placental weight and extremely low birth weight, not accounted for by the lack of limbs. The average birth weight for an infant with amelia is less than the third percentile for its age.

Diagnosis

Detection of an absent limb is generally simple. Clinical observation of the missing limb is either made at birth or prenatally by ultrasonography. However, more than 50% of amelia cases are accompanied by malformations of other organ systems, and in these cases, determination of a specific syndrome can be difficult. Defects overlap greatly between conditions. A family history including a pedigree chart to map other affected family members can be very helpful in detecting genetic causes. A prenatal history should include determination of maternal exposure to alcohol, thalidomide and other teratogenic drugs. Maternal diabetes mellitus should be considered a risk factor for congenital abnormalities.

QUESTIONS TO ASK YOUR DOCTOR

- What are my chances of having another baby with amelia?
- How can I reduce the risk of amelia in future pregnancies?
- What chromosome studies do you recommend?
- What are the risks of craniofacial surgery compared to the benefits?

Roberts SC phocomelia must be differentiated from other autosomal recessive or X-linked amelias. Genetic testing for PCS should be performed on cells from amniotic fluid. Darkly staining heterochromatin of the chromosome puffs out abnormally and splits in a positive test. The PCS test will be positive in nearly 80% of Roberts SC phocomelia cases but negative in the other syndromes. A positive PCS test along with some of the signs listed above, is diagnostic for Roberts SC phocomelia. Further chromosome studies should be done to detect gross chromosomal aberrations such as deletions or trisomy 8.

Treatment and management

Preventive measures to avoid serious limb defects such as amelia include avoidance of thalidomide and other teratogens in women of childbearing years, avoidance of alcohol during pregnancy and comprehensive management of diabetes mellitus throughout pregnancy. A prenatal ultrasound that detects an absence of limbs can be followed by chromosome analysis and genetic counseling to make informed decisions regarding termination.

Children with amelia can be fitted with a prosthesis to substitute for the missing limb. Surgery is often performed to repair craniofacial defects. Minimal to full time care may be needed depending on the degree of mental retardation.

Prognosis

When amelia occurs as an isolated abnormality, prognosis is good. However, when amelia is combined with multiple other defects, the prognosis is grim. Abnormalities accompanying amelia may include cleft lip and/or palate, body wall defects, malformed head, and abnormalities of the neural tube, kidneys and diaphragm. Many infants die prior to birth. 60% of newborns die within the first year, with half not surviving the first day. Mild cases of Roberts SC phocomelia are likely to survive past the

first few years and reach adulthood. Patients with more severe forms of amelia, such as severe growth deficiency and craniofacial defects, do not live past the first few months.

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ORGANIZATIONS

- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Amelogenesis imperfecta

Definition

Amelogenesis imperfecta (AI) is a genetic disorder of tooth development that occurs in at least 14 different forms. It may occur as an autosomal dominant, autosomal recessive, or X-linked disorder. The specific features of each type of the disorder vary significantly from type to type. The name of the disease comes from the fundamental problem involved, imperfect ("imperfecta") development of tooth enamel (amelogenesis). AI results in the improper development of both primary and permanent teeth.

Description

There are four categories of AI, defined by the primary symptoms associated with each. However, small, discolored, underdeveloped teeth—both primary and permanent—are characteristic of all categories. Due to

KEY TERMS

Autosomal dominant—A genetic trait that is expressed when only a single copy of a gene is present.

Autosomal recessive—A genetic trait that appears only when two copies of a mutated gene are present.

Dentin—A hard, calcareous material that covers the tooth root and, in turn, is covered by cementum and enamel.

Enamel—The hard, white coating that covers teeth. Enamel is the hardest material in the body.

X-linked—A genetic trait that is related to a gene on the X chromosome, characterized by transmission patterns that are different from those of autosomal traits.

insufficient development of the enamel, teeth are usually prone to pitting or breakage. Tooth loss, gum disease, and jaw misalignment may also occur.

Genetic profile

Some dental researchers estimate that there may be thousands of genes involved in the formation of dental enamel. Thus far, all forms of AI have been traced to mutations in just four genes, *AMELX*, *ENAM*, *MMP20*, and *KLK-4*. These mutations result in the body's failure to synthesize essential proteins required for the complex process by which adequate amounts of sufficiently strong enamel is produced, resulting in AI's characteristic features. The most abundant protein affected by gene mutations is amelogenin, whose production is controlled by the *AMELX* and *AMELY* genes (although the latter has not been implicated in mutations associated with AI). The precise role of amelogenin in enamel production is not known, although there is abundant evidence that loss of the protein results in significantly insufficient production of enamel in experimental animals and humans. Other proteins whose production is impaired by mutations are enamelin (*ENAM* gene), enamelysin (*MMP20* gene), and kallikrein 4 (*KLK-4* gene). Researchers suspect that mutations of the *AMBN* gene may be responsible for depleted quantities of the protein ameloblastin, the second most abundant protein involved in enamel synthesis.

AI may be inherited in at least four different ways, depending on the gene that has been altered. In most instances, the disorder occurs because of a mutation in the *ENAM* gene that is transmitted as an autosomal dominant trait, in which cases only a single copy of the gene is

needed to cause manifestation of the disorder. A mutation in either the *ENAM* or *MMP20* gene may also be transmitted as an autosomal recessive trait, in which cases two copies of the mutant gene are required for expression of the disorder. In about 5% of all cases, a mutation in the *AMELX* gene is transmitted as an X-linked trait. Finally, AI may result from a *de novo* (new) mutation in any one of these genes.

Demographics

Current data suggest a rather wide variability in the prevalence of AI, ranging from roughly 1 in 700 people in northern Sweden to 1 in 14,000 people in the United States. Data for prevalence in other populations are sparse.

Signs and symptoms

The 14 types of AI are grouped into four major categories, based on the primary development problem involved with enamel development:

- **Type I:** Hypoplastic AI is characterized by the production of an insufficient amount of enamel material to provide necessary protection for teeth. The disorder is transmitted as autosomal dominant, autosomal recessive, or an X-linked trait. Enamel varies from abnormally thin and smooth to normal thickness with pronounced grooves. Teeth may be insufficiently short to allow normal closure and may be colored anywhere from typically white and off-white to yellow or even brown.
- **Type II:** Hypomaturation AI occurs when enamel does not develop normally, and the tooth's structure may lack adequate amounts of crystalline material that constitutes its basic composition. The condition may also occur as autosomal dominant, autosomal recessive, or an X-linked trait. The condition is characterized by sufficient amounts of enamel that lacks normal strength, leading to frequent chipping and abrasion. Teeth may range in color from creamy white to yellowish brown and tend to be sensitive to touch and extremes in temperature.
- **Type III:** Hypocalcified AI is similar to type II AI in that it results from an inadequate development of calcium crystals that provide enamel with its typical strength. It occurs as an autosomal dominant or autosomal recessive trait. General features of the disorder are similar to those of type II AI, with frequent chipping and abrasion and color variations the dominant characteristics. Type II and type III AI are distinguished from each other on the basis of other morphological characteristics, such as contrasts between enamel and dentin.
- **Type IV:** Hypomaturation/hypoplastic/taurodontism AI is characterized by localized areas of low mineralization, resulting in the formation of pits in the teeth. The condition is transmitted only as an autosomal dominant trait. In addition to pitting, teeth tend to be foreshortened,

QUESTIONS TO ASK YOUR DOCTOR

- What kinds of treatment are available for each form of AI?
- How permanent can I expect any given treatment to be?
- At what point should I begin to consider starting treatments for AI?
- To what extent, if at all, does dental insurance cover the costs of treatments for AI?
- For each specific type of AI, which treatments are desirable, but not essential, (cosmetic) and which are essential to dental and general health?

abnormally small, and colored from milky white to yellow to brown.

Diagnosis

Diagnosis of AI is based on symptomatology of the condition, including the presence of thin, discolored, easily damaged teeth with indications of poorly developed and fragile enamel.

Treatment and management

The treatment of AI depends on the type of the disorder in question. In the case of type I AI, for example, sufficient amounts of enamel may not be present, although the strength of existing enamel may allow the installation of traditional crowns to produce teeth of adequate size. In the case of hypomineralized teeth, the enamel itself may be too weak and fragile to permit successful attachment of crowns, and tooth removal and replacement may be necessary. Series of treatments may be required for primary teeth during the period when both primary and permanent teeth are in place and again when all permanent teeth have erupted. Treatments may range in severity from relatively modest procedures to improve the appearance of the patient's mouth to extensive reconstruction needed to permit her or him to carry out normal daily procedures, such as mastication and maintaining oral hygiene. In more serious forms of AI, ancillary problems may develop that also require treatment, such as the development of gingivitis and malocclusions.

Prognosis

Treatments are generally available for all types of AI, with the result that prognosis is generally good for almost

all cases. Patients may expect improvements ranging from improved oral aesthetics to vastly improved dental structure and facility.

AI cannot be prevented, because it is a genetic disorder. It is possible to begin any one of a number of treatments, however, to prevent the condition from becoming worse and leading to other dental and general health problems. The precise treatment required depends on the type of AI a person has and its severity.

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ORGANIZATIONS

National Institute of Dental and Craniofacial Research, National Institutes of Health, 31 Center Dr., MSC 2290, Bethesda, MD 20892, (866) 232-4528, (301) 480-4098, nidcrinfo@mail.nih.gov, <http://www.nidcr.nih.gov>

David E. Newton, EdD

Amniocentesis

Definition

Amniocentesis is an optional procedure offered to women during pregnancy in order to obtain more information about a developing fetus. Women who undergo amniocentesis typically do so either to obtain reassurance

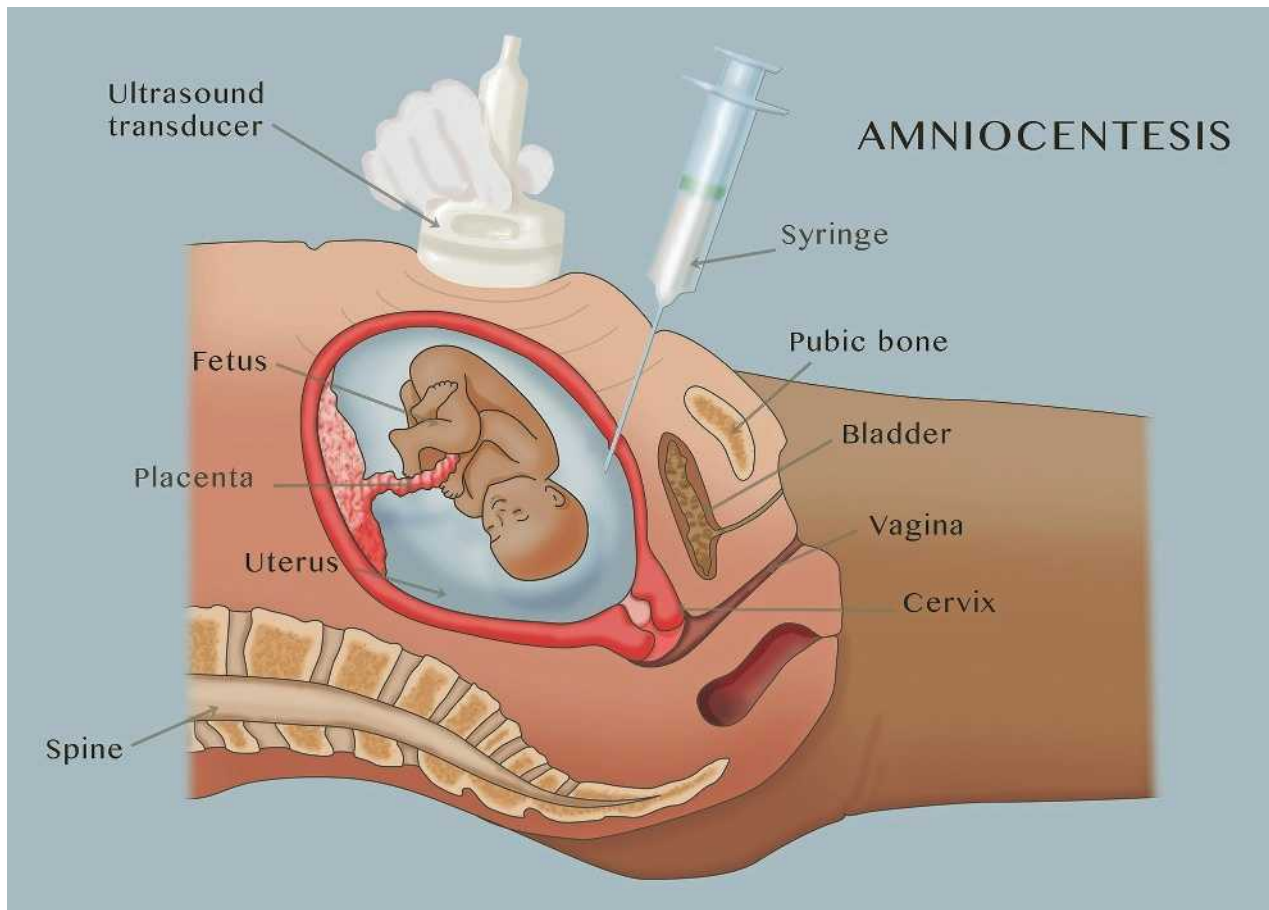
about fetal well-being or, if the results are abnormal, to plan for the remainder of their prenatal care.

Description

Amniocentesis is the most common invasive prenatal diagnosis technique offered to pregnant women. A doctor uses a thin, hollow needle to remove a small sample of amniotic fluid from around the developing baby. An ultrasound exam is usually performed at the same time to help guide the needle. The sample of amniotic fluid can be used to detect chromosomal abnormalities in a fetus, certain other types of congenital disorders, or other medical indicators. Tests done on amniotic fluid obtained by amniocentesis cannot evaluate the fetus for every potential kind of problem. The information it does provide, however, is very accurate, and it is generally considered the "gold standard" by which other prenatal diagnosis techniques are measured. The procedure is associated with a slightly increased chance of pregnancy loss.

The word "amniocentesis" is derived from the Greek words "amnion" and "kentesis," meaning "lamb" and "puncture," respectively. In order to perform the procedure, a doctor inserts a thin needle into the mother's uterus and the amniotic sac. A continuous ultrasound evaluation is typically used so that the doctor can avoid touching both the baby and the umbilical cord with the needle. The amniotic sac is made up of two membranes: the inner *amnion* and the outer *chorion*. The amnion and chorion both develop from the fertilized egg. They are initially separate but begin to fuse early in pregnancy. This fusion is usually completed by approximately the fourteenth to fifteenth week of pregnancy.

Amniocentesis is usually performed in the second trimester, usually during weeks 16 to 18 (mid-trimester). The amniotic sac holds the fetus suspended within the amniotic fluid, an almost colorless fluid that protects the fetus from harm, helps maintain a consistent temperature, and prevents the fetus, or parts of it, from becoming attached to the amnion. The amniotic fluid is produced and absorbed by the fetus throughout pregnancy. Fetal cells, primarily derived from the skin, digestive system, and urinary tract, are suspended within the fluid. A smaller number of cells from the amnion and placenta are also present. Finally, the fetus produces a number of different chemical substances that also pass into the amniotic fluid. These substances may be used, in some higher-risk pregnancies, either to assess fetal lung maturity or to determine whether the fetus has a viral infection. In the second trimester of pregnancy, one particular protein, called alpha-fetoprotein, is commonly used to screen for certain structural birth defects.



Amniocentesis (amniotic fluid test or AFT), a medical procedure in which a small amount of amniotic fluid, which contains fetal tissues, is sampled and tested for chromosomal abnormalities and fetal infections. (Monica Schroeder/Science Source)

It is possible to perform amniocentesis in a twin pregnancy. Amniocentesis in some higher-order pregnancies, such as triplets, has also been reported. In a multiple pregnancy, it is important to ensure that a separate sample of amniotic fluid is obtained from each fetus. To accomplish this, a doctor injects a small amount of harmless blue dye into the amniotic sac of the first baby after a sample has been withdrawn. The dye will temporarily tinge the fluid blue-green. A second needle is inserted into the next amniotic sac with ultrasound guidance. If the fluid withdrawn is pale yellow, a sample from the next fetus has been successfully obtained. In the case of monoamniotic (in one amniotic sac) twins or triplets, the genetic material in each fetus is identical, so only one sample needs to be taken.

Indications for amniocentesis

Amniocentesis has been considered a standard of obstetrical care since the 1970s. It is not, however, offered to all pregnant women. The American College of Obstetricians and Gynecologists (ACOG) recommends that

amniocentesis be offered to all expectant mothers aged 35 and older. This age cutoff has been selected because advancing maternal age is associated with an increasing risk of having a baby with a numerical chromosome abnormality. At age 35, this risk is approximately equivalent to the risk of pregnancy loss associated with amniocentesis.

A person normally has a total of 46 chromosomes in each cell of his or her body, with the exception of sperm or egg cells, which each have only 23. As women get older, there is an increased risk of producing an egg cell with an extra chromosome. This leads to an egg cell with 24 chromosomes rather than the normal 23. Pregnancies with an abnormal number of chromosomes are referred to as aneuploid. Aneuploidy results in a conceptus (product of conception) with either too much or too little genetic material. This, in turn, leads to abnormal development. Common effects of aneuploidy include an increased risk for pregnancy loss or, in live births, for intellectual disability and physical abnormalities.

Down syndrome is the most common form of aneuploidy in live born infants, occurring in approximately

1 in 700 births, regardless of maternal age. In women who are 35 years old, the risk of having a child with Down syndrome is higher, or roughly 1 in 385 at delivery. It is important to realize that Down syndrome is not the only chromosome abnormality that may occur. Other numerical abnormalities are possible, yielding genetic conditions that may be either more or less severe than Down syndrome. Thus, a woman is often given a risk, based solely on her age, of having a child with *any* type of chromosome abnormality. At age 35, this total risk is approximately 1 in 200. By age 40, this risk has increased to 1 in 65, and, at age 45, this risk is 1 in 20. These numbers reflect the risk at the time of delivery.

Women younger than 35 years may also have children with chromosomal or other genetic disorders. Therefore, other indications for amniocentesis or other forms of prenatal diagnosis include a family history of, or a previous child with, a known genetic condition; abnormal prenatal screening results, such as ultrasound or a blood test; or one parent with a previously identified structural chromosome rearrangement. All of these factors may make it more likely for a couple to have a child with a genetic condition.

Side effects

Women who have had an amniocentesis often describe it as uncomfortable, involving some mild pressure or pain as the needle is inserted. Fewer women describe it as extremely painful. A local anesthetic may be used to numb the upper layer of the mother's skin prior to testing. This medicine has no effect on the fetus, but it may help the mother feel more comfortable during the procedure. An experienced physician can, on average, perform amniocentesis in approximately one to two minutes.

Common complaints after amniocentesis include mild abdominal tenderness at the site of needle insertion or mild cramping. These usually go away within one or two days. More serious complications are significantly less common but include leakage of amniotic fluid, vaginal bleeding, or uterine infection. These complications are estimated to occur in fewer than 1% of pregnancies. In some women, complications after amniocentesis may lead to a miscarriage, or loss of the pregnancy. A woman's background risk of having a miscarriage, without amniocentesis, is approximately 2% to 3% in her



This doctor is using ultrasound as a guide to withdraw amniotic fluid, which is analyzed for chromosomal abnormalities. (Bork/Shutterstock)

KEY TERMS

Amnion—Thin, tough membrane surrounding the embryo and containing the amniotic fluid.

Anesthetic—A drug used to temporarily cause loss of sensation in an area of the body. An anesthetic may either be general, associated with a loss of consciousness, or local, affecting one area only without loss of consciousness. Anesthetics are administered via either inhalation or needle injection.

Chorion—The outer membrane of the amniotic sac. Chorionic villi develop from its outer surface early in pregnancy. The villi establish a physical connection with the wall of the uterus and eventually develop into the placenta.

Chromosome—A microscopic thread-like structure found within each cell of the body and consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Conceptus—The products of conception, or the union of a sperm and egg cell at fertilization.

Cystic fibrosis (CF)—A respiratory disease characterized by chronic lung disease, pancreatic insufficiency, and an average age of survival of 20 years. Cystic fibrosis is caused by mutations in a gene on chromosome 7 that encode a transmembrane receptor.

Down syndrome—A genetic condition characterized by moderate to severe intellectual disability, a characteristic facial appearance, and, in some

individuals, abnormalities of some internal organs. Down syndrome is always caused by an extra copy of chromosome 21, or three rather than the normal two chromosomes. Therefore, Down syndrome is also known as trisomy 21.

Fetus—The term used to describe a developing human infant from approximately the third month of pregnancy until delivery. The term “embryo” is used prior to the third month.

Sickle cell disease—A chronic, inherited blood disorder characterized by sickle-shaped red blood cells. It occurs primarily in people of African descent and produces symptoms including episodic pain in the joints, fever, leg ulcers, and jaundice.

Tay-Sachs disease—An inherited biochemical disease caused by lack of a specific enzyme in the body. In classical Tay-Sachs disease, previously normal children become blind and mentally handicapped, develop seizures, and decline rapidly. Death often occurs between the ages of three and five years. Tay-Sachs disease is more common among individuals of eastern European Jewish background, but it has been reported in other ethnic groups as well.

Trimester—A three-month period. Human pregnancies are normally divided into three trimesters: first (conception to week 12), second (week 13 to week 24), and third (week 25 until delivery).

Uterus—A muscular, hollow organ of the female reproductive tract. The uterus contains and nourishes the embryo and fetus from the time the fertilized egg is implanted until birth.

second trimester. When performed by an experienced physician or technician, the risk for an amniocentesis-related pregnancy loss is estimated to be an additional 0.25% to 0.50%, or roughly 1 in every 200 to 400 pregnancies.

Much attention is often paid to the physical side effects of amniocentesis. However, it is important to also emphasize some of the emotional side effects. Many of these are applicable to other forms of prenatal diagnosis.

The offer of prenatal testing is associated with increased anxiety. This appears to be true whether a woman knew that prenatal testing would be offered to her during the pregnancy or if it came about unexpectedly, as is usually the case following abnormal screening results. Women to whom genetic amniocentesis is

presented must consider the perceived benefits of testing, such as the reassurance that comes when results are normal, and compare them to the possible risks. Potential risks include not only complications after testing but also learning that the child may have a serious disability or chronic medical condition.

The nature of the child’s possible diagnosis is also important. For example, it could lead to an early death, be more subtle, and cause few outward signs of a problem, or be somewhere in between. There are few treatments available to correct the hundreds of genetic disorders so far described. Couples may consider early termination of the pregnancy if a serious abnormality is detected. The definition of “serious” is often a matter of personal opinion. A couple’s value system and family

history, including other pregnancies and their outcomes, all influence the decision regarding amniocentesis. Ideally, a woman and her partner will have discussed at least some of these issues with each other and with either the woman's doctor or a genetic counselor prior to testing. The choice to have amniocentesis depends on many factors and should remain a personal decision.

Results

Genetic testing is available on amniotic fluid obtained by amniocentesis. The most common test result is a complete analysis of the fetal chromosomes. After a sample of amniotic fluid is obtained, the genetic laboratory isolates the cells, referred to as amniocytes, from the fluid. The cells are placed into two or more containers filled with liquid nutrients, establishing different cultures in which the cells will continue to grow. The cells are cultured anywhere between one and two weeks before the actual analysis begins, in order to synchronize the growth of the cells within a culture. Chromosomes are only microscopically visible at a specific point during cell division.

Once there appear to be an adequate number of cells to study, the cultures are harvested. Harvesting prevents additional cell growth and stops the cells at whatever point they were in their division process. A careful study of the total number and structure of the chromosomes within the cells may then be performed. Typically, chromosome results are available within 7 to 14 days after amniocentesis. Results may be delayed by a slowly growing culture, which rarely reflects an abnormal result but does extend the time until final results are ready.

Many laboratories are beginning to incorporate a special technique called fluorescence in situ hybridization (FISH) into their chromosome studies. This adjunct testing provides limited information about certain chromosomes within one to two days after amniocentesis. It does not replace a complete chromosome study using amniocyte cultures. In fact, FISH results are often reported as preliminary, pending confirmation by cultured results. They can, however, be very useful, particularly when there is already a high level of suspicion of a fetal chromosome abnormality.

FISH is performed using a small sample of uncultured amniotic fluid cells. Special molecular tags for particular chromosomes are used. These tags attach themselves to the chromosome. Under specific laboratory conditions, they can be made to "light up" or fluoresce. Their signals can then be counted using a special kind of microscope. FISH is most often used to quickly identify a change in the number of chromosomes from pairs 13, 18, 21, and the two sex chromosomes, X and Y. Abnormalities of these chromosomes account for nearly 95% of all chromosomal

QUESTIONS TO ASK YOUR DOCTOR

- In my specific case, do you recommend amniocentesis?
- How many amniocentesis procedures have you performed?
- What is my risk compared with the benefits of amniocentesis in my case?
- How long will it take to receive the results?

abnormalities. Other chromosomal abnormalities will be missed, since FISH cannot identify structural rearrangements of the chromosomes or abnormalities involving other pairs. A full chromosome evaluation on cultured cells is a necessary follow-up to interphase FISH results.

A sample of amniotic fluid may be used to measure alpha-fetoprotein (AFP). AFP is a protein made by the fetal liver. It passes out of the fetus and enters both the amniotic fluid and the mother's blood. Screening for open neural tube defects, abnormal openings in the fetal head or spinal cord, or ventral wall defects (openings along the belly wall) can be done by measuring AFP during the fifteenth to twentieth weeks of pregnancy. AFP levels normally show a gradual increase during this time. An unusually high level of serum AFP does not necessarily indicate a problem with fetal development, but it is cause for some concern. A high AFP level in amniotic fluid will detect up to 98% of all openings on the fetal body that are not covered by skin. Further studies may be suggested if the AFP is high. Most initial AFP results are available within two to three days after amniocentesis.

Finally, amniotic fluid samples obtained by amniocentesis may also be used for more specialized genetic studies, such as biochemical or DNA testing. Both often require cell cultures and additional time to complete. These studies are not done on every sample. Rather, they are offered to those couples who, based on their family history or other information, are at increased risk of having a child with a single gene, or Mendelian, disorder. Hundreds of such disorders have been described. Examples include Tay-Sachs disease, cystic fibrosis, and sickle cell disease. If biochemical or DNA studies are performed, all of the results may not be ready until three to four weeks after testing, although the waiting time may be slightly different for each patient.

It is important to emphasize that normal results from tests done on amniotic fluid do not necessarily guarantee the birth of a normal infant. Each couple in the general

population faces a risk of roughly 3% to 4% of having a child with any type of congenital birth defect. Many of these will not be detected with tests done on amniotic fluid samples obtained by amniocentesis. Babies with birth defects are often born into families with no history of genetic disorders.

Chorionic villus sampling

Mid-trimester amniocentesis has been available for nearly 30 years. Chorionic villus sampling (CVS) has been available in the United States since the 1980s. CVS is usually performed between 11 and 14 weeks of pregnancy. Chorionic villi are tiny finger-like projections on the placenta that contain some fetal cells. This material can be extracted for genetic analysis between weeks 11 and 14 of pregnancy. As of 2021, the risk of miscarriage from performing chorionic villus sampling is close to the risk with amniocentesis. Chorionic villus sampling can give results earlier in pregnancy, but it cannot detect certain fetal abnormalities (such as neural tube defects) that are detectable with amniocentesis. The pros of cons of both procedures should be discussed with the woman's physician to determine which will most effectively address her concerns.

Early amniocentesis

The Canadian early and mid-trimester amniocentesis trial (CEMAT), a large multi-center randomized clinical trial of early amniocentesis in the late 1990s, was designed to examine and compare the safety and accuracy of early (EA) versus mid-trimester amniocentesis (MTA). In order to accomplish this, 4,374 pregnant women were identified and enrolled in the study. Ultrasound was performed in the first trimester to confirm the gestational age of all pregnancies. Computer randomization was used to evenly divide the women into either the EA or MTA groups. Ultimately, 1,916 women underwent EA, and 1,775 women had MTA. Follow-up was obtained on nearly all pregnancies. Two striking conclusions were reached: EA is associated with an increased incidence of clubfoot and an increased risk of procedure-related pregnancy loss.

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ORGANIZATIONS

- American College of Obstetricians and Gynecologists, P.O. Box 70620, Washington, DC 20024-9998, (202) 638-5577, (800) 673-8444, resources@acog.org, <https://www.acog.org>.

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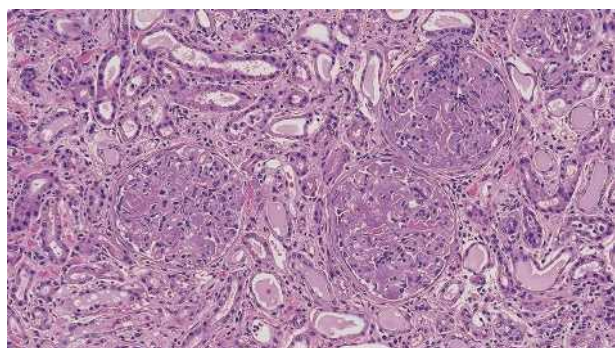
Amyloidosis

Definition

Amyloidosis is the name of a group of diseases caused by the deposition of abnormal proteins called amyloids in different tissues or organs of the body, resulting in the loss of normal function in these tissues or organs. Some physicians prefer to use the plural form "amyloidoses" to refer to these disorders because they are caused by different amyloids, they have a wide range of clinical symptoms, and they have different origins—some are hereditary, while others are acquired. All of the amyloidoses are rare disorders.

Description

The classification of the amyloidoses has undergone considerable change in recent years due to the discovery of the many different types of amyloid protein. In general, the term "amyloid" refers to misfolded proteins that form insoluble waxy fibrils in body tissues or organs. The name comes from the Greek word for starch because German pathologist Rudolf Virchow, the first person to



Amyloid deposits in the glomeruli of kidney. (Vetpathologist/Shutterstock)

identify amyloid under a microscope, mistakenly believed it was a form of starch. Until the 1970s, amyloid was thought to be a single type of protein; however, the discovery of various chemical techniques for dissolving amyloid fibrils led to the recognition that there are at least 27 different types of amyloids in humans.

Two different classification systems for the amyloidoses were used as of 2015, the older system based on clinical presentation and the newer and preferred system based on the type of amyloid involved. Some physicians still use the clinical classification system, which divides the amyloidoses into primary (occurring without any connection to another disease process), secondary (resulting from an existing disease), and familial (hereditary). This system also distinguishes between systemic amyloidoses, which affect the entire body, and localized amyloidoses, which are limited to one region of the body.

The newer system of classification categorizes the amyloidoses according to the type of amyloid that causes the disorder. Each type begins with the capital letter A for amyloid, followed by a second letter or abbreviation that identifies the type of protein in the fibrils. The three most common types of amyloidosis are AL, AA, and ATTR, or AF, amyloidosis. The third type is the most common type of amyloidosis associated with a genetic mutation.

- **AL amyloidosis:** Also known as amyloid light-chain amyloidosis, AL is a primary amyloidosis and is the most common type of systemic amyloidosis diagnosed in the United States. It develops when the antibody-producing white blood cells (called plasma cells) derived from the bone marrow form abnormal proteins made up of antibody fragments called light chains. These light chains then form amyloid deposits in such organs as the kidneys, liver, spleen, heart, digestive tract, and blood vessels. AL amyloidosis may occur together with malignancies such as multiple myeloma or lymphoma.

- **AA amyloidosis:** AA amyloidosis is a secondary amyloidosis caused by the accumulation of abnormal serum amyloid A protein, which is normally produced in the body during the acute phase of response to inflammation. It is sometimes called autoimmune amyloidosis. Patients with such long-term inflammatory disorders as Crohn's disease, rheumatoid arthritis, familial Mediterranean fever, tuberculosis, lupus, ankylosing spondylitis, and certain types of cancer are at increased risk of AA amyloidosis. The amyloid deposits in this type of amyloidosis are most likely to occur in the kidneys, liver, and spleen. More than 90% of patients with AA amyloidosis develop nephrotic syndrome, a kidney disorder.

- **ATTR (AF) amyloidosis:** Also known as familial amyloidosis or AF, ATTR is the most common form of amyloidosis associated with a genetic mutation. The gene involved is the *TTR* gene on the long arm of chromosome 18 at 18q11-q12. This gene codes for a protein found in blood serum and cerebrospinal fluid called transthyretin, which serves as a carrier of the thyroid hormone thyroxine. ATTR amyloidosis includes several types of familial amyloid polyneuropathy (FAP) formerly classified by the patients' ethnic origins. FAP is characterized by damage to the nerves in the arms and legs, carpal tunnel syndrome, cardiomyopathy, digestive disturbances, visual disturbances, and amyloid deposits in the brain stem and spinal cord. These symptoms typically appear in middle-aged or older adults. More than 100 mutations of the *TTR* gene have been identified; most of them cause ATTR amyloidosis.

Less common types of amyloidosis include the following:

- **Beta2-microglobulin amyloidosis (Abeta2m):** This is a relatively rare type of amyloidosis; it is also called dialysis-related amyloidosis because it occurs primarily in patients undergoing hemodialysis over long periods of time (usually five years or longer). Long-term treatment of kidney disorders with hemodialysis results in the buildup of a protein in blood serum called beta2-microglobulin. This protein accumulates in the patient's blood because it cannot cross the filter in the dialysis machine. It forms into amyloid fibrils that are deposited in the patient's joints.
- **Hereditary visceral (renal) amyloidoses:** These are rare forms of amyloidosis caused by mutations in three different genes on chromosomes 4, 11, and 12, respectively. They are sometimes called *Ostertag* amyloidosis after the German physician who identified the first case in 1932. These amyloidoses are grouped together as familial visceral amyloidoses. They are characterized by enlargement of the liver and spleen (hepatosplenomegaly), hypertension, edema, kidney

dysfunction, high levels of blood and protein in the urine, and generalized weakness. Unlike TTR-related hereditary amyloidosis, these familial amyloidoses are not marked by disorders in the peripheral nervous system.

- **Localized amyloidoses (ALoc):** Localized amyloidoses are a variant form of light-chain amyloidosis, except that the plasma cells that produce the abnormal proteins are found in the affected tissues rather than in the bone marrow. The amyloid deposits resemble tumors and are most commonly found in the bladder or the airway, but they may also occur in the eyes, skin, digestive tract, or breasts.

Genetic profile

Most amyloidoses are not hereditary. Those that are caused by genetic mutations are autosomal dominant in inheritance pattern, which means that only one copy of the mutated gene is required for the disorder to manifest. Men and women are equally affected. Most cases of amyloidosis associated with a genetic mutation are caused by mutations in the TTR gene on the long arm of chromosome 18. Mutations in this gene are found in most ethnic groups worldwide.

The hereditary visceral amyloidoses are caused by mutations in one of three genes: the FGA gene on the long arm of chromosome 4 at 4q31.3, the APOA1 gene on the long arm of chromosome 11 at 11q23.3, and the LYZ gene on the long arm of chromosome 12 at 12q15. The role of mutations in these genes and the formation of abnormal amyloid proteins were not well understood as of 2015.

Demographics

The amyloidoses as a group are rare disorders, affecting between 2,500 and 4,000 people in the United States each year. Most of these are patients diagnosed with AL amyloidosis. AA amyloidosis and the hereditary amyloidoses are much less common in the developed countries; however, AA amyloidosis is the most common form of the disorder in the developing world. Although the amyloidoses are thought to affect men and women equally, about 60% of the patients seen in specialized amyloid clinics are males. Most patients are between 50 and 65 years of age at the time of diagnosis. Amyloidosis is almost never seen in children, the exception being children with Crohn's disease.

Hereditary amyloidosis associated with mutations in the TTR gene occurs in about 1 in every 100,000 Caucasian persons in the United States; the rate in the African-American population is 4 in every 100,000. Transthyretin-associated amyloidosis has been reported

KEY TERMS

Amyloid—Any of a group of insoluble abnormal proteins that accumulate in body organs and tissues and interfere with their normal functioning.

Cardiomyopathy—Measurable deterioration of the heart muscle's ability to contract normally, eventually leading to heart failure.

Dyspnea—Shortness of breath or difficulty in breathing.

Goiter—An enlargement of the thyroid gland, causing tissue swelling that may be seen and/or felt in the front of the neck. It may occur in people who have overactive production of thyroid hormones (hyperthyroidism), decreased production of thyroid hormones (hypothyroidism), or normal production of thyroid hormones.

Light chains—The two small polypeptide chains found in an immunoglobulin (antibody) molecule. The other two components of the antibody are so-called heavy chains.

Macroglossia—Abnormal enlargement or thickening of the tongue.

Nephrotic syndrome—A kidney disorder characterized by high levels of protein in the urine, low levels of albumin in the blood, and edema (abnormal accumulation of fluid in the body). It may be caused by genetic mutations, infections, certain medications, or such other disorders as diabetes and cancer.

Periorbital purpura—A purplish or brownish discoloration caused by bleeding from the fragile capillaries in the skin around the eyes.

Peripheral neuropathy—Any disease of the nerves outside of the spinal cord, usually resulting in weakness and/or numbness.

Plasma cells—White blood cells that originate in the bone marrow and secrete large quantities of antibodies.

in families in Greece, Portugal, Finland, France, Germany, Sweden, Spain, Ireland, and Japan. Patients with TTR-associated amyloidosis may develop symptoms as early as 30 years of age.

Hereditary visceral amyloidosis may be more common than is usually thought; one study in the United Kingdom reported that about 5% of patients being treated for AL amyloidosis were found to have a genetic mutation associated with hereditary visceral amyloidosis.

Most families identified with this type of amyloidosis are of northern European ancestry, but the mutations have also been reported in families from northern India, Peru, Korea, and Mexico. Most of the cases reported in the United States have been identified in African American families.

Signs and symptoms

The signs and symptoms of amyloidosis are seen (with very rare exceptions) only in adults. They vary widely in body location and severity, depending on which organs or tissues are affected. The amyloidoses can be difficult to diagnose because none of the symptoms of these disorders is unique to them. Symptoms that may indicate amyloidosis are as follows:

- **Kidneys:** The kidneys are the organ most likely to be affected by AL, AA, ATTR, and hereditary visceral amyloidosis. Symptoms may include slight enlargement of the kidneys, complete shutdown of kidney function, or foamy urine (a sign of large amounts of protein in the urine).
- **Digestive system:** Constipation or diarrhea, unexplained weight loss, feeling of unusual fullness after a meal, gastrointestinal reflux disease (GERD), clay-colored stools, and unusual thickening of the tongue (macroglossia).
- **Liver:** Abnormal enlargement of the liver (hepatomegaly) and elevated levels of serum aminotransferases and alkaline phosphatase, which are biomarkers of liver injury.
- **Heart:** Abnormal EKG readings, abnormal heart rhythms, and heart failure.
- **Thyroid gland:** Unusual fatigue, low levels of thyroid hormone (hypothyroidism), and goiter.
- **Lungs:** Difficulty breathing or shortness of breath (dyspnea).
- **Nervous system:** Numbness, tingling sensations, or weakness (peripheral neuropathy) in the arms and legs; carpal tunnel syndrome in the arms.
- **Skin:** Bleeding into the skin around the eyes (periorbital purpura) leading to a “raccoon eyes” appearance.

Diagnosis

The diagnosis of the type of amyloidosis is critical, as effective treatment depends on identifying the type of amyloid responsible for the patient’s symptoms. The basic diagnosis of amyloidosis is made from a tissue biopsy, in most cases a sample of tissue taken from abdominal fat through a biopsy needle inserted into the skin over the abdomen. If the patient’s symptoms suggest amyloidosis in other organs, however, the tissue sample may be taken from those organs. The next step is staining the biopsy sample with Congo red, a dye that colors

QUESTIONS TO ASK YOUR DOCTOR

- What type of amyloidosis do I have?
- If I have a hereditary form of amyloidosis, would you recommend genetic testing for other family members?
- What treatment do you recommend?
- What is the prognosis?

amyloid protein and also causes it to look green when the slide is viewed under a microscope with polarized light.

Because AL amyloidosis is the most common type of amyloidosis in the United States, further testing is done to either confirm its identification or rule it out. The tests most commonly used are tests for free light chains in the blood serum or a bone marrow biopsy with immunochemical staining of plasma cells. The most accurate method for distinguishing among the different types of amyloid that may be causing the patient’s symptoms is laser microdissection with mass spectrometry. In this method, the laboratory technician uses a laser to dissect Congo red-stained biopsy samples that have already tested positive for amyloid. This process breaks down the sample into smaller units of amino acids called peptides. The peptides can then be analyzed by liquid chromatography-mass spectrometry.

The imaging study most often done in patients with amyloidosis is ultrasound. Sound waves are reflected differently from amyloid deposits than from normal tissue. In addition, ultrasound is useful in detecting abnormal enlargement of the patient’s internal organs.

The diagnosis of ATTR amyloidosis is suspected in persons with peripheral neuropathy or a family history of neuropathy and heart failure who are not found to have abnormal plasma cells when their bone marrow is tested. The diagnosis of ATTR or hereditary visceral amyloidosis is confirmed by molecular genetic testing.

Treatment and management

The treatment of the different types of amyloidosis varies considerably. Chemotherapy is the first line of treatment for AL amyloidosis. Patients are usually given melphalan (Alkeran) alone or in combination with dexamethasone. The goal is to eliminate the abnormal plasma cells in the bone marrow that produce the light chains that form the amyloid deposits. Another option is stem cell transplantation. Experimental treatments include two

medications developed to treat multiple myeloma: bortezomib (Velcade) and lenalidomide (Revlimid).

Treatment for AA amyloidosis requires treatment of the underlying inflammatory disease or condition. An investigational drug for this form of amyloidosis called Kiacta is presently undergoing clinical trials at Boston University's Amyloidosis Center.

The most effective treatment for ATTR is liver transplantation because the mutated transthyretin that forms the amyloid deposits is produced in the liver. An experimental drug that is being used to treat ATTR amyloidosis is tafamidis (Vyndaqel). The drug works by slowing the process of amyloid fibril formation.

Prognosis

The prognosis varies for different types of amyloidosis. Untreated AL amyloidosis has a very poor prognosis, with the median length of survival being about two years after diagnosis. Patients with severe heart disease related to AL amyloidosis have a life expectancy of only six months. The prognosis of AA amyloidosis depends on the type and severity of the underlying disease. Patients with ATTR amyloidosis have the best prognosis, living on average for ten years after diagnosis and liver transplantation.

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Amyloidosis Foundation, 7151 N. Main Street, Suite 2, Clarkston, MI 48346, (248) 922-9610, info@amyloidosis.org, <http://www.amyloidosis.org>

Amyloidosis Support Groups, 232 Orchard Drive, Wood Dale, IL 60191, (630) 350-7539 or (866) 404-7539, info@amyloidosisupport.com, <http://amyloidosisupport.org>

Boston University Amyloidosis Center, Boston University School of Medicine, 72 East Concord Street, K-503, Boston, MA 02118, (617) 358-4750, (617) 358-4735, amyloid@bmc.org, <http://www.bu.edu/amyloid>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 263-9938, <http://rarediseases.org>

Rebecca J. Frey, PhD

Amyotrophic lateral sclerosis

Definition

Amyotrophic lateral sclerosis (ALS) is a disease that breaks down tissues in the nervous system. It affects the nerves that are responsible for movement. ALS is also known as motor neuron disease. It is sometimes referred to as Lou Gehrig's disease, named after the baseball player whose career it ended.

Description

Amyotrophic lateral sclerosis is a progressive disease of the central nervous system. "A" means "no," "myo" implies muscle cells, and "trophic" refers to nourishment. The upper and lower motor neurons degenerate and die for unexplained reasons. The upper motor neurons are the nerve cells that extend from the brain to the spinal cord. The lower motor neurons are the nerve cells that extend from the spinal cord to the peripheral nerves. "Lateral" refers to the areas of the spinal cord that are affected, and "sclerosis" occurs as hard tissue replaces the previously originally healthy nerve.

The parts of the body that are not affected by ALS are not involved in the use of motor neurons. The mind remains very sharp and in control of sight, hearing, smell, touch, and taste. Bowel and bladder functions are generally not affected. Amyotrophic lateral sclerosis rarely



Degradation of motor neurons. Amyotrophic lateral sclerosis is the most common of the motor neuron diseases. Nerve degeneration and restricted production of the neurotransmitter dopamine result in deterioration of muscle tissue. This debilitating disease is characterized by rapidly progressive weakness, muscle atrophy and twitching, muscle spasticity, difficulty speaking (dysarthria), difficulty swallowing (dysphagia), and difficulty breathing (dyspnea). (Kateryna Kon/Science Source)

causes pain, yet it leaves patients dependent on the care of others during advanced stages.

ALS progresses rapidly, and paralyzed patients are usually under the intensive care of nursing facilities or loved ones, which can have a devastating psychological effect on the family members and the patient. In most cases, ALS is fatal within two to five years, although approximately 10% of those with the disorder live eight or more years.

Genetic profile

Most cases (90%) of ALS occur in people with no family history of the condition. These cases are most likely multi-factorial in cause, meaning that they are caused by primarily unknown environmental and genetic factors. Some suspected environmental causes are farming chemicals such as pesticides and insecticides, as well as mercury and manganese. An increase in ALS has been noted in Gulf War veterans as well.

Ten percent of cases of ALS are familial, although even in the same families there can be great variability in the type and severity of symptoms. Of those cases, most appear to follow an autosomal dominant pattern of inheritance, which means that an affected person has a 50% chance of passing the condition on to each child. Thirteen genes have been

identified in familial cases of ALS, although some are more common than the others. The *C9ORF72* gene is seen in 30 to 40% of familial cases. The *SOD1* gene is seen in 15 and the *FUS* and *TARDBP* genes are each seen in about 5% of familial cases.

A smaller number of cases are inherited in an autosomal recessive pattern, meaning that both parents of an affected person carry one mutated gene, which they both passed on to a child who then has two copies and is affected. Four genes have been identified in autosomal recessive cases. Some of these genes result in childhood onset of symptoms. There is also an X-linked form of ALS, which is most often carried by unaffected or mildly affected females on one of their two X chromosomes. This form of ALS can be passed on to their sons, who are then more severely affected because males have only one X chromosome. Only one gene has been identified in X-linked cases so far.

In 2021, scientists reported that the DNA of individuals with ALS in Malta, a small Mediterranean island with a relatively isolated genetic population, had no flaws in the genes that are known to contribute to a major number of ALS cases worldwide, but they *did* have flaws in other genes that caused their ALS symptoms.

There is some correlation between the genotype in familial cases and the phenotype or clinical symptoms. For instance, half of those with a mutation in the *SOD1* gene have symptoms by age 46. Half to 70% of those with mutations in the *FUS* gene have symptoms by age 51. As genetic technology is improving, a better understanding of the genetics of ALS may follow. Whole genome sequencing and whole exome sequencing are becoming more widely available and used.

Demographics

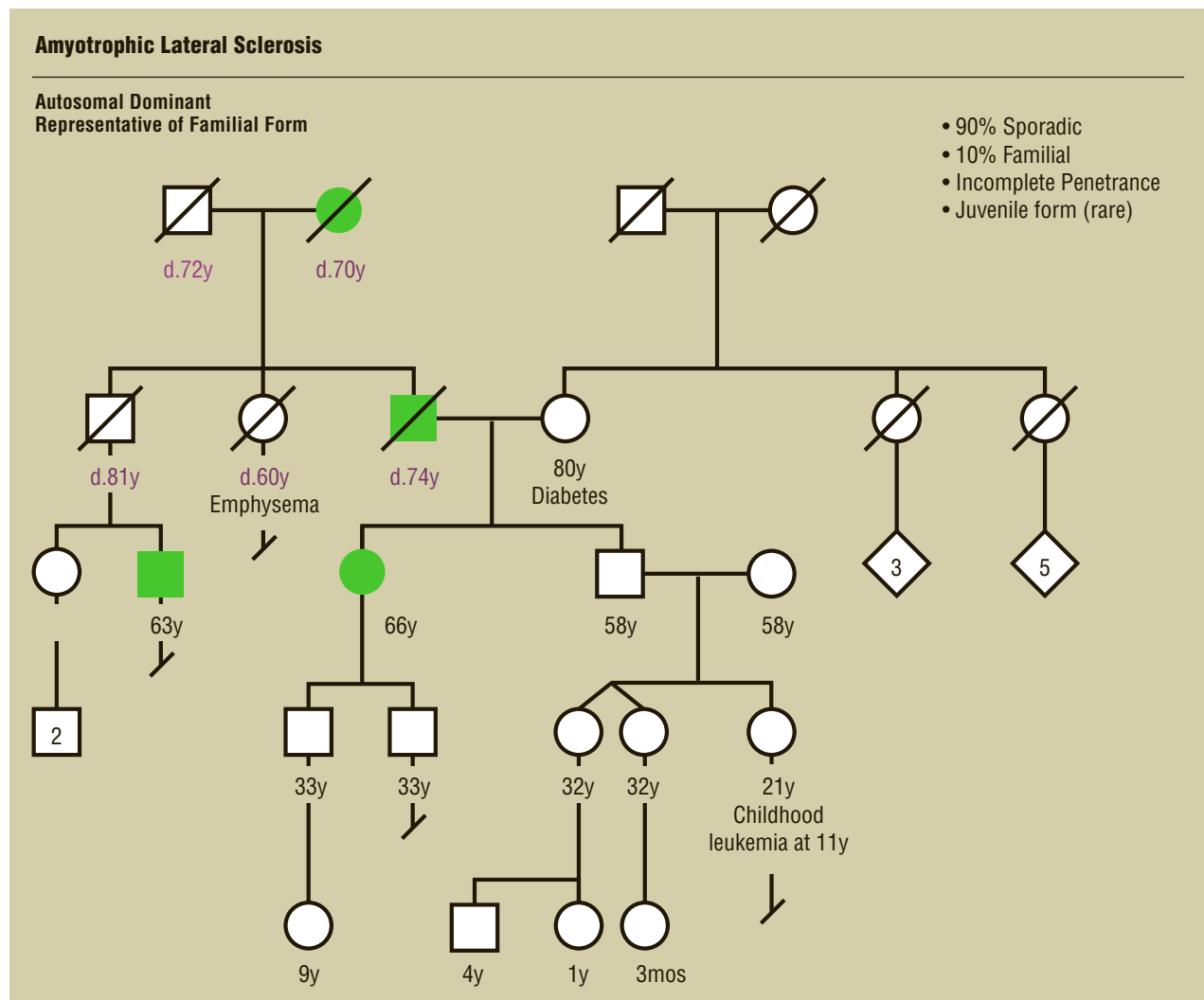
According to data from 2018, about, 2.6 per 100,000 people have ALS. About 5,600 people in the United States are newly diagnosed with ALS each year. The rate is slightly higher for women than for men. African Americans are less likely than Caucasians to have ALS, although this may be an artifact of reporting rather than

a true difference. Onset of ALS most commonly occurs between ages 40 and 60, but younger and older people may also develop ALS. Most often, ALS occurs in persons with no family history of ALS. With no family history, the average age of onset is 56 years. In cases where there is a family history, the average age of onset is 46 years.

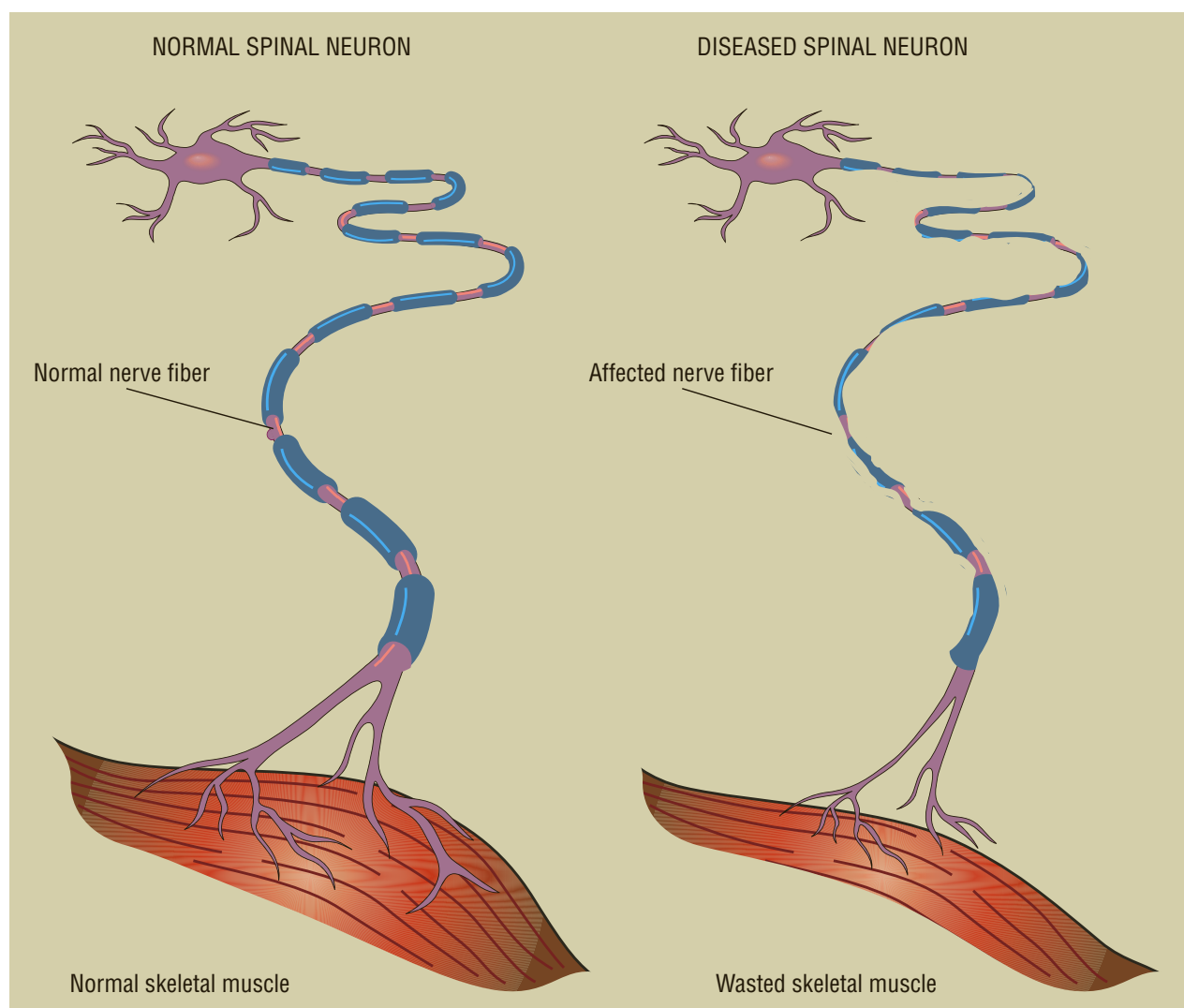
Globally, ALS is considered one of the most common neuromuscular diseases. Finland has the highest rate of ALS in the world. An increased incidence of a condition that involves ALS and Parkinsonism has been reported in Guam.

Signs and symptoms

The cause of ALS is unknown. The reason why ALS strikes some people and not others is also unknown. Most likely, there are a number of different, yet biologically



Amyotrophic lateral sclerosis: pedigree analysis chart (Gale)



Spinal neuron comparison (Gale)

related, causes for ALS, possibly combined with environmental factors. The symptoms of ALS are caused by the death of motor neurons in the spinal cord and brain. Normally, these neurons convey electrical impulses from the brain to the muscles to stimulate movement in the arms, legs, trunk, neck, and head. As motor neurons die, their respective muscles cannot be moved as effectively. Muscle weakness results. In addition, lack of stimulation leads to muscle wasting or loss of bulk. Involvement of the upper motor neurons causes spasms, abnormal reflexes, and increased tone in the limbs. Involvement of the lower motor neurons causes persistent muscle wasting, twitching (fasciculations), and, eventually, paralysis.

The disease starts slowly, affecting just one limb, such as the hands or feet, and steadily progresses to more limbs and muscles. When muscles lack the nourishment they require, they begin to thin and deteriorate, which is the

hallmark of ALS. Muscle wasting is due to the inability of degenerating motor neurons to stimulate the muscles in a way that allows them to function and grow. Common examples of symptoms for ALS are muscle cramps and twitching, weakness in the hands, feet, or ankles, speech slurring, and swallowing difficulties. Other early symptoms include arm and leg stiffness, foot drop, weight loss, fatigue, and difficulty making facial expressions.

One of the earliest symptoms of ALS is weakness in the bulbar muscles. These muscles in the mouth and throat assist in chewing, swallowing, and speaking. Weakness of these muscle groups usually causes problems such as slurred speech, difficulty with conversation, and hoarseness of the voice.

As the disease progresses, the respiratory muscles (breathing muscles) weaken, resulting in increased difficulty

KEY TERM

Whole genome sequencing—Identifying the DNA code of a person's entire set of genes to look for mutations that may cause a disease or disorder.

with breathing, as well as coughing and possibly inhaling food or saliva. The potential for lung infection increases when food is inhaled into the lungs, which can cause death. Many patients find it more comfortable to use ventilators at that stage of the disease. Communication becomes very difficult. One way to accomplish feedback with others is to make use of the eyes. Blinking is one mode that patients with ALS can use to continue communication. About 5% of those with ALS develop a type of dementia in which they have cognitive deficits and personality changes. Some subtypes of ALS have been described primarily on the basis of symptoms involved in those cases.

As the disease progresses, victims gradually lose the use of their foot, hand, leg, and neck muscles, and paralysis results in affected muscle groups. They are able to speak and swallow only with great struggle. Sexual function is not affected. Breathing becomes increasingly difficult, and the patient may decide to prolong life with the use of assisted ventilation, which may decrease the risks of death from infections such as pneumonia. ALS is a complex and puzzling condition for a number of reasons, including clinical variability in symptoms, variability of age and site of onset, mixture of cognitive involvement, variable rate of progression, and mixture of those with a family history and those without. Furthermore, both upper and lower motor neurons are involved.

Diagnosis

ALS is difficult to diagnose. There is no single test for the disease. A second opinion is frequently recommended if ALS is suspected, since it is a fatal neurological disease. There is a set of diagnostic criteria for ALS called the Escorial Criteria, which suggest that in order to have a diagnosis of ALS, it must be clear that both upper and lower motor neurons are involved, the condition must be progressive, and there must be no evidence for the diagnosis of another similar condition. There are also classifications for the ALS diagnosis, such as definite, probable, possible, and suspected.

Examination

The diagnosis of ALS begins with a complete medical history and physical exam, plus neurological examinations to determine the distribution and extent of weakness.

The examinations are repeated at regular intervals to assess whether symptoms are getting progressively worse.

Tests

A series of diagnostic tests are performed to rule out other possible causes and diseases that resemble ALS, such as tumors of the skull base or high cervical spinal cord, thyroid disease, spinal arthritis, lead poisoning, or severe vitamin deficiency. Other possibilities to rule out include multiple sclerosis, spinal muscular atrophy, spinal bulbar muscular atrophy, spastic paraplegia, spinal cord neoplasm, polyarteritis, syringomyelia, myasthenia gravis, and muscular dystrophy. Electro-diagnostic tests such as electromyography (EMG) and nerve conduction velocity (NCV) are used to help diagnose ALS. Blood and urine tests, examination of spinal fluid, x-rays, and muscle and/or nerve biopsy are performed, as are imaging studies like magnetic resonance imaging (MRI), myelograms of the cervical spine, and CT (computed tomography) scans. ALS is rarely misdiagnosed following a careful review of all these tests.

Genetic testing for ALS is recommended when a person has a family history of the condition. Testing starts with the *SOD1* gene. If no mutations in that gene are identified, then other genes can be considered based on the clinical symptoms present. There are genetic tests for ALS that include gene panels, or a way to test several genes at once.

Treatment and management

As of 2021, there is no cure for ALS and no treatment that can significantly alter its course. Clinical trials for treating ALS including experimental drug treatments, and procedures are ongoing. Participation in a clinical trial is voluntary and normally at no cost to the participant. All clinical trials receiving U.S. government funding, and some supported by private industry, are posted at <https://www.clinicaltrials.gov>. Foreign trials are listed at <https://www.orpha.net>

Traditional

Emotional, psychological, and physical support are needed to ease the difficulty associated with this disorder. A team of medical specialists will be needed, including a neurologist, specialized nurses, pulmonologists, social workers, physical, speech and occupational therapists, and nutritionists.

Moderate activities are recommended in the early stages of the disease. Physical therapy can help muscles stay active and delay the resulting weakness. Eventually, walkers and wheelchairs will be needed. ALS patients are encouraged to maintain a healthy diet and to exercise

regularly for as long as possible. Education about ALS is very important in developing an understanding of the disease for family members as well as patients.

A physical therapist works with an affected person to implement exercise and stretching programs to maintain strength and range of motion. Swimming may be a good choice for people with ALS, as it provides a low-impact workout to most muscle groups. Regular stretching can prevent contracture (or muscle shortening), which is one result of chronic inactivity. Contracture limits a person's range of motion and is often painful. Several drugs are available to reduce cramping, a common complaint in ALS.

An occupational therapist can help design solutions to movement and coordination problems. This therapist can also provide advice on adaptive devices and home modifications.

Speech and swallowing difficulties can be minimized or delayed through training provided by a speech-language pathologist. This specialist can also provide advice on communication aids, including computer-assisted devices and simple word boards.

Nutritional advice can be provided by a nutritionist. A person with ALS often needs softer foods to prevent jaw exhaustion or choking. Later in the disease progression, nutrition may be provided by a gastrostomy tube inserted into the stomach.

Mechanical ventilation may be used when breathing becomes too difficult. Modern mechanical ventilators are small and portable, allowing a person with ALS to maintain the maximum level of function and mobility. Ventilation may be administered through a mouth or nose piece. It might also be administered through a tracheotomy tube, inserted through a small hole made in the windpipe. In addition to providing direct access to the airway, the tube decreases the risk of aspiration. While many people with rapidly progressing ALS choose not to use ventilators for lengthy periods, ventilators are increasingly being used to prolong life for a short time.

The progressive nature of ALS means that most persons with the disease will eventually require full-time nursing care, often provided by a spouse or other family member. While the skills involved are not difficult to learn, the physical and emotional burden of care can be overwhelming. Caregivers need to recognize and provide for their own needs, as well as those of people with ALS, to prevent depression, burnout, and bitterness.

Throughout the disorder, a support group can provide important psychological aid to the affected persons and their caregivers in coming to terms with the losses that ALS inflicts. Support groups are sponsored by both

QUESTIONS TO ASK YOUR DOCTOR

- What research is being done in ALS treatment?
- How will my ALS be treated?
- How can physical therapy help?
- How will the disease progress?
- How can quality of life be improved?

the ALS Society and the Muscular Dystrophy Association.

Drugs

The drug riluzole (Rilutek, Tiglutik) is approved in both the United States and the European Union for treatment of ALS. Riluzole has been shown to delay the need for ventilator usage and to extend life by approximately one year. Otherwise, management aims to treat the symptoms that patients experience.

Alternative

Given the serious prognosis and absence of traditional medical treatments, it is not surprising that a large number of alternative treatments have been tried for ALS. Some studies have suggested that amino-acid therapies may provide some improvement for some people with ALS. While individual reports claim benefits for megavitamin therapy, herbal medicine, and removal of dental fillings, no evidence suggests that these offer any more than a brief psychological boost, often followed by a more severe let-down when it becomes apparent the disease has continued unabated. However, once the causes of this disorder are better understood, alternative therapies may be more intensively studied.

Prognosis

Amyotrophic lateral sclerosis normally progresses rapidly and leads to death from respiratory failure within three to five years. If the person involved is young, and the initial symptoms appear in the limbs, the disease tends to develop more slowly. About 10% of individuals with ALS live up to 10 years.

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ALS Association, 1300 Wilson Boulevard, Suite 600, Arlington, VA 22209, (800) 82-4747, <https://www.als.org>

ALS Therapy Development Institute, 480 Arsenal Street, Suite 201, Watertown, MA 02472, (617) 441-7200, <https://www.als.net>

Muscular Dystrophy Association, 161 N. Clark, Suite 3550, Chicago, IL 60601, (800) 572-1717, mda@mdausa.org, <https://www.mda.org>

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Revised by Tish Davidson, AM

Androgen insensitivity syndrome

Definition

Androgen insensitivity syndrome is a genetic condition where affected people have male chromosomes and male gonads (testicles). The external genitals, however, have mild to complete feminization.

Description

Normal sexual development

In normal development, the chromosome sex determines the gonadal sex, which in turn determines the phenotypic sex. The chromosome sex is determined at conception; a male has the sex chromosome pair XY and a female has the chromosome pair XX. During the first 40 days of gestation, a male and female embryo appear the same and have undifferentiated gonads, which have the potential of becoming testes or ovaries. The presence of the Y chromosome in the male directs the undifferentiated gonads to become testicles. If no Y chromosome is present, such as in the female chromosome pair, the undifferentiated gonads become ovaries.

In males, the phenotypic sex, including the internal male structures and the external male genitalia, arises as a result of the hormones secreted from the testicles. The two main hormones secreted by the testicles are testosterone and mullerian duct inhibitor. Testosterone acts directly on the Wolffian duct, which give rise to the internal male structures including the epididymides, vasa deferentia, and seminal vesicles. Testosterone is converted into dihydrotestosterone, the hormone responsible for the development of the male urethra and prostate, and the external genitalia of the penis and the scrotum. The mullerian duct inhibitor is the hormone that suppresses the mullerian ducts and prevents the development of fallopian tubes, upper vagina, and uterus in males.

If no testicles are present, as with females, no mullerian duct inhibitor is formed and the mullerian ducts become the fallopian tubes, the upper vagina, and the uterus. The Wolffian ducts regress. Due to the lack of dihydrotestosterone, the external genitals are not masculinized and become female. Studies have shown that an ovary is not required for the formation of the internal female structures or the feminization of the genitals. If a testicle is not present, the development of the embryo will default to female development.

In most cases, the chromosomal sex, the gonadal sex, and the phenotypic sex are in agreement. Males have 46, XY chromosomes, testicles, and male internal structures and genitals. Females have 46, XX chromosomes, ovaries, and internal female structures and genitals.

Androgen insensitivity syndrome

Androgen insensitivity syndrome (AIS), also known as testicular feminization, is one of the most common conditions where the chromosome sex and gonadal sex do not agree with the phenotypic sex. Affected people have normal male chromosomes, 46, XY and testicles. The testicles secrete both testosterone and mullerian duct

Classification of AIS Phenotypes

Type	External genitalia (synonyms)	Findings
CAIS	Female ("testicular feminization")	Absent or rudimentary wolffian duct derivatives Inguinal or labial testes; short blind-ending vagina Little or no pubic and/or axillary hair
CAIS or PAIS	Predominantly female (incomplete AIS)	Inguinal or labial testes Labial fusion and enlarged clitoris Distinct urethral and vaginal openings or a urogenital sinus
PAIS	Ambiguous	Microphallus (<1 cm) with clitoris-like underdeveloped glans; labia majora-like bifid scrotum Descended or undescended testes Perineoscrotal hypospadias or urogenital sinus Excessive development of the male breasts during puberty
	Predominantly male	Simple (glandular or penile) or severe (perineal) "isolated" hypospadias with a normal-sized penis and descended testes or severe hypospadias with micropenis, bifid scrotum, and either descended or undescended testes Excessive development of the male breasts during puberty
MAIS	Male (undervirilized male syndrome)	Impaired sperm development and/or impaired masculinization Overdevelopment of the male breasts during puberty

Classification of AIS Phenotypes (Gale)

inhibitor as normal and no internal female structures form. However, due to defective androgen receptors, the Wolffian ducts and genitals cannot respond to the androgens testosterone and dihydrotestosterone. As a result, no male internal structures are formed from the Wolffian ducts and the external genitals are feminized.

The amount of feminization depends on the severity of the androgen receptor defect and is often characterized as complete androgen insensitivity (CAIS), partial androgen insensitivity (PAIS), and mild androgen insensitivity (MAIS). In complete androgen insensitivity, the alteration in the androgen receptor results in complete female external genitals. In partial androgen insensitivity, also called Reifenstein syndrome, partial androgen insensitivity results in female genitalia with some masculinization, ambiguous genitalia, or male genitalia with partial feminization. With mild androgen insensitivity, mild androgen resistance results in normal male genitalia or a male with mild feminization.

In both CAIS and PAIS, affected individuals are sterile (cannot have a child). In MAIS, the affected male may have fertility problems because of oligospermia (low sperm production) or azoospermia (no sperm production). In all types of AIS, secondary sex characteristics such as body and pubic hair can be abnormal. Mental impairment is not found in any of the types of androgen insensitivity syndromes, though poor visual-spatial ability has been observed. People with AIS can also be rather tall, though bone age is usually normal.

Genetic profile

Androgen insensitivity syndrome is a genetic condition that results from mutations (pathogenic variants) of the *AR*

gene, named for the androgen receptor. The androgen receptor is located on the long arm of the X chromosome (Xq11-q12). As women have two X chromosomes, they also have two androgen receptor genes. Men have only one X chromosome and a Y chromosome. Hence, they only have one copy of the androgen receptor gene.

When women have one copy of the androgen receptor altered, they are considered carriers of AIS. In most cases, the second, normal copy of the androgen receptor can compensate for the altered copy. However, in approximately 10% of women who are carriers for the altered androgen receptor gene, clinical signs such as sparse pubic and armpit hair or a delay to the start of their first menstrual period is observed.

46,XY conceptions that have alterations in the androgen receptor gene do not have a second copy to compensate for the altered copy. Hence, these people will have AIS. If the androgen receptor is severely altered, they will have CAIS. If not severely altered, they will have PAIS or MAIS.

All forms of AIS are inherited in an X-linked pattern. This means women who are carriers have a 25% chance of having an affected child. If a woman who carries one altered *AR* gene has a 46,XY conception, there is a 50% chance the child will have AIS. If a woman who carries one altered *AR* gene has a 46,XX conception, there will be a 50% chance the daughter will be a carrier.

When a person has AIS and has no other family history of the condition, approximately two-thirds of the time the affected person inherited the gene alteration from his mother. The other one-third of the time, the alteration of the androgen receptor was a new event (new mutation) in the affected person and was not inherited.

Cases of both gonadal mosaicism and somatic mosaicism have been reported with AIS. Gonadal mosaicism occurs when the alteration in the androgen receptor occurred not at conception, but in one of the gamete cells (sperm or egg). The rest of the cells of the body do not have the altered androgen receptor. With AIS, this can occur when one of a woman's early gamete cell has the new alteration in the androgen receptor but the rest of the cells in her body do not. All the eggs that come from the early gamete cell will also have the alteration. Her risk for having a child with AIS is increased. Somatic mosaicism occurs when the alteration in the androgen receptor occurs after conception but not in a gamete cell. Some of the person's cells will have the altered androgen receptor and other cells will not. The amount of cells with altered receptors and the location of those cells within the body will determine how severely affected a person will be.

A specific type of mutation, called a CAG repeat, within the androgen receptor gene is responsible for the neuromuscular condition spinobulbar muscular atrophy or Kennedy disease. See separate entry for more information.

Demographics

Complete androgen insensitivity syndrome occurs in approximately 1 in 64,000 46,XY births or 2-5 in 100,000 births overall. Partial AIS is at least as common as complete AIS. The incident of mild AIS is unknown, but is estimated to account for approximately 40% of male infertility due to severe oligospermia or azoospermia.

Signs and symptoms

Complete androgen insensitivity

Individuals with CAIS are born looking like normal female babies. Often, the condition is discovered in one of two ways. The child can have an inguinal hernia that upon repair is found to contain testicles. The most common presentation is during puberty with primary amenorrhea, or lack of the onset of the menstrual period. Affected individuals have a short, blind ending vagina and no uterus, cervix, fallopian tubes, or ovaries. During puberty, some girls will have absent or decreased pubic hair. Breasts develop normally and can be large in size with pale and immature nipples and areola. People with CAIS are usually raised as females and have normal female sexual orientation. All women with CAIS are sterile. In families with CAIS, all affected members will have complete androgen insensitivity and similar physical features.

KEY TERMS

Androgens—A group of steroid hormones that stimulate the development of male sex organs and male secondary sexual characteristics.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Mullerian ducts—Structures in the embryo that develop into the fallopian tubes, the uterus, the cervix and the upper vagina in females.

Wolffian ducts—Structures in the embryo that develop into epididymides, vasa deferentia, and seminal vesicles in males.

Partial androgen insensitivity syndrome

Children with PAIS usually present at birth due to ambiguous genitalia. The genitalia can look like female genitals with some masculinization, completely ambiguous genitals where the sex of the baby cannot be immediately determined or male genitals with some feminization. The degree of severity is a direct result of the severity of the genetic alteration in the androgen receptor and resulting amount of functional androgen receptor. The internal structures of PAIS are the same as CAIS, with absent fallopian tubes, cervix, uterus, and ovaries. Testes are present but do not produce sperm. Hence, people with PAIS are also sterile. People with PAIS also have primary amenorrhea, and breast development occurs in puberty. Unlike CAIS, affected individuals in the same family with presumably the same genetic alteration can have varying degrees of masculinization. As a result, some affected people may be raised as females, whereas others may be raised as males. Sex assignment is made based upon the structure of the genitals, the surgical correction needed, and the predicted response to androgens during puberty.

Mild androgen insensitivity

Males with mild androgen insensitivity usually have normal male genitals and internal male structures. During puberty, males with MAIS may have breast enlargement, sparse facial and body hair, and small penises. Some affected males may also have impaired sperm production resulting in oligospermia or azoospermia. As with CAIS, affected men within the same family usually have similar features.

Diagnosis

Diagnosis is usually made based upon clinical features, chromosome analysis, hormone levels, analysis of androgen receptor function in skin fibroblasts, and results of DNA testing of the AR gene. Clinical features are listed above for CAIS, PAIS, and MAIS. Chromosome analysis reveals normal male chromosomes. Affected individuals can have elevated luteinizing hormone, normal to slightly elevated testosterone, and high estradiol for men. Follicle stimulating hormone may also be normal to elevated. Reduced androgen receptor function in skin fibroblast cells is also used to aid in a diagnosis.

Direct genetic testing for molecular defects in the androgen receptor (AR) gene is available. DNA sequencing of the AR gene is the most productive form of DNA testing for detecting AR mutations (also known as pathogenic variants). DNA sequencing is the molecular determination of the precise sequence of nucleotides in a sample of DNA. By looking at the coding regions (exons) of the AR gene and the junctions between these coding regions, mutations or changes in the sequence of nucleotides can be found. The likelihood of finding a mutation (pathogenic variant) depends of the type of AIS the individual has:

- In individuals with CAIS, 65% to 95% of mutations in the AR gene will be found.
- In PAIS, DNA sequencing finds less than 50% of the AR mutations
- In individuals with MAIS, assessment of the accuracy of the testing is difficult to assess due to the suspected large number of undiagnosed cases.

If no mutations are detected by sequencing the AR gene, then deletion/duplication testing which looks for copy number variants is performed. Deletions or duplications in the AR gene are rare.

If DNA sequencing does not detect a mutation (pathogenic variant) in a person who clinically appears to have AIS, then other DNA testing techniques may be used. Multigene panels analyze groups of genes—the AR gene and other genes—that cause diseases that have symptoms similar to AIS disease simultaneously. However, while molecular DNA testing methods are very thorough, recent research has revealed that a significant percentage (perhaps as high as 40 percent) of individuals with clinical diagnosis consistent with AIS do not have detectable mutations in the AR gene. No other genes have been identified as contributing the phenotype of AIS. Research in this area is ongoing.

QUESTIONS TO ASK YOUR DOCTOR

- What surgical risks are associated with such procedures as breast reduction or testicle removal?
- What are the risks of hormone therapy?
- In CAIS, how long is estrogen therapy needed?
- How can I offer my child emotional support?

Treatment and management

Complete androgen insensitivity

Historically, treatment of CAIS often required the removal of the testicles from the pelvis or inguinal canal to decrease risk of testicular malignancy. Because the overall risk of malignancy is approximately 5% and rarely occurs before age 25, the testicles were usually removed after the development of the secondary sex characteristics, as the testes are needed for estrogen formation. After the removal of the testes, estrogen supplementation is started to aid in the development of secondary sex characteristics and to help prevent osteoporosis. Because the risk of malignancy is low, surgical removal of the gonads is becoming increasingly controversial. Surgery to lengthen the vagina may be necessary.

Partial androgen insensitivity syndrome

In individuals with ambiguous genitalia, the determination of the sex assignment during infancy is of primary importance. Health professionals and parents should make a decision as early as possible after a full multidisciplinary evaluation has been completed.

For those affected individuals raised as females, treatment is similar to CAIS except that removal of the testicles, if done, may be done earlier because it may cause enlargement of the clitoris during puberty. Reconstructive surgery of the genitals and lengthening of the vagina may be necessary.

People with PAIS raised as boys may need surgery to improve the appearance of the genitals. Androgen supplementation may be implemented, though long-term effects of androgen therapy are not known. Breast reduction surgery may be necessary after puberty.

Mild androgen insensitivity

Males with MAIS may require no treatment at all or breast reduction surgery after puberty. Males who are infertile may benefit from assisted reproductive technologies.

Prognosis

For CAIS and MAIS, the prognosis is excellent. Generally, gender assignment is not difficult and sexual orientation is female for CAIS and male for MAIS. Treatment usually involves minimal surgery and hormone supplementation. For individuals with PAIS, the prognosis is very dependent upon the severity of the condition. Assignment of gender can be difficult and should be done after an expert evaluation has been completed. Genital surgery can be more involved and some individuals with PAIS and other intersex conditions have encouraged the delay of assigning gender until the child is old enough to express a preference. This idea has not been readily embraced in the medical community of the United States but attitudes regarding gender are shifting.

It is important to provide information about the diagnosis of AIS to affected individuals in a caring, supportive environment that encourages questions and provides updated information. Support groups and psychological counseling can be beneficial as well.

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ORGANIZATIONS

Intersex Society of North America, 979 Golf Course Dr., No. 282, Rohnert Park, CA 94928, <http://www.isna.org>

Carin Lea Beltz, MS, CGC
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Anencephaly

Definition

Anencephaly is a lethal birth defect characterized by the malformation of the brain and the absence of all or part of the skull and scalp. Anencephaly is a type of neural tube defect.

Description

Anencephaly is one of a group of malformations of the central nervous system collectively called neural tube defects. These birth defects occur very early in pregnancy, usually within the first four weeks and often before a woman knows she is pregnant.

Anencephaly is readily apparent at birth because of the absence of the skull and scalp and exposure of the underlying brain. The condition is also called acrania (absence of the skull) and acephaly (absence of the head). In its most severe form, the entire skull and scalp are missing. In some cases, termed "meroacrania" or "meroanencephaly," a portion of the skull may be present. In most instances, anencephaly occurs as an isolated birth defect with the other organs and tissues of the body forming correctly. In approximately 10% of cases, other malformations are present.

Risk factors

It is known that nutritional insufficiency, specifically folic acid insufficiency, is a predisposing environmental factor. Mutations of genes involved in folic acid metabolism are genetic risk factors. The recurrence risk of parents' having a second infant with a neural tube defect after the birth of an infant with anencephaly is 3%–5%. The recurrence may be anencephaly or another neural tube defect such as spina bifida.

Demographics

Anencephaly occurs in all races and ethnic groups. The prevalence rates range from less than one in 10,000 births (European countries) to more than ten per 10,000 births (Mexico, China). Factors involved in the difference of prevalence rates have not yet been determined.

Signs and symptoms

As an isolated defect, anencephaly appears to be caused by a combination of genetic factors and environmental influences that leads to the faulty formation of the nervous system. The specific genes and environmental conditions that contribute to this multifactorial causation are not completely understood.

A newborn affected by anencephaly is usually blind, deaf, unconscious, and unable to feel pain. In some cases, reflex action may be observed.

Diagnosis

Examination

Anencephaly is diagnosed by observation.

Tests

Prenatal diagnosis may be made by ultrasound examination after 12 to 14 weeks' gestation. Prenatal diagnosis of anencephaly can also be detected through maternal serum alpha-fetoprotein screening. The level of alpha-fetoprotein in the maternal blood is elevated because of the leakage of this fetal protein into the amniotic fluid.

Treatment and management

No treatment is indicated for anencephaly. Affected infants are stillborn or die within the first few days of life. The risk for occurrence or recurrence of anencephaly may be reduced by half or more by taking folic acid during the months immediately before and after conception. Natural folic acid, a B vitamin, may be found in many foods

QUESTIONS TO ASK YOUR DOCTOR

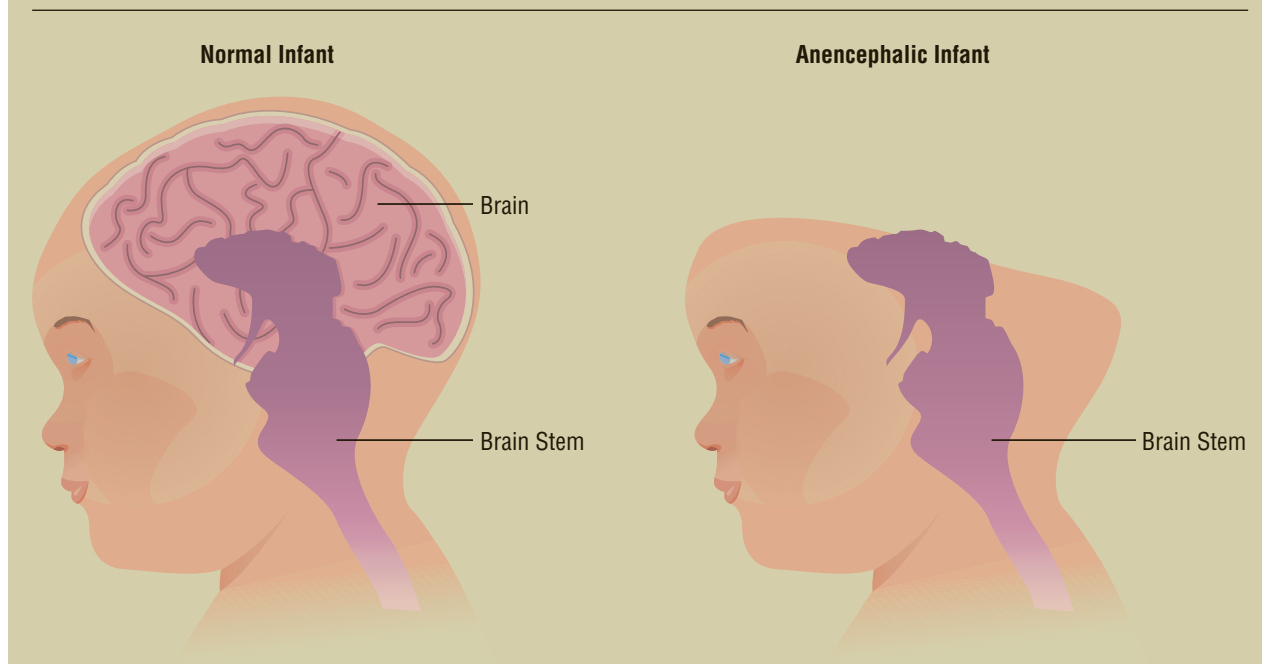
- What research is being done?
- Are you aware of any clinical trials?
- What can I do to decrease the risk of anencephaly occurring in future pregnancies?
- What supportive or comfort measures can I offer the baby?
- What genetic testing is recommended?
- Can you provide the name of a support group for parents who have had anencephalic babies?

(green leafy vegetables, legumes, orange juice, liver). Synthetic folic acid may be obtained in vitamin preparations and in certain fortified breakfast cereals. In the United States, all enriched cereal grain flours have been fortified with folic acid.

Prognosis

Anencephaly is uniformly fatal at birth or soon thereafter.

Diagram of Anencephaly



Infants born with anencephaly have either a severely underdeveloped brain or total brain absence. A portion of the brain stem usually protrudes through the skull, which also fails to develop properly. (Gale)

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- "Facts about Anencephaly." CDC. 2019. <https://www.cdc.gov/ncbddd/birthdefects/anencephaly.html> (accessed March 20, 2021).

ORGANIZATIONS

- March of Dimes Birth Defects Foundation, 1275 Mamaroneck Ave., White Plains, NY 10605, (914) 997-4488, resourcecenter@modimes.org, <http://www.modimes.org>
- National Birth Defects Prevention Network, Atlanta, GA (770) 488-3550, <http://www.nbdpn.org>
- National Center on Birth Defects and Developmental Disabilities, Division of Birth Defects and Developmental Disabilities, Mail-Stop E87, 1600 Clifton Rd., Atlanta, GA 30333, <http://www.cdc.gov/ncbddd/birthdefects/Anencephaly.html>

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Angelman syndrome

Definition

Angelman syndrome (AS) is a genetic condition that causes severe intellectual disability, severe speech impairment, and a characteristic happy and excitable demeanor.

Description

Individuals with AS show evidence of delayed development by 6–12 months of age. Eventually, this delay is recognized as severe intellectual disability. Unlike some genetic conditions causing severe intellectual disability,

AS is not associated with developmental regression (loss of previously attained developmental milestones).

Severe speech impairment is a striking feature of AS. Speech is almost always limited to a few words or no words at all. However, receptive language skills (listening to and understanding the speech of others) and non-verbal communication are not as severely affected.

Individuals with AS have a balance disorder, causing unstable and jerky movements. This typically includes gait ataxia (a slow, unbalanced way of walking) and tremulous movements of the limbs.

AS is also associated with a unique “happy” behavior, which may be the best-known feature of the condition. This may include frequent laughter or smiling, often with no apparent stimulus. Children with AS often appear happy, excited, and active. They may also sometimes flap their hands repeatedly. Generally, they have a short attention span. These characteristic behaviors led to the original name of this condition, the “happy puppet” syndrome. However, this name is no longer used, as it is considered insensitive to AS individuals and their families.

Genetic profile

The genetics of AS are complex. There are at least five different genetic abnormalities that can cause the condition, all of which involve a specific region of the chromosome 15 inherited from the mother. This region is designated 15q11-13 (bands 11 through 13 on the long arm of chromosome 15). The fact that AS occurs only when there are abnormalities in this region of the maternal copy of chromosome 15 reflects a unique phenomenon known as imprinting. Imprinting is a chemical modification of DNA that acts as an “identification tag,” indicating which parent contributed the chromosome. Imprinted genes or chromosome regions are expressed or not expressed depending on which parent transmitted the chromosome. Abnormalities in the paternally (from the father) inherited 15q11-13 region cause a different genetic condition called Prader-Willi syndrome.

Chromosome deletion

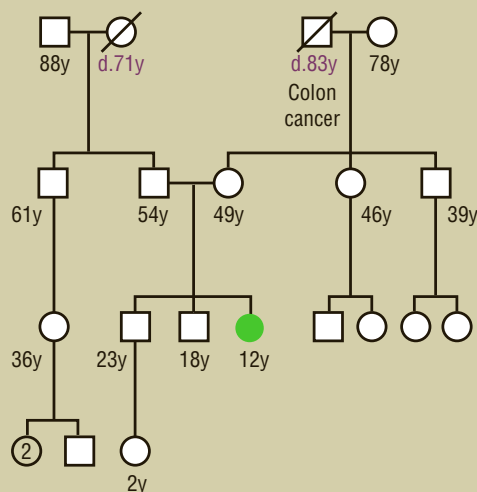
The most common cause of AS is a small deletion (missing piece) in the maternally inherited chromosome 15. Specifically, the deletion occurs within 15q11-13. Approximately 70% of AS individuals have this deletion.

UBE3A mutation

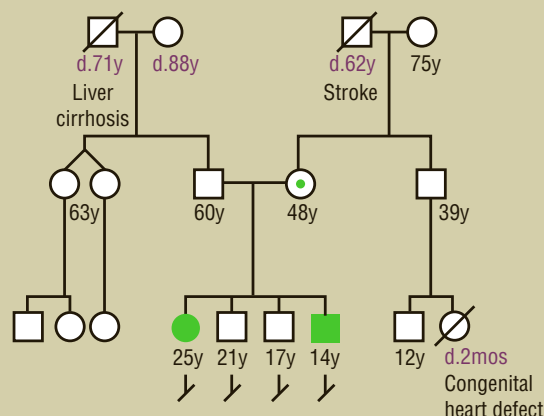
In approximately 11% of AS cases, there is a mutation within the maternally inherited *UBE3A* gene. All the genetic mechanisms leading to AS appear to compromise expression of this gene, which is located

Angelman Syndrome

1. Etiology: Deletion, Uniparental Disomy or Unknown



2. Etiology: UBE3A mutation, Imprinting mutation or Unknown



Angelman syndrome: pedigree analysis chart (Gale)

within the 15q11-13 region. This gene is considered to be the “critical gene” responsible for AS, although its specific function is unknown.

Uniparental disomy

Some cases of AS result from inheritance of both chromosomes in the 15 pair from the father, an unusual genetic phenomenon known as uniparental disomy. In this circumstance, there is no chromosome 15 from the mother. Approximately 7% of AS cases result from this mechanism.

Imprinting defect

Approximately 3% of AS cases result from an imprinting defect on the maternally inherited chromosome 15. As noted above, imprinting is a chemical modification to the DNA that serves as a marker indicating the parent of origin and controls gene expression. If there is defective imprinting on the maternally inherited 15, then the genes in the 15q11-15q13 region may not be expressed, leading to AS.

Chromosome rearrangement

Rarely, AS may be caused by chromosomal breaks that occur in the maternally inherited 15q11-13 region. The breaks may occur as the result of a translocation (in which two chromosomes break and exchange material), an inversion (in which a piece of a chromosome breaks

and rejoins in the opposite orientation), or another disturbance of the chromosome structure involving the maternal 15q11-15q13. This mechanism is responsible for about 1% of AS cases.

Unknown mechanism(s)

In about 10%–15% of individuals with AS, no genetic cause can be identified. This may reflect misdiagnosis or the presence of additional, unrecognized mechanisms leading to AS.

Demographics

AS has been reported in individuals of diverse ethnic backgrounds. The incidence of the condition is estimated at 1 in 10,000 to 1 in 30,000.

Signs and symptoms

The first abnormalities noted in an infant with AS are often delays in motor milestones (those related to physical skills, such as sitting up or walking), muscular hypotonia (poor muscle tone), and speech impairment. Some infants seem unaccountably happy and may exhibit fits of laughter. By age 12 months, 50% of infants with AS have microcephaly (a small head size). Tremulous movements are often noted during the first year of life.

Seizures occur in 80% of children with AS, usually by three years of age. No major brain lesions are typically seen on cranial imaging studies.

The achievement of walking is delayed, usually occurring between two-and-a-half and six years of age. The child with AS typically exhibits a jerky, stiff gait, often with uplifted and bent arms. About 10% of individuals with AS do not walk. Additionally, children may have drooling, protrusion of the tongue, hyperactivity, and a short attention span.

Many children have a decreased need for sleep and abnormal sleep/wake cycles. This problem may emerge in infancy and persist throughout childhood. Upon awakening at night, children may become very active and destructive to bedroom surroundings.

The language impairment associated with AS is severe. Most children with AS fail to learn appropriate and consistent use of more than a few words. Receptive language skills are less severely affected. Older children and adults are able to communicate by using gestures or communication boards (special devices bearing visual symbols that correspond to commonly used expressions or words).

Some individuals with AS caused by a deletion of the 15q11-q13 chromosomal region may have a lighter skin complexion than would be expected given their family background.

Diagnosis

The clinical diagnosis of AS is made on the basis of physical examination and medical and developmental history. Confirmation requires specialized laboratory testing.

There is no single laboratory test that can identify all cases of AS. Several different tests may be performed to look for the various genetic causes of AS. When positive, these tests are considered diagnostic for AS.

DNA methylation studies

DNA methylation studies determine whether the normal imprinting pattern associated with the maternal (mother's) copy of the number 15 chromosome is present. The 15q11-q13 region is differently methylated (or "imprinted") depending on which parent contributed the chromosome. If an individual has a deletion of this region on the maternal chromosome 15, paternal uniparental disomy of the number 15 chromosomes (with no number 15 chromosome from the mother), or a defective imprinting mechanism, DNA methylation studies will be abnormal and indicate AS. This test detects the majority (approximately 78%) of cases of AS. Additional studies are then required to determine which of these three mechanisms led to AS development.

QUESTIONS TO ASK YOUR DOCTOR

- At what point do you recommend surgery rather than medication for gastric reflux?
- What will be the long-term benefit of speech therapy?
- What is the surgical risk for scoliosis repair?
- At what age should I take my child to an ophthalmologist (eye doctor)?

UBE3A mutation analysis

Direct DNA testing of the *UBE3A* gene is necessary to detect cases of AS caused by mutations in this gene. Cases of AS caused by *UBE3A* mutations usually have a normal imprinting pattern.

Fluorescent in situ hybridization (FISH)

FISH studies may be necessary to detect chromosome rearrangements that disrupt the 15q11-q13 region on the maternal copy of chromosome 15. The FISH method is a special way of checking for the presence, absence, or rearrangement of very small pieces of chromosomes. FISH testing can also readily detect AS caused by chromosome deletions, which account for approximately 70% of AS cases. FISH testing is often performed following an abnormal methylation study to determine whether a chromosome deletion accounts for the abnormal methylation pattern.

Treatment and management

There is no specific treatment for AS. A variety of symptomatic management strategies may be offered for hyperactivity, seizures, intellectual disability, speech impairment, and other medical problems.

The typical hyperactivity in AS may not respond to traditional behavior modification strategies. Children with AS may have a decreased need for sleep and a tendency to awaken during the night. Drug therapy may be prescribed to counteract hyperactivity or aid sleep. Most families make special accommodations for their child by providing a safe yet confining environment.

Seizures in AS are usually controllable with one or more anti-seizure medications. In some individuals with severe seizures, dietary manipulations may be tried in combination with medication.

Children with AS appear to benefit from targeted educational training. Physical and occupational therapy may improve the disordered, unbalanced movements typical of AS. Children with a severe balance disorder may require special supportive chairs. Speech therapy is often directed towards the development of nonverbal communication strategies, such as picture cards, communication boards, or basic signing gestures.

Individuals with AS may be more likely to develop particular medical problems, which are treated accordingly. Newborn babies may have difficulty feeding, and special bottle nipples or other interventions may be necessary. Gastroesophageal reflux (heartburn) may lead to vomiting or poor weight gain and may be treated with drugs or surgery. Constipation is a frequent problem and is treated with laxative medications. Many individuals with AS have strabismus (crossed eyes), which may require surgical correction. Orthopedic problems, such as tightening of tendons or scoliosis, are common. These problems may be treated with physical therapy, bracing, or surgery.

Prognosis

Individuals with AS have significant intellectual disability and speech impairment that are considered to occur in all cases. However, they do have the capacity to learn and should receive appropriate educational training.

Young people with AS typically have good physical health aside from seizures. Although lifespan data are not available, the lifespan of people with AS is expected to be normal.

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ORGANIZATIONS

Angelman Syndrome Foundation, 414 Plaza Dr., Suite 209, Westmont, IL 60559, (800) IF-ANGEL or (630) 734-9267, (630) 655-0391, info@angelman.org, <http://www.angelman.org>

Jennifer Ann Roggenbuck, MS, CGC

Ankylosing spondylitis

Definition

Ankylosing spondylitis (AS) is a relatively common disease that causes inflammation of the area where ligaments and tendons insert into the bone. The inflammatory process eventually leads to reduced mobility or immobility of affected joints. Specific joints are characteristically involved, notably in the spine and pelvis.

Description

Ankylosing spondylitis belongs to a group of disorders called the seronegative spondyloarthropathies. Each disease in this group is characterized by arthritis affecting the spine, as well as the absence of rheumatoid factor, a diagnostic marker that is present in rheumatoid arthritis and helps distinguish it from the group of diseases that includes AS. AS affects primarily the spine and the sacroiliac joint where the spine meets the hips. Progressive symptoms eventually result in fusion of these joints, pain, and markedly decreased joint mobility. AS is considered an autoimmune disease, meaning that symptoms are the result of the action of the immune system of the body against its own tissues. Although the exact mode of action is unknown, there is a strong association between AS and a specific type of human leukocyte antigen, HLA-B27. HLA are genetically determined proteins that play an important role in the functioning of the immune response of the body, in that they enable the immune system to distinguish between its own cells and foreign cells. Therefore, HLA type is important in immunity as well as organ and tissue transplantation.

Genetic profile

AS is considered a multifactorial disorder, or one that is the result of an interaction between genetic and environmental factors. Two genes have been identified that confer susceptibility to AS, both of which are forms of an HLA gene on chromosome 6. Some HLA types have been implicated in various autoimmune diseases, or diseases in which the immune system attacks the body's own cells and tissues.



An X-ray image of a spine showing ankylosing spondylitis.
(Suttha Burawonk/Shutterstock)

The association of HLA B-27 and AS has been clearly established. Ninety to 95% of individuals with AS are B-27 positive, and since AS appears to be a dominant trait, the presence of at least one B-27 allele (a form of the gene) confers a greatly increased chance of developing symptoms. While this population risk may seem relatively high, it is important to realize that only about 9% of the population carries the B-27 allele. Of these individuals who are B-27 positive, only 2%–8% will develop AS.

Other environmental and genetic factors most certainly contribute to development of the disease. This becomes more evident when considering that B-27 positive individuals with an affected first-degree relative have a significantly higher chance of developing AS than a B-27 positive individual with no family history. In

families with multiple affected members, studies estimate that no more than half of AS recurrence is explained by HLA type. Additionally, there are several B-27 subtypes that have been studied; some confer susceptibility and some do not. Importantly, about 5% of people with AS are B-27 negative. Other environmental and/or genetic factors must certainly be associated with disease in these individuals. Another HLA type—B-60—has also been shown to confer susceptibility, although the association appears to be much weaker and is not seen in all studies. Certain infections are suspected of being necessary for triggering AS in some individuals. In the future, additional susceptibility genes and environmental factors can be expected to be identified.

Demographics

Approximately 0.25% to 1.5% of the population is affected with AS. Prevalence of the disease is comparable to the frequency of the HLA B-27 allele in the population, which varies among ethnic groups. Native North Americans, Alaskan Eskimos, and Norwegian Lapps all have relatively high levels of B-27 and AS. Low levels of B-27 and AS occur among individuals of most types of African ancestry, Australian aborigines, and Native South Americans. Generally, for every affected female, there are two to three affected males.

Signs and symptoms

The signs of AS vary, but a typical case involves progressive lower back pain and morning stiffness. The immune response at the point where the ligaments or tendons insert into the bones initially causes bone inflammation and fragility, followed by fibrosis, or the formation of fiber tissue. The area reacts by forming new bone, which eventually fuses, limiting motion. AS can also affect peripheral joints in a manner similar to other types of arthritis. The vertebral joints of everyone with AS are affected, and 50% of people will also have significant hip arthritis. Osteoporosis in advanced AS commonly results in fractures of the spine.

AS also affects areas other than the bones and joints. An eye complication called *anterior uveitis*, which is easily treated and generally does not affect vision, develops in 40% of people with AS. Rarely, the disease may affect the heart or aorta. Kidney failure is a rare complication. Lung function can be affected because of bone changes that affect the mechanics of breathing. Therefore, individuals with AS should refrain from smoking to avoid early respiratory failure. Ninety percent of affected individuals experience the first symptoms before age 45. Males are more commonly affected than females, who tend to be diagnosed later partly because of milder symptoms.

KEY TERMS

Ankylosis—Immobility of a joint due to the formation of new bone at the site of inflammation.

Cervicitis—Inflammation of the cervix.

Enthesitis—Inflammation at the place where the ligaments insert into the bone.

Enthesopathy—Disorder of the ligament attachment to the bone.

HLA-B27—Stands for a specific form of human leukocyte antigen, the proteins involved in immune system function. Strongly associated with ankylosing spondylitis.

Human leukocyte antigens (HLA)—Proteins that help the immune system function, in part by helping it to distinguish “self” from “non-self.”

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Osteoporosis—Loss of bone density that can increase the risk of fractures.

Psoriasis—A common, chronic, scaly skin disease.

Rheumatoid arthritis—Chronic, autoimmune disease marked by inflammation of the membranes surrounding joints.

Rheumatoid factor—Antibodies present in the majority of individuals with rheumatoid arthritis. A

diagnostic marker for rheumatoid arthritis that is absent from ankylosing spondylitis and other seronegative spondyloarthropathies.

Sacroiliac joint—The joint between the triangular bone below the spine (sacrum) and the hip bone (ilium).

Sacroiliitis—Inflammation of the sacroiliac joint.

Sensitivity—The proportion of people with a disease who are correctly diagnosed (test positive based on diagnostic criteria). The higher the sensitivity of a test or diagnostic criteria, the lower the rate of “false negatives,” people who have a disease but are not identified through the test.

Specificity—The proportion of people without a disease who are correctly classified as healthy or not having the disease (test negative based on diagnostic criteria). The higher the specificity of a test or diagnostic criteria, the lower the number of “false positives,” people who don’t have a disease but who “test” positive.

Spondyloarthritis (spondylitis)—Inflammatory disease of the joints of the spine.

Urethritis—Inflammation of the urethra.

Uveitis—Inflammation of all or part of the uvea, which consists of the middle vascular portion of the eye, including the iris, ciliary body, and choroid.

Diagnosis

Diagnostic criteria that were established by the European Spondyloarthropathy Study Group in the early 1990s are still used today. A clinical diagnosis of AS requires the presence of spinal pain caused by inflammation or inflammation of the membrane surrounding the joints, which can be either asymmetric or involving primarily the lower limbs. One or more of the following conditions must also be present:

- family history of AS
- sacroiliitis (inflammation of the sacroiliac joint) demonstrated by x-ray
- acute diarrhea within one month before the appearance of symptoms
- inflammatory bowel disease
- psoriasis (a scaly skin disease)
- urethritis (inflammation of the urethra)
- cervicitis (inflammation of the cervix)

- alternating buttock pain
- enthesopathy (disorder of the ligament attachment to the bone)

This diagnostic description has close to an 87% sensitivity, meaning that 87% of those with AS are picked up using this description. Conversely, 13% of those with AS will not be identified as having the disease based on this description. The description has a specificity that is also approximately 87%, meaning that 87% of the time, a person classified as having AS actually has AS, as opposed to another disease or no disease. Conversely, about 13% of the time, this description will incorrectly classify someone who actually has a different disease as having AS.

This is a challenging diagnosis to make correctly. Testing for HLA B-27 can improve diagnosis by confirming specificity. In other words, when it looks like someone has AS based on the above description of conditions, a positive B-27 test will make the physician

QUESTIONS TO ASK YOUR DOCTOR

- At what point should physical therapy be initiated?
- What are the risks and benefits of surgery?
- What are the risks and benefits of long-term use of nonsteroidal anti-inflammatory medications?
- How often should I have eye exams?

more certain that person is a true positive for AS. As imaging of the sacroiliac joint improves through the use of a technology called magnetic resonance imaging (MRI), diagnosis of AS may also improve. However, diagnosing a person with AS prior to the development of signs seen on x-ray or MRI will continue to be very difficult.

Treatment and management

Physical therapy plays a major role in maintaining flexibility, range of motion, posture, and, ultimately, mobility. Surgery can improve joint function, as well as minimize associated pain, which may be treated with nonsteroidal anti-inflammatory medications. Other medications—sulfasalazine and methotrexate—can provide some relief for peripheral arthritis. Cycloplegics (medications that paralyze the ciliary muscle of the eye) and local steroids are effective at treating anterior uveitis. Rare complications are treated depending on their symptoms. Avoidance of smoking is encouraged to maintain lung function.

Prognosis

For most affected individuals, treatment and management is successful at maintaining quality of life. Quality can be significantly impacted, however, for the occasional individual with a severe, progressive course of the disease. Vision can be affected in some individuals with anterior uveitis that is not responsive to treatment, but this is rare. The rare complication of kidney failure can limit life expectancy, as can respiratory failure that may result from smoking.

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Anxiety neurosis see **Panic disorder**

Apert syndrome

Definition

Apert syndrome is a rare genetic disorder that causes certain skull bones to close, or fuse, too soon in development. The premature closure leads to a distorted face with an unusually tall skull. Children with Apert syndrome also have fused fingers and toes, known as syndactyly. Another name for this disorder is acrocephalysyndactyly.

Description

A French physician named E. Apert first reported in 1906 the syndrome that bears his name. He detailed the skull malformation, midface hypoplasia (underdevelopment) and the hand abnormalities. The hand of a person born with Apert syndrome appears mitten-shaped because of the finger fusion. The child can have normal intellectual ability or severe intellectual disability.



Webbing of the toes is a characteristic sign of Apert syndrome. (M.A. Ansary/Science Source)

Apert syndrome also is known as FGFR-related craniosynostosis, and is one of eight known disorders in the group. FGFR refers to the fibroblast growth factor receptor (FGFR) gene responsible for the disorder, and craniosynostosis describes the premature skull fusion.

Genetic profile

Apert syndrome (AS) is an autosomal dominant disorder, meaning that a person only has to inherit one non-working copy of the gene for the condition to occur. In most cases, AS is sporadic, meaning that the parents are usually unaffected, but a fresh mutation or gene change occurring in the egg or sperm is passed to the affected child. For these families, the chance to have another affected child is very low. An affected parent has a 50% chance of passing on the abnormal gene to their child, who will then also have Apert syndrome.

Two unique mutations in the FGFR2 gene located on chromosome 10 were discovered in 1995. This gene directs the development of bone formation. At least seven mutations of the FGFR2 gene have been identified that cause Apert syndrome. Most mutations are influenced by either of two more common mutations found in people with the syndrome.

After comparing the physical findings with gene mutations causing AS, researchers noted that one mutation was associated with facial disorder. The other mutation produced a more severe form of syndactyly. With the facial mutation, corrective surgery can lead to much more improved facial appearance.

Demographics

Apert syndrome has been estimated to occur in 1 of every 60,000-160,000 births. All races and both sexes are equally affected.

Signs and symptoms

At birth the craniofacial (pertaining to the skull and face) appearance is striking. Early or premature closure of the skull sutures (layer of fibrous tissue connecting the skull bones) makes the skull grow taller than normal with a short distance from the front to the back of the head. The coronal suture that connects the frontal and parietal bones fuses early in infants with Apert syndrome. The buildup of pressure on the brain is minimal because the fontanelles, or soft spots, and midline of the skull remain open. Because the space within the eye sockets is small, the eyeballs bulge outward and to the side. The child's eyelids also have a downward slant and cannot completely close.

From the middle of the eye sockets to the upper jaw, the affected child's face is sunken in or concave when viewed from the profile. This midfacial hypoplasia causes the upper jaw to slope backward, pushing the lower teeth in front of the back teeth.

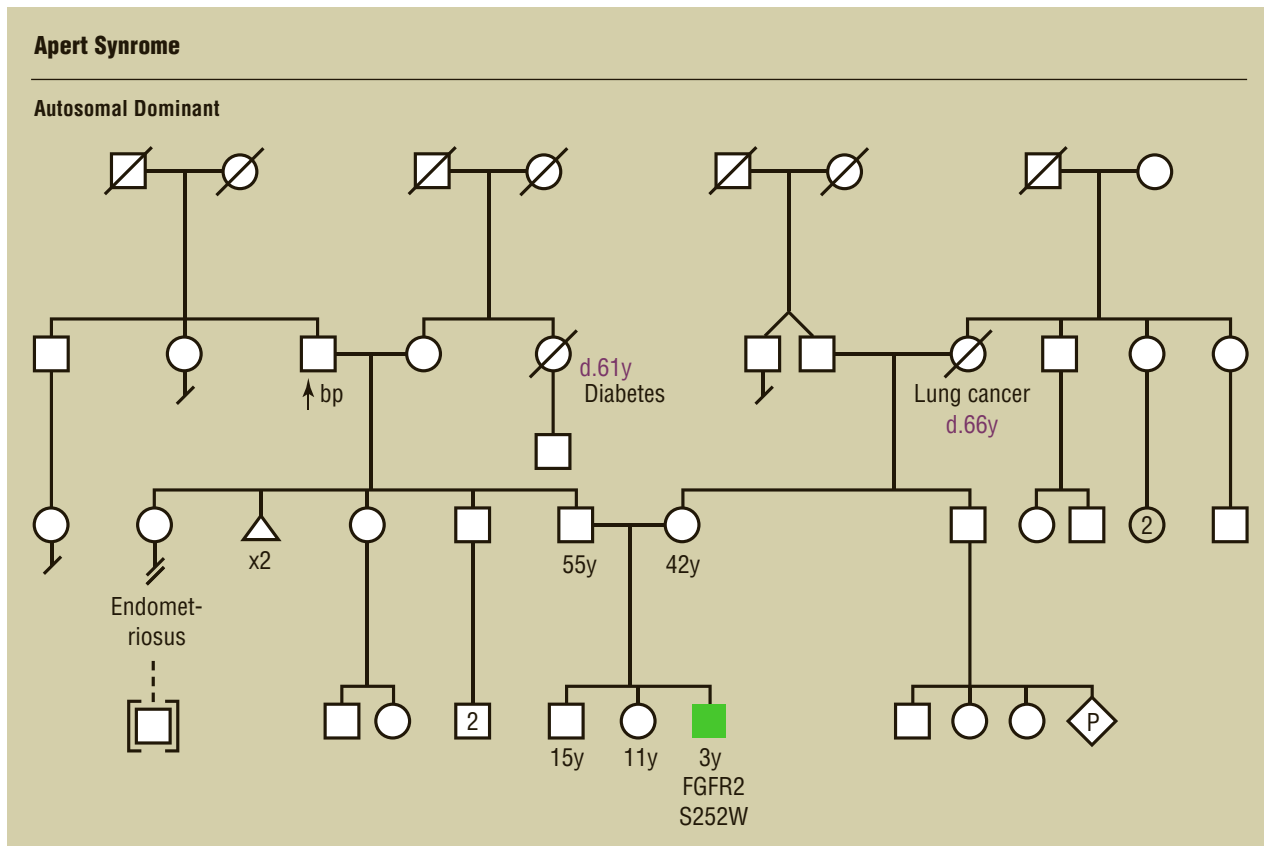
The child's mouth area has a prominent mandible (lower jaw), down-turned corners, a high arched palate, cleft palate (an opening in the roof of the mouth), crowded upper teeth, poor contact between the upper and lower teeth, and delayed tooth eruption.

Syndactyly of the fingers and toes involves not only soft tissues but also the bones, nerves, and tendons. The child usually cannot flex the fingers and toes after the first digit. The thumb can be unattached or fused to the other fingers. Also, the other fingers may or may not be fused to each other in varying degrees. Fusion of the toes is less worrisome. Correction only becomes necessary when walking is difficult.

Most children with AS are noisy breathers. The nose and airways leading to the lungs are smaller than usual. These narrow passageways probably make breathing more difficult. If breathing is more troublesome at night, sleep apnea can occur. This stoppage of breathing while sleeping deprives the brain and body of oxygen. The child may experience mental impairment as a result of oxygen deprivation.

Excessive sweating is often seen in people with AS. Researchers do not know why the sweat glands are overactive. As the children reach puberty, they develop excessive acne. A skin specialist or dermatologist can help to control it.

The height and weight of children with AS is usually normal. However, their learning ability can be affected. A small number of children with Apert syndrome have a normal level of intelligence, but most have some degree of intellectual disability. Studies have shown that the IQs of children with AS tend to be lower than normal.



Apert syndrome: pedigree analysis chart (Gale)

Diagnosis

During the newborn period, most babies are diagnosed after a geneticist examines them. This doctor specializes in diagnosing and explaining hereditary conditions. The unusual facial features and hand syndactyly are unique to AS. Testing for the mutations known to cause AS should be arranged to make a diagnosis. When a mutation is not found, the physical findings alone can support the diagnosis.

Occasionally during an ultrasound examination, a fetus shows characteristics suggesting AS. This examination is best done after 16 weeks of pregnancy. Ultrasound is the use of high-frequency sound waves to create a real-time image of the fetus. Unlike x-rays, ultrasound uses no radiation and the fetus can be examined for size, viability, and birth defects.

An experienced physician or ultrasound technologist performing the examination may detect the caved-in profile and syndactyly. More than one examination may be necessary to confirm the findings. If AS is suspected, genetic testing can be offered during the pregnancy. The pregnant woman can undergo an amniocentesis to obtain fetal cells that can be analyzed for the mutations causing

AS. Amniocentesis is the removal of the amniotic fluid surrounding the fetus by inserting a needle through the uterus. Results may take as long as four weeks.

Treatment and management

The best treatment for AS begins at birth with the correct diagnosis. To provide better care, a craniofacial team should be involved. With the team approach all the specialists are in one center to minimize the number of appointments and corrective surgeries. More important, this team consists of specialists who understand the complex problems of AS and the family's concerns. Included on this team are a craniofacial surgeon, neurosurgeon, otolaryngologist (specialist of the ears, nose, and throat), ophthalmologist (eye specialist), orthodontist, speech therapist, and psychologist. A pediatric nurse, geneticist or genetic counselor, and social worker may also be part of the team during the first few years of the child's life. Many major medical centers will have a craniofacial team, or the family can be referred to one.

Working together, the craniofacial surgeon and neurosurgeon perform the multiple surgeries to reshape the tower skull. They reopen the prematurely closed sutures

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that causes improper connection of the nasal passages and the mouth.

Craniofacial—Relating to or involving both the head and the face.

Dermatologist—A physician who specializes in disorders of the skin.

Fontanelle—One of several “soft spots” on the skull where the developing bones of the skull have yet to fuse.

Hypoplasia—Incomplete or underdevelopment of a tissue or organ.

Mandible—Lower jaw bone.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an

individual, or manifest as disease, and can be transmitted to offspring.

Ophthalmologist—A physician specializing in the medical and surgical treatment of eye disorders.

Orthodontist—A dentist who specializes in the correction of misaligned teeth.

Otolaryngologist—A physician who specializes in the care of the ear, nose, and throat and their associated structures.

Psychologist—An individual who specializes in the science of the mind.

Sleep apnea—Temporary cessation of breathing while sleeping.

Speech therapist—A professional who specializes in teaching simple exercises to improve speech.

Suture—A seam that joins two surfaces together.

Syndactyly—Webbing or fusion between the fingers or toes.

Ultrasound—An imaging technique that uses high-frequency sound waves to help display internal structures in the body.

between the skull bones and then pull the front of the skull forward to create space within it and enlarge the eye orbits. Average age of patients for these operations is about 4–8 months.

From ages five to nine, the child often has a surgical procedure called a midface advancement. This technique corrects the concave profile that becomes pronounced because the child's upper and lower face grow normally while the middle of the face grows slowly. Corrective facial surgeries continue until the early adult years when growth is finally completed.

The neurosurgeon may perform the operations to unfuse and straighten the fingers. However, a completely normal hand cannot be created.

Frequent ear infections can decrease a child's hearing level. The otolaryngologist can monitor the hearing. Sometimes tiny plastic tubes are placed in the ears to prevent hearing loss from repeated infections.

The abnormal placement of the eyes and its muscles can sometimes prevent a child from looking straight ahead with both eyes. An ophthalmologist should examine the eyes regularly and correct a muscle imbalance of the eyes with surgery.

An orthodontist (dentist who specializes in correcting misaligned teeth) monitors the teeth because the abnormal jaw structure causes poor development and placement. An oral surgeon may correct the misalignment of the teeth. Proper positioning of the teeth improves speech and facial appearance.

Speech and language delay can result from decreased hearing and an unusual jaw shape. A speech therapist works with the child to develop language skills through simple exercises.

The facial appearance of Apert syndrome can have a devastating emotional effect on the child and family. Support from a psychologist (a specialist in science of the mind) can help the child develop a positive self-image and help parents cope with feelings of guilt. Often parents will blame themselves for a child's condition even when they in no way caused it or could have prevented it. The multiple doctors' visits and surgeries can create undue stress as well.

During the many hospitalizations, a pediatric nurse will care for the child. This nurse has received specialized training in the treatment of children with craniofacial disorders. Also, the nurse may introduce the child to the hospital.

QUESTIONS TO ASK YOUR DOCTOR

- What are the risks of surgery during infancy?
- What is the risk of my child having mental deficiencies?
- Do you recommend occupational or physical therapy, and at what age should these therapies begin?
- What measures can we implement at home to improve the prognosis?

Diagnosis of Apert syndrome will usually be made by the geneticist. The family will discuss with the genetic counselor how AS is inherited and the chance for future children to be affected.

Having a child with AS can place a tremendous financial strain on the family. A social worker gives the family important information about medical coverage. This person can also help coordinate medical care and special-needs education.

Prognosis

Many factors affect the prognosis of a child with AS. The age at which the first surgery takes place to create spaces between the skull bones is important. Intellectual disability can result from the buildup of pressure on the brain. Having a supportive, loving family environment increases the chances for normal development. Children with complex medical problems who lack a supportive setting often have delayed mental, social, and emotional development.

Although the hands will never be completely normal, surgeries to separate and straighten the fingers can be done. Tasks such as writing and manipulating buttons can be difficult. Adaptive devices in school and home will allow for more independence. Separation of the toes usually does not improve walking but may improve the child's self-image.

Persons with AS who have a normal intelligence level can have full, productive lives. Vocational training will help those with borderline intelligence.

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ORGANIZATIONS

Apert International, PO Box 2571, Columbia, SC 29202, (803)732-2372, info@apert-international.org, <http://www.apert-international.org>

FACES: The National Craniofacial Association, PO Box 11082, Chattanooga, TN 37401, (423) 266-1632, (800) 332-2373, faces@faces-cranio.org, <http://www.faces-cranio.org/Disord/Apert.htm>

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Arginase deficiency

Definition

Arginase deficiency is an inborn error of metabolism that results from a defect in the urea cycle. This cycle is a series of biochemical reactions that occur in the body in order to remove ammonia from the bloodstream.

Description

Arginase deficiency is also known as ARG deficiency, argininemia, or hyperargininemia. The disorder belongs to a group of conditions known as urea cycle disorders. During normal cellular function, proteins are broken down into nitrogen waste products and put into the blood stream as ammonia. The urea cycle transforms this toxin into urea, which can be safely removed by the kidneys as urine. Lack of an enzyme from the urea cycle, such as arginase, can result in the buildup of toxins in the body. There are eight diseases that belong in the

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Urea cycle disorder—A disease caused by a lack of an enzyme that cleans the blood of ammonia.

group of urea cycle disorders. Arginase deficiency is thought to be one of the rarest of these disorders.

The enzyme arginase is the last step of the urea cycle, where it turns arginine into ornithine and urea. If a person is born with arginase deficiency, he or she will build up arginine in the blood. Since earlier steps in the urea cycle are left intact, patients may or may not build up ammonia in the blood. If not treated, children can develop muscle problems and developmental delays.

Genetic profile

Arginase deficiency is inherited in an autosomal recessive fashion and linked to mutations in the *ARG1* gene. Thus, both parents of an affected child are typically found to be carriers of a mutation in *ARG1*. The chance of having an additional child with arginase deficiency is 25%.

Demographics

Like other autosomal recessive diseases, arginase deficiency remains rare. The first signs of this disease tend to occur while the patient is still very young. A child may have a normal birth, infancy, and may not show any signs of the disease for quite a few years. There is no racial difference. Furthermore, men and women are both as likely to have the disease.

Arginase deficiency, along with N-acetylglutamate synthetase deficiency, is considered to be the least common of the urea cycle defects. Its incidence has been estimated at between one in 350,000 and fewer than one in 1,000,000, but the true incidence in non-related populations is unknown. Arginase deficiency may be more common in parts of Japan and among French Canadians.

Signs and symptoms

The onset of this disease tends to be subtle. While the first symptoms of this disease show up while the patient is still a baby, some infants are said to be normal before beginning to have the symptoms. In many cases, the disease is not found at first. When the initial symptoms

manifest themselves, the child is diagnosed with “cerebral palsy” (a general term for neurologic problems that result in altered development—often starting at birth). The symptoms include: missing developmental milestones, poor feeding, fussy behavior, lower alertness, spasticity of lower limbs, poor coordination, tremors, seizures, and mental disability. Other symptoms include choreoathetotic movements (strange, uncontrollable writhing movements of limbs). Additionally, for affected patients, a high-protein meal makes symptoms worse. Affected children may also have an enlarged liver from the buildup of toxins.

Diagnosis

In the United States, most affected individuals will be identified by newborn screening at birth and before the onset of symptoms. However, in the absence of newborn screening, diagnosis is made after children are observed with symptoms. The illness should be considered for children who have both a developmental delay and stiffness of the ankles and legs that interfere with walking. It should also be included anytime that other urea cycle disorders are considered. A diagnosis is made when an individual is either found to have biallelic mutations in *ARG1* or reduced red blood cell arginase enzyme activity. Almost all individuals with arginase deficiency have no detectable arginase enzyme activity in red blood cells. In other urea cycle disorders, patients tend to have hyperammonemia (a high amount of ammonia in the blood), but in arginase deficiency the ammonia levels are rarely raised.

If patients have one child with this disease, they can be counseled about the risk of disease in future children. Since this disease is inherited in an autosomal recessive pattern, each time carrier parents have a child there is a 25% chance that they will have an affected child. Prenatal diagnosis for at-risk pregnancies is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15–18 weeks’ gestation. However, both disease-causing alleles of an affected family member must be identified in the family before prenatal testing can be performed. If molecular genetic testing is not possible, prenatal diagnosis for pregnancies at 25% risk may be possible by measuring arginase enzyme activity in fetal red blood cells obtained by percutaneous umbilical blood sampling after 18 weeks’ gestation.

Treatment and management

Treatment of arginase deficiency is similar to treatment methods for other urea cycle disorders. One would want to decrease, as much as possible, the amount of

QUESTIONS TO ASK YOUR DOCTOR

- What signs or symptoms indicate that our child may have arginase deficiency?
- Are tests available to confirm a diagnosis of arginase deficiency?
- What do the diagnostic tests for arginase deficiency involve?
- What kinds of treatment or other medical care is available for a child with arginase deficiency?

arginine that is building up. This is done through control of protein intake in foods. Arginine is one of the twenty amino acids that make up proteins, and if its intake is stopped, then the amount that can build up in a patient will be lessened. Supplements of essential amino acids (amino acids that cannot be made by the body and must be obtained through food) are given so that children do not become ill from malnourishment. Medications may be used that help block ammonia production. These medications are typically administered intravenously, but sometimes orally.

Other symptoms can also be controlled. For example, patients who have seizures should be treated with an anti-seizure medication. Also, physical therapy can be helpful for patients with stiff legs and walking problems.

Carrier testing for at-risk family members using red blood cell arginase activity detects most carriers. Carrier testing for at-risk family members is available once the mutations have been identified in the family line.

Prognosis

The long-term effects of arginase deficiency are better than that for other urea cycle disorders. With proper food intake and medical management, children can have much milder symptoms. Prior to newborn screening, the disease was often not found until after severe problems occurred. Data about patients that live until they are adults is limited, but many cases of patients living through teenage years have been reported. Hence, prognosis is clearly related to how early the disease can be found.

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CLIMB (Children Living with Inherited Metabolic Diseases), Climb Building, 176 Nantwich Rd., Crewe, United Kingdom CW2 6BG, (440) 845-2412173, enquiries@climb.org.uk, <http://www.CLIMB.org.uk>

National Information Center for Metabolic Diseases (NICMD), Climb Building, 176 Nantwich Rd., Crewe, UK CW2 6BG, (0800) 652-3181, <http://www.climb.org.uk>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., PO Box 1968, Danbury, CT 06813-1968, (203) 744-0100, (800) 999-6673, (203) 798-2291, <http://www.rarediseases.org>

National Urea Cycle Disorders Foundation, 75 S. Grand Ave., Pasadena, CA 91105-1602, (626) 578-0833, (800) 386-8233, info@nucdf.org, <http://www.nucdf.org>

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Arginemia see **Arginase deficiency**

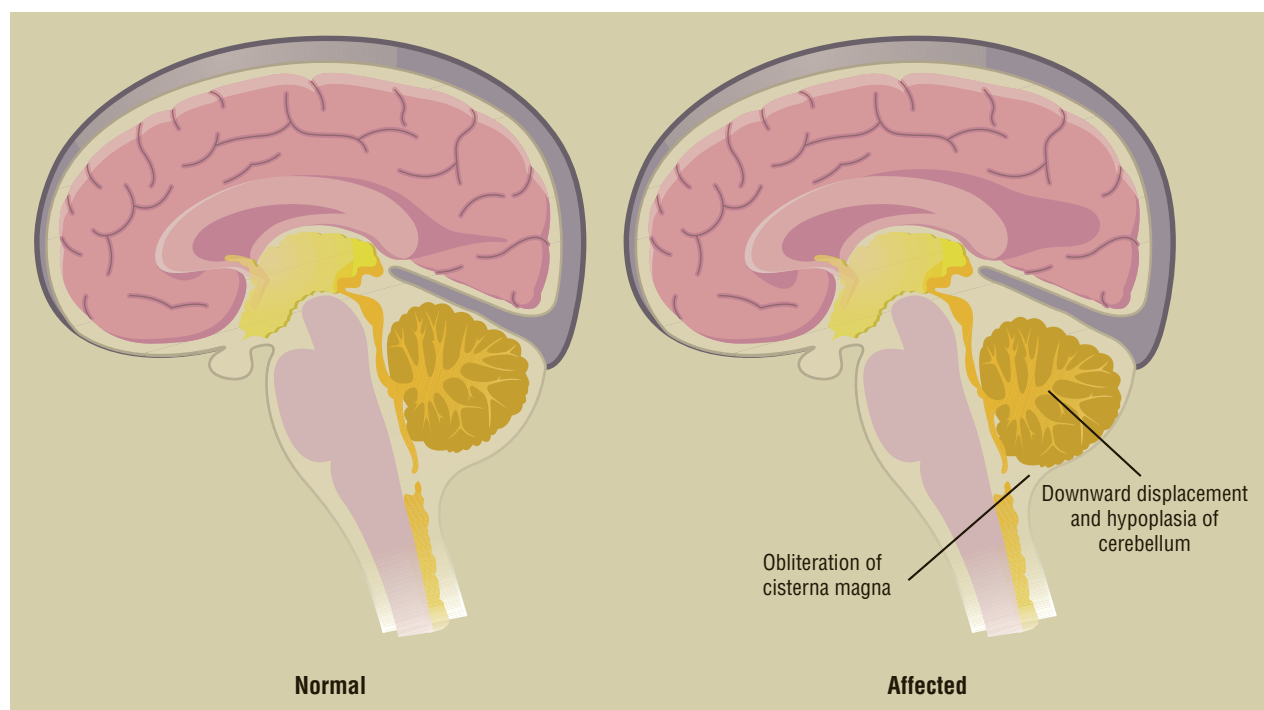
Arnold-Chiari malformation

Definition

Arnold-Chiari malformation is an abnormality in the lower portion of the skull and either the cerebellum or the brain stem. There are several different types of Arnold-Chiari malformations, which may be caused by rare genetic abnormalities.

Description

In 1891, Austrian pathologist Hans Chiari first described what have become known as Arnold-Chiari malformations types I, II, and III. The German pathologist Julius Arnold expanded the definition of type II.



Arnold-Chiari malformation: brain comparison (Gale)

The term “Arnold-Chiari malformation” is now used to define all four types. Arnold-Chiari malformation is also called Arnold-Chiari syndrome or Chiari malformation.

The cerebellum and brain stem are located in the posterior fossa, an area at the base of the skull attached to the spinal cord. In an Arnold-Chiari malformation, the posterior fossa does not form properly. Because the posterior fossa is small, the brain stem, cerebellum, or cerebellar tonsils are squeezed downward through an opening at the bottom of the skull. The cerebellum, brain stem, or both may extend beyond the skull or protrude into the spinal column. Therefore, Arnold-Chiari malformations are also known as congenital tonsillar herniation, tonsillar ectopia, or tonsillar descent. The displaced tissues may obstruct the flow of cerebrospinal fluid (CSF), the fluid that flows through and around the brain and spinal cord to nourish and protect them. Obstructed CSF flow can cause various symptoms, including dizziness, muscle weakness, numbness, vision problems, headache, and problems with balance and coordination.

Although the malformation is almost always present at birth (congenital), symptoms may not develop until later in life. Some mild forms never cause symptoms and those affected are unaware that they have the condition. However, there is much variety in symptoms and severity of Arnold-Chiari malformation.

Types

Arnold-Chiari malformations are classified according to their severity and the portion of the brain that protrudes into the spinal column.

- Type 0—in which there is little or no descent of the cerebellar tonsils—may still produce symptoms because of abnormalities in the flow of the CSF.
- Type I, in which the base of the skull and upper spine do not form properly, is the most common and least severe malformation. Symptoms may arise during adolescence or adulthood, or there may be no symptoms, and the malformation is only discovered during examination for another condition.
- Type II is more severe. The back of the brain protrudes through the bottom of the skull. It is almost always associated with a form of spina bifida, in which the spinal canal and backbone do not close before birth. A sac called a myelomeningocele protrudes through the abnormal opening in the spinal column and may contain part of the spinal cord, spinal membranes, or CSF. Type II is diagnosed in childhood and can cause partial or complete paralysis of the body below the opening in the spinal column.
- Types III and IV are very rare and cause severe neurological defects. In type III, the back of the brain protrudes through an opening in the back of the skull.

With Type IV, the back of the brain fails to develop properly.

Arnold-Chiari malformations can be associated with other conditions in addition to spina bifida. These can include excessive fluid in the brain (hydrocephalus), a fluid-filled cyst in the spinal cord (syringomyelia), or spinal curvature.

Genetic profile

The causes of Arnold-Chiari malformations are unknown. The malformation almost always occurs during fetal development. It has been hypothesized that the cerebellum is forced downward because the base of the skull is too small or that there is overgrowth in the cerebellar region that pushes the cerebellum downward into the spinal canal. In some cases there appears to be a genetic component, with the abnormality affecting multiple family members. However, no genes responsible for the malformation have yet been identified. It is also possible that Arnold-Chiari malformations are caused by exposure to harmful substances during prenatal development.

Demographics

In the past, Arnold-Chiari malformation was estimated to occur in about 1 in every 1,000 births. However, the increased use of diagnostic imaging has suggested that it may be much more common. Its incidence appears to be higher in females than in males. Type II appears to be more prevalent in certain groups, including people of Celtic descent.

Signs and symptoms

Symptoms of Arnold-Chiari malformations vary greatly. Some people with type I malformations never develop symptoms. More often, symptoms appear in the third or fourth decade of life. Most symptoms arise from pressure on the cranial nerves or brain stem. They may be vague or resemble symptoms of other medical problems, delaying diagnosis. Headache is one of the most common symptoms. The headache generally begins in the neck or base of the skull and may radiate through the back of the head. Coughing, sneezing, or bending forward may bring on these headaches, which can last minutes or hours and may have associated nausea.

When Arnold-Chiari malformation occurs in association with other congenital defects, diagnosis may be made shortly after birth. In infants, symptoms are caused by pressure on the lower portion of the brain and the brain stem. These symptoms may include:

- vomiting
- chronic cough or hoarseness

KEY TERMS

Brain stem—The lower part of the brain that connects to the spinal cord.

Cerebellar tonsils—Lobes on the undersurface of each hemisphere of the cerebellum.

Cerebellum—The part of the brain between the brain stem and back of the cerebrum, consisting of two lateral lobes, and a median lobe. Its primary functions include muscle coordination and maintenance of equilibrium.

Cerebrospinal fluid (CSF)—Clear fluid that circulates in the brain and spinal cord to nourish, cushion, and maintain uniform pressure.

Hydrocephalus—Excess accumulation of cerebrospinal fluid in and around the brain, causing increased pressure.

Magnetic resonance imaging (MRI)—A technique that uses magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Myelomeningocele—A sac protruding through an abnormal opening in the spinal column.

Posterior fossa—The area at the base of the skull attached to the spinal cord.

Spina bifida—An abnormal opening in the spine.

Syringomyelia—Excess fluid in the spinal cord.

- choking
- weakness
- limb paralysis
- developmental delays

Some people with Arnold-Chiari malformations have difficulty swallowing. They may report that food “catches” in their throat when they swallow. Other symptoms can include:

- pain in the neck or upper arm, which is often more severe on one side of the body
- tingling, burning, numbness, or sensations of “pins and needles”
- lightheadedness
- fainting
- weakness in an arm, a hand, or the legs
- unsteadiness or leaning to one side
- uncontrolled shaking or trembling
- difficulty walking

QUESTIONS TO ASK YOUR DOCTOR

- What type of Arnold-Chiari malformation do I have?
- Are there treatments other than surgery?
- Am I a candidate for a clinical trial?
- What is the prognosis for my type of malformation?
- What type of research is being conducted on Arnold-Chiari malformation?

- visual problems, including blurred vision, double vision, blind spots, eye pain, or rapid eye movement
- hearing impairment or ringing in the ears

Diagnosis

Arnold-Chiari malformation is diagnosed with a complete neurologic exam and magnetic resonance imaging (MRI), computed tomography (CT) scans, or x-rays. An MRI uses magnets and radio waves to produce a picture of the brain and can reveal crowding between the brain and spinal cord. The length of brain stem located in the spinal canal is measured. Analysis is used to evaluate the flow of CSF in the brain and spinal cord.

Treatment and management

Treatment depends on symptoms and the degree of pressure on the brain. Arnold-Chiari malformation may be treated with surgery to remove a small portion of the bone at the base of skull to enlarge and decompress the posterior fossa and relieve pressure on the cerebellar area. Surgery may also be required to correct the flow of CSF and to prevent progressive damage to the central nervous system. Multiple surgeries are sometimes required.

Other treatments include:

- drugs to manage headaches, pain, and other symptoms
- physical or occupational therapies for improving muscular coordination and trembling
- speech therapy for speech or swallowing problems

Clinical trials

Updated clinical-trial information on Chiari malformation and related conditions can be found at <http://clinicaltrials.gov>.

Prognosis

Prognosis depends on the type of Arnold-Chiari malformation and its severity. Patients with type I who undergo surgery to treat symptoms have an excellent long-term prognosis, although full recovery may take several months. Prognosis for type II depends on the severity of the myelomeningocele and spina bifida. Many patients with more severe forms may improve with surgery, although any paralysis is usually permanent.

Resources

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"Chiari Malformation." WebMD. October 29, 2020. <https://www.webmd.com/brain/chiari-malformation-symptoms-types-treatment> (accessed May 21, 2021).

ORGANIZATIONS

American Syringomyelia & Chiari Alliance Project, PO Box 1586, Longview, TX 75606-1586, (903) 236-7079, (800) ASAP-282, (903) 757-7456, Info@ASAP.org, <http://asap.org>

National Institute of Neurological Disorders and Stroke, NIH Neurological Institute, PO Box 5801, Bethesda, MD 20824, (301) 496-5751, (800) 496-5751, <http://www.ninds.nih.gov>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Spina Bifida Association, PO Box 17427, Arlington, VA 22216, (202) 944-3285, (202) 944-3295, sbaa@sbaa.org, <http://www.spinabifidaassociation.org>

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Arteriohepatic dysplasia (AHD) see **Alagille Syndrome**

Arthrogryposis multiplex congenita

Definition

Arthrogryposis multiplex congenita (AMC) is a term used to describe the presence of two or more (multiplex) joint contractures (arthrogryposis) present at birth (congenita). A joint contracture is a limitation of the normal range of motion of a joint. AMC is a clinical finding, an observation made during examination, not a diagnosis.

Description

Arthrogryposis is a finding in more than 300 conditions. The conditions are classified based on the presence or absence of neurological problems such as intellectual disability or brain malformations. If there are no neurological issues, then the AMC may be caused by amyoplasia, distal arthrogryposis, connective tissue disorders, or fetal crowding. If neurological problems are present, then the condition may be caused by a central nervous system abnormality or muscular disease. AMC disorders are not progressive, meaning the symptoms do not worsen with age.

Genetic profile

Various forms of arthrogryposis have been traced to a variety of gene mutations and inheritance patterns. Amyoplasia is typically sporadic, and does not run in families. Most of the distal arthrogryposes are inherited in an autosomal dominant pattern. If a person is affected with the condition, they have a 50% chance to pass it to each child. The chromosomal location of many of the DAs are known, and genetic testing is available.

In about 30% of cases of AMC, a genetic cause can be identified. Genetic syndromes are inherited in various ways with a recurrence risk from low to 50%. Genetic testing is available for many genetic syndromes. Recurrence risks with chromosomal changes can vary as well and are specific to the chromosomal change in the family. AMC may also be caused by a combination of unknown genetic and environmental factors and have a minimally increased recurrence risk. Environmental causes would be associated with a low recurrence risk assuming another fetus is not exposed to that same environmental factor. Often the cause for AMC is not known. Thorough testing will help identify a diagnosis. Genetic counseling can be provided to describe the recurrence risks in the family.

Demographics

Arthrogryposis occurs in approximately one in every 3,000 live births. Most cases of arthrogryposis are caused by a lack of normal joint movement during fetal

development. For this reason, cases of non-genetic arthrogryposis are more frequent in multiple-birth pregnancies than in single-birth pregnancies. Most forms of arthrogryposis are not known to affect one sub-population more than another. All forms of AMC appear to affect males and females at the same rate, with the exception of the x-linked forms, which are more common in males.

Signs and symptoms

The symptoms of AMC are primarily immobility of two or more joints. The most common joints affected are those in the fingers and toes. Less commonly affected joints are the knees and elbows. Rarely affected joints are the jaws, hips, and shoulders.

Neurological Features Absent

"Amyoplasia" means absence of muscle development and is the most common form of arthrogryposis without neurological symptoms; it is generally sporadic in appearance. Amyoplasia is characterized by contractures of the wrists, elbows, and knees, an abnormal internal rotation of the shoulders, and clubfeet. Those with amyoplasia are more likely to have a facial hemangioma, or red birthmark, an abdominal defect like gastroschisis, and normal intelligence.

Distal arthrogryposis (DAs) are all characterized by contractures of the fingers and toes. Each type can be distinguished by specific characteristics:

- Type 1a DA: camptodactyly, clubfeet that point inward and down (talipes equinovarus).
- Type 2 DA: down-slanting palpebral fissures (the line from the inner corner of an eyelid to the outer corner), a small mouth with pursed lips, malformations of the nose that cause a whistling sound when breathing, scoliosis, and some instances of mild developmental delays. This type is also known as Freeman-Sheldon Syndrome.
- Type 2b DA: consists of the characteristics of Type 2 with the addition of earlobes that are attached to the skin of the face, prominent nasolabial folds, and a permanent bending of one or more fingers (camptodactyly). This form is also called Sheldon-Hall Syndrome.
- Type 3 DA: cleft palate, talipes equinovarus, camptodactyly, short stature, and vertebral abnormalities.
- Type 4 DA: short stature, an abnormally short neck, immobile facial expressions, camptodactyly, and the lack of the normal prominent creases (flexion creases) on the palms of the hands.
- Type 5 DA: contractures of the arms and legs, limited eye movement, deep-set eyes, and abnormal coloring of the retina of the eye.

KEY TERMS

Amniocentesis—A procedure performed during pregnancy to obtain amniotic fluid. A needle is inserted into the maternal abdomen and amniotic sac and fluid is withdrawn. Fetal cells found in the fluid can be used for genetic studies.

Amniotic fluid—The fluid that surrounds a developing baby during pregnancy. Having an adequate amount of amniotic fluid is important for fetal muscle and joint development.

Amyoplasia—The most common form of arthrogryposis multiplex congenita, characterized by sporadic and recurrent contractures of the wrists, elbows, and knees; an abnormal internal rotation of the shoulders; and clubfeet.

Arthrogryposis—Abnormal joint contracture.

Camptodactyly—An abnormal permanent bending of one or more fingers or toes.

Computerized tomography (CT)—A series of x rays combined to provide a cross section view of bones and soft tissue.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Distal arthrogryposis—A disorder characterized by contractions of the muscles in the hands.

Electromyography—An electrical recording of muscle activity used to diagnose neuromuscular disease.

Flexion creases—The lines on the palms of the hands and the soles of the feet from normal bending of these body parts. Some individuals affected with arthrogryposis lack these characteristic lines.

Gastroschisis—An opening in the abdomen near the umbilical cord that allows the intestines to protrude outside the body.

Magnetic resonance imaging (MRI)—A method of visualizing organs and tissues with a magnetic field and radio waves.

Palpebral fissures—The opening between the upper and lower eyelids.

Scoliosis—An abnormal, side-to-side curvature of the spine.

Talipes equinovarus—A type of clubfoot characterized by a downward and inward-pointing foot.

- Type 6 DA: camptodactyly, an abnormally small head (microcephaly), and hearing loss caused by an abnormality of the auditory nerve (sensorineural hearing loss).
- Type 7 DA: camptodactyly when an affected individual attempts to open the hand, short stature, abnormally short muscles in the legs, and an inability to open the mouth completely (trismus).
- Type 8 DA: contractures of the wrist or ankles or both, short stature, and scoliosis.
- Type 9 DA: lack of muscle tone and development, abnormally low shoulder-to-shoulder width to body height ratio (marfanoid habitus), severe outward curvature of the spine in the neck and upper back (kyphoscoliosis), and contractures of the hips and shoulders.
- Type 10DA: plantar contractures or those involving the feet and ankles.

The most serious forms of DA are types 6 and 9.

Fetal crowding is another cause of AMC. A low amount of amniotic fluid around the fetus, more than one fetus, a septation of the uterus, or growths in the uterus can all result in less space for the fetus to move.

Neurological features present

When neurological features are present, then genetic or infectious causes are more likely. In these cases, the contractures are more often unilateral rather than symmetric. Genetic causes of AMC include changes in the number or structure of chromosomes, or packages of genetic information found in the cells. For instance, a deletion or rearrangement of chromosomal material or an extra chromosome may cause AMC. There are also many single-gene disorders associated with AMC. These conditions can be inherited in a variety of ways. One example is X-linked spinal muscular atrophy. Some infections (rubella, varicella, cytomegalovirus, toxoplasmosis) or maternal conditions are also associated with an increased risk for AMC. If a mother is affected with myasthenia gravis, then there is an increased risk for AMC. Children born with muscular disorders like myotonic dystrophy and connective tissue disorders like pterygium syndrome are also more prone.

Diagnosis

A diagnosis of AMC is indicated by the presence of two or more joint contractures present from birth. The symptoms that are present allow the differential diagnosis

QUESTIONS TO ASK YOUR DOCTOR

- What is the likely cause for AMC in this case?
- What other clinical features may be present with the diagnosis for AMC in this case?
- What is the recurrence risk with the particular diagnosis of AMC in this case?
- What are the surgical risks?
- What form of treatment do you find more beneficial, splints, braces, or removable casts?
- How many hours a day should a splint, brace, or removable cast be worn while my child is awake?
- How does massage therapy benefit this condition?

among the many causes of AMC. Sometimes AMC is noted on a prenatal ultrasound. Some of the typical findings are lack of motion, unusual position of joints, joints that are fixed into position, extra fluid in the brain, small growth, and scoliosis. When AMC is suspected during a pregnancy, prenatal testing like amniocentesis may be offered for more information about a possible diagnosis. By collecting some of the fetal cells, it is possible to view the chromosomes of the fetus and perform a more detailed genetic study called a comparative genomic hybridization. When a child is born with contractures, it is important to obtain x rays of all joints as well as the pelvis and spine. In addition, imaging studies such as a computerized tomography (CT) or magnetic resonance imaging (MRI) may provide more information about the brain and muscles. Electromyography can be useful in identifying neuromuscular disorders. Blood work for viral and genetic studies can also be performed. If an infant or child dies, an autopsy can be considered for more information towards a diagnosis.

Treatment and management

A multi-disciplinary team approach is best for those with AMC. Members of the team should include a pediatrician, neurologist, orthopedist, and geneticist. Physical therapy has proven an effective treatment for almost all forms of AMC. Splints, braces, and removable casts are often used to improve joint positioning. In most cases, these orthopedic devices are used only at night so that proper joint mobility can be encouraged during the waking hours. Occasionally, surgery to repair foot and ankle position may be necessary, especially in the case of talipes equinovarus. Much less frequently, orthopedic surgery of the hips, knees, elbows, shoulders, and wrists is required. Tendon replacement surgery has also been successful in some individuals affected with AMC.

Prognosis

Prognosis for those with AMC depends on the underlying cause of the condition. In cases of AMC that do not involve complications of the central nervous system, the outlook is quite good and lifespan is not shortened. Most individuals can achieve a sufficient range of motion in their affected joints to live healthy, complete lives. AMC is non-progressive; therefore, once a joint contracture has been repaired through physical therapy, surgery, or both, it will generally not return to a state of abnormal contracture.

When AMC is complicated by involvement of the central nervous system, approximately half of affected individuals die in infancy. Among the surviving half, many have varying degrees of intellectual disability.

Many families find it helpful to connect to other families dealing with a similar condition. One national support organization for those affected with AMC and their families is called Avenues. They offer resources, research information, updates, publications and ways to connect to other families. Another similar group is called Arthrogryposis Multiplex Congenita Support, Inc. It sponsors events and newsletters and hosts an annual conference.

Resources

BOOKS

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Hall, Judith G. "The Mystery of Monozygotic Twinning II: What Can Monozygotic Twinning Tell Us about Amyoplasia from a Review of the Various Mechanisms and Types of Monozygotic Twinning?" *American Journal of Medical Genetics. Part A* 185, no. 6 (June 2021): 1822–1835. DOI: 10.1002/ajmg.a.62177.

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ORGANIZATIONS

Arthrogryposis Multiplex Congenita Support, PO Box 6291,
Spartanburg, SC 29304, <http://www.amcsupport.org>
AVENUES (National Support Group for Arthrogryposis
Multiplex Congenita), info@avenuesforamc.com, <http://www.avenuesforamc.com>

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Arthropathy-camptodactyly syndrome

Definition

Arthropathy-camptodactyly syndrome is a disorder affecting the joints of the fingers. “Arthropathy” refers to a disease or disorder affecting a joint, and camptodactyly is a congenital condition, meaning present at birth, characterized by the bending of one or more fingers.

Description

In people with arthropathy-camptodactyly syndrome, one or more fingers are bent. Other joints may be affected as well. Some children with arthropathy-camptodactyly syndrome also have swollen knees and ankles and hip pain.

Problems with the pericardium, the sac that surrounds the heart, are also common in children with arthropathy-camptodactyly syndrome. In many cases, the pericardium is removed, a surgical procedure called pericardiectomy.

Genetic profile

Arthropathy-camptodactyly syndrome typically occurs in children (both male and female) whose parents are related by blood. In one case, it was determined that the parents of children with arthropathy-camptodactyly syndrome shared the haplotype A1-Bw21. The gene map locus 1q24-q25 is also implicated.

Demographics

Cases of arthropathy-camptodactyly syndrome have been diagnosed in Canada, India, Mexico, Newfoundland, Pakistan, Saudi Arabia, and Turkey, as well as in African Americans.

Signs and symptoms

People with arthropathy-camptodactyly syndrome have a bend in the joint of one or more fingers. Other symptoms include swollen knees and ankles and hip pain.

KEY TERMS

Allele—One of two or more alternate forms of a gene.

Arthropathy—Any disease or disorder that affects joints.

Camptodactyly—A condition characterized by the bending of one or more fingers.

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Congenital disorder—Refers to a disorder that is present at birth.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Gene—A building block of inheritance that contains the instructions for the production of a particular protein and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Haplotype—The set of alleles on one chromosome.

Locus—The physical location of a gene on a chromosome.

Inflammation of the sac lining the heart (pericarditis) is another observed symptom, often accompanied by chest pain. The pain is usually sharp and felt behind the breast bone (sternum).

Diagnosis

Aside from the physical observation of bent fingers, no test is presently available to confirm diagnosis.

Treatment and management

Surgery can correct the bent fingers disorder that characterizes arthropathy-camptodactyly syndrome. Removal of the tendon sheaths in the affected fingers can help keep them mobile. Removal of the membranes surrounding a joint (synovectomy) of other body joints, such as knees, can also help maintain mobility.

In at least one case, a bent finger straightened without intervention.

QUESTIONS TO ASK YOUR DOCTOR

- What do you expect will be the outcome of surgery?
- What are the risks associated with surgery?
- What are the chances that the joint bending will resolve without surgery?
- What are the risks and expected benefits of pericardiectomy?

Pericardiectomy is often performed to relieve the pericarditis often associated with the disorder.

Prognosis

Case studies show that children with arthropathy-camptodactyly syndrome have lived into their teens. There is reason to believe that with the proper treatment, the disorder is not life shortening.

Resources

BOOKS

Moore, Keith L., et al., eds. *Before We Are Born: Essentials of Embryology and Birth Defects*. 10th ed. London: Elsevier, 2019.

Saudubray, Jean-Marie, Georges van den Berghe, and John H. Walter, eds. *Inborn Metabolic Diseases: Diagnosis and Treatment*. 7th ed. New York: Springer, 2021.

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Ekinci, Rabia Miray Kislal, et al. "Camptodactyly-Arthropathy-Coxa Vara-Pericarditis Syndrome Resembling Juvenile Idiopathic Arthritis: A Single-Center Experience from Southern Turkey." *Molecular Syndromology* 12, no. 2 (April 12, 2021): 112–117. DOI: 10.1159/000513111.

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ORGANIZATIONS

Genetic Disease Foundation, 1425 Madison Ave., Box 1498, New York, NY 10029, <http://www.geneticdiseasefoundation.org>

Sonya Kunkle

Asperger syndrome

Definition

Asperger syndrome (AS) is the name formerly applied to some individuals with autism spectrum disorder (ASD) who are considered to function at a significantly higher level than most people with ASD. AS was first described by Hans Asperger, an Austrian psychiatrist, in 1944. Asperger's work was unavailable in English before the mid-1970s; as a result, AS was often unrecognized in English-speaking countries until the late 1980s. Before the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV 1994), there was no official definition of AS. While AS was defined in the DSM-IV, the most recent revision of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), released in 2013, does not contain Asperger syndrome, which is now included under the umbrella of Autism Spectrum Disorders (ASD). However, this source includes a table by which ASD can be categorized into three levels, including Level I, which requires support; Level 2 which requires substantial support, and Level 3, for which the individual with ASD requires very substantial support. With regard to ASD, individuals with AS would be categorized as Level 1, requiring the least amount of support. Prior to the DSM-5, Asperger syndrome was sometimes referred to as high-functioning autism (HFA), as it is considered to be the mildest form of AS and thus requires the lowest level of needed assistance.

Description

Children with AS learn to talk at the usual age and often have above-average verbal skills. They have normal or above-normal intelligence. They also have the ability to take care of themselves, although personal interactions with others may be confusing and challenging for them. The distinguishing features of people with ASD are problems with social interaction, particularly reciprocating and empathizing with the feelings of others; difficulties with nonverbal communication (e.g., understanding and interpreting facial expressions and body language); peculiar speech habits that include repeated words or phrases, and sometimes a flat, emotionless vocal tone; a fascination with obscure or limited subjects often to the exclusion of other interests; sometimes clumsy and awkward physical movements; and odd or eccentric behaviors (hand wringing or finger flapping; swaying or other repetitive whole-body movements; and watching spinning objects for long periods of time).

Risk factors

Research clearly indicates a hereditary risk for ASD, very few genes involved have been identified. According to Seyed Alireza Hosseini and Mohammed Molla, genomic sequencing data indicates that as many as one thousand genes may be implicated in a predisposition to ASD. Some researchers have noted that people with AS and other disorders related to ASD may carry variations of the gene *GABRB3*, which is related to differing capacities for empathy; however, much further research is needed. Researcher Dan Bai and colleagues have found an 80% genetic risk for ASD in a very large study involving children in five countries, including Denmark, Finland, Israel, Sweden, and western Australia. The researchers analyzed data from children from 1998 through 2011, which included two million children. Of those, 22,156 were diagnosed with ASD. This study provided strong evidence that most of the risk for ASD stems from genetics rather than environment. Of course, the environment also plays a role in ASD, including the prenatal environment. In a study of more than 273,000 pregnant women and their children in Sweden by H. Gardener and colleagues, the researchers found that the women who took multivitamins, iron, and folic acid supplements during pregnancy had children with about half the rate of ASD, compared to the mothers who did not take these supplements, or 0.26%, versus 0.48% among the mothers who did not take nutritional supplements. This is a tiny difference in that both were less than 1%; however, most pregnant women, upon hearing this data, would be willing to take supplements during pregnancy to decrease their odds of having a child with ASD.

Most children with AS are diagnosed between the ages of five and nine years of age; however, some are not diagnosed until adolescence or adulthood. In addition, misdiagnoses are common. AS has been confused with other neurological disorders, such as Tourette syndrome as well as attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), or obsessive-compulsive disorder (OCD).

Demographics

Based on an analysis of the prevalence of ASD in the United States by Matthew J. Maenner and colleagues, published in 2016, one in 54 children is diagnosed with ASD by the age of eight years. The researchers analyzed data from 11 states, including Arizona, Arkansas, Colorado, Georgia, Maryland, Minnesota, Missouri, New Jersey, North Carolina, Tennessee, and Wisconsin. They found that boys had four times the rate of ASD prevalence of girls. There were few racial differences in the prevalence of ASD; for example, the researchers found about the same prevalence of ASD in non-Hispanic whites and non-

Hispanic Black children; however, there was a lower prevalence among Hispanic children. The reasons for this are unknown. The researchers also found the prevalence of ASD varied considerably from state to state; for example, the rate (not a percentage) was 13.1 per 1,000 children in Colorado, and it was a much higher rate of 31.4 per 1,000 children in New Jersey. Some studies suggest that the incidence of autism spectrum disorders is increasing. Others suggest that increased awareness and broadening of the diagnostic criteria play a role in the perceived increase.

Research studies have made no connection between Asperger syndrome and childhood trauma, abuse, or neglect. Nor does receiving childhood immunizations increase the risk for the development of ASD.

Signs and symptoms

In young children, the symptoms of AS typically include problems recognizing and responding to social cues and understanding the basics of interacting with other children. The child may wish to have friendships yet struggle to make friends. Behaviors that are easy for other children, such as appropriate eye contact and interpreting body language, are baffling to people with ASD. Another issue is that children with AS or ASD may be bullied in school, largely because of their differences in behavior. However, Brooke N. Winchell and colleagues note that when children who do not have AS or ASD have the opportunity to learn about the disorder, they have more positive attitudes toward people with ASD. The authors assert that similarities between children with AS and others should be emphasized to children who are learning about AS, and that perceptions of lower ability or status should be minimized. In addition, peers should learn about ways to interact with people with ASD, and the strengths of individuals with ASD should be pointed out. These actions can decrease the risk for bullying.

Most children with Asperger syndrome are diagnosed during the elementary school years, because the symptoms of the disorder become more apparent at that point. They include:

- Poor pragmatic language skills. This phrase means that the child does not use the right tone or volume of voice for a specific context and does not understand that using humorous or slang expressions also depends on social context.
- Problems with hand-eye coordination and other visual skills.
- Problems making eye contact with others.
- Learning difficulties, which may range from mild to severe.
- Tendency to become absorbed in a particular topic and not know when others are bored with conversation about

it. At this stage in their education, children with AS are likely to be labeled as “nerds.”

- Repetitive behaviors. These include such behaviors as counting a group of coins or marbles over and over, reciting the same song or poem several times, or buttoning and unbuttoning a jacket repeatedly.

Adolescence is one of the most painful periods of life for young people with Asperger’s, because social interactions are more complex in this age group and require more subtle social skills. According to author Tony Attwood, the person with AS is likely to experience great difficulty with planning and organizing, skills increasingly that are needed in school and that affect grades when they are absent. In their teenage years, memorized information becomes less important than learning to analyze the meaning of the information. In addition, teens are often expected to work in groups or with partners, which is an area where adolescents with AS have difficulty.

Little research has been done regarding adults with AS. Some have serious difficulties with social and occupational functioning, but others are able to finish their schooling, join the workforce, and marry and have families.

Diagnosis

There are no blood tests or brain scans that can be used to diagnose AS. However, as of 2021, the National Institutes of Health is actively conducting brain studies of the infant siblings of children diagnosed with ASD to see whether there are identifiable brain changes in the younger child that may be predictive for the later development of ASD. While the DSM-IV (1994) had an “official” list of symptoms for the disorder, the DSM-5 (2013) placed Asperger syndrome under the more-encompassing term of autism spectrum disorders. Prior to this change, having two separate categories with significant overlap of symptoms—Asperger syndrome and high-functioning autism—made the diagnosis of either condition both difficult and inexact. Having a single encompassing category and recognizing that symptoms fall along a spectrum of behavior are anticipated to aid research efforts.

Although most children with AS are diagnosed between ages five and nine, many are not diagnosed until adulthood. Misdiagnoses are common.

The original inclusion of AS as a separate diagnostic category in DSM-IV was justified on the basis of a large international field trial of over one thousand children and adolescents. Nevertheless, the diagnosis of AS is also complicated by confusion with such other diagnostic categories as “high-functioning (IQ 70) autism,” or HFA, and “schizoid personality disorder of childhood.” With regard to the latter, AS is not an unchanging set of personality traits but instead has a developmental dimension.

DSM-IV criteria for Asperger syndrome

DSM-IV specified six diagnostic criteria for AS:

- The child’s social interactions are impaired in at least two of the following ways: markedly limited use of nonverbal communication, lack of age-appropriate peer relationships, failure to share enjoyment, interests, or accomplishment with others, lack of reciprocity in social interactions.
- The child’s behavior, interests, and activities are characterized by repetitive or rigid patterns, such as an abnormal preoccupation with one or two topics, or with parts of objects; repetitive physical movements; or rigid insistence on certain routines and rituals.
- The patient’s social, occupational, or educational functioning is significantly impaired.
- The child has normal age-appropriate language skills.
- The child has normal age-appropriate cognitive skills, self-help abilities, and curiosity about the environment.
- The child does not meet criteria for another specific PDD or schizophrenia.

DSM-5 criteria for autism spectrum disorders

DSM-5 specifies five diagnostic criteria for Autism Spectrum Disorder:

- A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:
 1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
 2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
 3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.
- B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history:
 1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypes, lining up toys or flipping objects, echolalia, idiosyncratic phrases).

2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
 3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
 4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g. apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).
- C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).
- D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
- E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Brain imaging findings

As mentioned earlier, in 2021, the NIH is studying the brain scans of the infant siblings of children with ASD, looking for possible changes that may be predictive for the later development of the disorder.

Treatment and management

As of 2021, there is no cure for AS or HFA (or ASD), and there is no prescribed regimen for all affected patients. Specific treatments are based on the individual's pattern of symptoms, particularly those that are problematic to the individual, such as depression, anxiety, hyperactivity, or aggression.

Traditional

Many children with ASD take multiple medications. According to the DSM-5, an estimated 70% of individuals with ASD have one other psychiatric disorder, while 40% have two or more such disorders. Often, the medications that people with AS or ASD take are directly related to the

QUESTIONS TO ASK YOUR DOCTOR

- Can Asperger syndrome be cured?
- What treatment options are available?
- How do they differ in terms of expected outcomes?
- Is drug therapy required?
- What may have caused my child to have Asperger syndrome?
- Do you recommend psychotherapy?
- Should my child be tested for learning disabilities?
- What is the long-term prognosis for my child?

symptoms that are most problematic for them, such as aggression, anxiety, depression, or hyperactivity. In an analysis by Aliya F. Geroe and colleagues, the medication use among 26,722 individuals with ASD was analyzed. Most of the subjects were male (78%), and the average age of the subjects was 14 years. There was a high variability in the medications used, but at least 15% of the prescribed drugs were medications for ADHD.

Drugs

In general, the drugs recommended most often for children with AS include psychostimulants (such as methylphenidate) or antipsychotics for anger or aggression, as well as selective serotonin reuptake inhibitors (SSRIs) for treating rituals and preoccupations or anxiety symptoms.

Clinical trials

As of 2021, many clinical trials for the treatment of autism spectrum disorders are being sponsored by the National Institutes of Health (NIH) and other agencies. Clinical trial information is constantly updated by NIH. The most recent information on autism spectrum disorder trials can be found at: <https://clinicaltrials.gov>.

Prognosis

AS or HFA is a lifelong but stable condition. The prognosis for the intellectual development of children with AS is generally good. An increasing number of school districts are becoming equipped to meet their special social needs. Effective prevention of Asperger disorder and autism spectrum disorders awaits further genetic mapping, together with ongoing research on the structures and functioning of the brain.

Resources

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- Grandin, Temple. *Navigating Autism: 9 Mindsets for Helping Kids on the Spectrum*. W.W. Norton & Company, 2021.

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ORGANIZATIONS

- Autism Society, 6110 Executive Boulevard, Suite 203, Rockville, MD 20852, (800) 328-8426, <http://www.autism-society.org>
- Autism Speaks, 1060 State Road, Second Floor, Princeton, New Jersey, 08540, (888) 288-4762, En Español (888) 772-9050, (646) 385-8500, Fax 1: (609) 430-9163, Fax 2: (609) 430-9505, help@autismspeaks.org, <https://www.autismspeaks.org>.
- Global and Regional Asperger's Syndrome Partnership (GRASP), 369 Lexington Avenue, 2nd Floor, New York, NY 10017, (888) 474-7277, info@grasp.org, <https://grasp.org>

National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Room 6200, MSC 9663, Bethesda, MD 20892-9663, (866) 415-8051, nimhinfo@nih.gov, <http://www.nimh.nih.gov>

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Asplenia

Definition

Asplenia in the strict sense is not a genetic disorder but a medical condition that may or may not have a genetic cause. Asplenia may be either congenital (present at birth) or acquired (developed later in life, most often as the result of surgical removal of the spleen). The term "asplenia" literally means the absence of a spleen or of splenic function. The spleen may be completely absent in congenital asplenia. However, in some subtypes of congenital asplenia, it may be present but not fully developed. It is then said to be hypoplastic.

Some forms of congenital asplenia are linked to disorders in the right-left distribution of the internal organs. Individuals with these conditions often have problems with other organs and organ systems. A related condition is polysplenia, which literally means multiple spleens. Both of these conditions affect the placement and development of the organs inside the body. There is controversy over whether asplenia and associated syndromes like polysplenia are actually different aspects of the same condition—referred to as heterotaxy syndrome—or separate and distinct syndromes. The ongoing lack of a standardized approach to diagnosis and reporting of these syndromes has been noted in several reports published in 2014. Other names for these syndromes include Ivemark syndrome, right isomerism sequence, right atrial isomerism (RAI), bilateral right-sidedness sequence, splenic agenesis syndrome, and asplenia with cardiovascular anomalies.

Description

The human body has laterality; it has a right and a left side. Normally, inside the human body, the right side and the left side are different with respect to the presence of unpaired organs. Several organs inside the body are placed asymmetrically, meaning that an unpaired organ like the spleen may be located on one side of the body but not on the other. In addition, there are some organs that are found on both sides of the body, but have differences that distinguish the right-side organ from its partner on the left side. The right and left sides of the heart are an example of this

pattern, as each side of the heart has a different function. The right side pumps blood to the lungs to be oxygenated. The left side receives the oxygenated blood from the lungs and pumps it through the aorta to the rest of the body.

Disturbances of the normal pattern of laterality of the internal organs in the chest and abdomen are called laterality defects. In asplenia, the position, location, appearance, and performance of some of the internal organs are altered. Organs can often be found on the wrong side of the body and/or have structural defects. Furthermore, in most people the right and left organs are different. In people with asplenia, both organs may appear to have the same structure. For example, their heart may have two left sides or two right sides.

Genetic profile

In most families, asplenia is believed to occur sporadically. In other words, it occurs for the first time in a family and has no known or identifiable pattern of inheritance. There appear to be two different types of congenital asplenia: isolated congenital asplenia or ICAS and congenital asplenia. ICAS is an extremely rare condition marked by the complete absence of the spleen. Congenital asplenia is associated with failure to establish the normal right/left organ placement and symmetry during the process of embryonic development. These disorders of normal laterality are grouped together as heterotaxy syndromes.

Isolated congenital asplenia (ICAS)

Isolated congenital asplenia or ICAS is distinct from the other forms of asplenia known as heterotaxy syndromes. ICAS was traced in 2013 by a team at Rockefeller University in New York to seven different mutations in the *RPSA* gene on chromosome 3p21. It has been shown to have an autosomal dominant pattern of inheritance, which means that only one abnormal gene from either parent is sufficient to produce ICAS in the offspring. The discovery establishes that the *RPSA* gene is essential to the normal development of the spleen in humans.

Heterotaxy syndromes

Heterotaxy syndromes appear to be inherited in three different patterns, each involving different genes.

AUTOSOMAL RECESSIVE. Ivemark syndrome is considered an example of asplenia inherited in an autosomal recessive manner. The condition has been traced to mutations in the *GFDI* gene on chromosome 19p12. In addition to Ivemark's case studies, there have been several couples described in the medical literature who have more than one child diagnosed with asplenia. In several of these families, the parents were related to each other. Individuals who are consanguineous (related to each

other by blood) are more likely to carry some of the same defective genes. Therefore, these families illustrate that some forms of asplenia can be inherited in an autosomal recessive manner. In 2012, a team of researchers in Jerusalem identified a mutation in the *CCDC11* gene on chromosome 18q21.1 as responsible for congenital asplenia in two brothers born to consanguineous parents. The researchers established that the gene is inherited in an autosomal recessive pattern.

Individuals who have an autosomal recessive condition have both genes in a pair that do not work as expected or are missing, thereby causing the disease. One defective gene is inherited from the mother, and the other is inherited from the father. These parents are called carriers of that condition. When two people are known carriers for an autosomal recessive condition, they have a 25% chance with each pregnancy of having a child affected with the disease.

Autosomal dominant

There are a few families in which congenital asplenia other than ICAS appears to be inherited in an autosomal dominant or X-linked manner. In autosomal dominant inheritance, only one gene in the pair needs to be abnormal to cause symptoms of the condition. In families in which asplenia appears to be inherited in an autosomal dominant manner, family members who carry the same defective gene can have different symptoms and the severity of the condition may vary. In autosomal dominant inheritance, if an individual carries the defective gene, he or she has a 50% chance of passing the gene on with each pregnancy. Congenital asplenia inherited in an autosomal dominant pattern has been traced to mutations in the *CFC1* gene on chromosome 2q21 and in the *ACVR2B* gene on chromosome 3p22.2.

X-LINKED. In families in which asplenia appears to be inherited in a X-linked manner, the gene causing the condition is located on the X chromosome. Mutations in the *ZIC3* gene on the X chromosome at Xq26.3 have been identified as causing X-linked forms of congenital asplenia. Because women have two X chromosomes, if a woman inherits the defective gene on one of her X chromosomes, typically she will not have any symptoms of asplenia or will have a milder form of the condition. A woman who carries the X-linked form of asplenia will have a 50% chance of passing on that defective gene with each pregnancy.

Because normal males have one Y chromosome and one X chromosome, a son who inherits the defective *ZIC3* gene will be affected with the condition. Men who have an X-linked form of asplenia will always pass on their X chromosome containing the defective gene to all their daughters, who will be carriers of the condition. In these families, asplenia will never be passed from the father to the son,

KEY TERMS

Anomalous—Irregular or different from normal.

Anomalous venous return—Normally, the veins that bring blood containing oxygen from the lungs to the heart (called pulmonary veins) are connected to the left atrium. In this situation, the pulmonary veins are connected to the right atrium.

Asplenia—The absence of the spleen or of normal splenic function in the body. It may be either congenital or acquired.

Atrium (plural, atria)—One of the two upper chambers of the heart. Typically, there are two atria, one on the right side of the heart and one on the left.

Atrial septal defect (ASD)—An opening between the right and left atria of the heart.

Congenital—Present at birth.

Cyanosis—A bluish color of the skin that results from insufficient oxygen in the blood transported throughout the body.

Echocardiography—An ultrasound examination targeted at the heart and performed by a cardiologist or an individual trained at detecting differences in the structure of the heart. The product of the examination is an echocardiogram.

Heterotaxy—A condition in which the thoracic and abdominal viscera are arranged abnormally across the left-right axis of the body. It is also referred to as heterotaxy syndrome or visceral heterotaxy.

Isomerism—In human anatomy, a condition in which organs normally found on only one side of the body are found on both sides. In reference to the heart, isomerism refers to a condition in which the heart has either two right sides with two right atria or two left sides with two left atria.

Ivemark syndrome—A rare disorder characterized by cardiovascular anomalies as well as asplenia or hypoplasia of the spleen. It is named for Biörn Ivemark (1925–2005), the Swedish pediatrician who first identified the syndrome in 1955.

Laterality—The right-left distribution of the internal organs.

Malrotation—An abnormality that occurs during the normal rotation of an organ or organ system.

Pulmonary atresia—A congenital malformation of the pulmonary valve in which the opening of the valve fails to develop. As a result, blood cannot flow out of the heart through the pulmonary artery to the lungs to be oxygenated.

Pulmonary stenosis—Narrowing of the pulmonary valve of the heart, between the right ventricle and the pulmonary artery, limiting the amount of blood going to the lungs.

Syndrome—A group of signs and symptoms that collectively characterize a disease or disorder.

Transposition of the great arteries (TGA)—A reversal of the two great arteries of the heart, causing oxygenated blood to be carried back to the lungs and deoxygenated blood to be transported throughout the body.

Truncus arteriosus—A condition in which a structure present during fetal development fails to develop normally into two separate structures, the aorta and the pulmonary trunk. Thus, there is only one arterial trunk structure leading from the heart instead of two. Often there is a ventricular septal defect (VSD) present.

Ventricular septal defect (VSD)—An opening between the right and left ventricles of the heart.

since men give their sons a Y chromosome. If a woman who carries an X-linked condition passes the X chromosome containing the non-working gene to a daughter, then that daughter will be a carrier like her mother.

The pattern of inheritance of asplenia in a family is usually not obvious when there is only one individual diagnosed with the condition. Based on the families and studies performed on asplenia, the chance of a couple who have one child with asplenia having another child with the condition is approximately 5% or less. This chance may be higher if it is determined that asplenia is part of heterotaxy syndrome, since there are a wider range of symptoms associated with that condition. Furthermore, if more than one

family member has the diagnosis of asplenia, the chance of it occurring again in the family is based on the pattern of inheritance that the condition appears to be following.

Demographics

ICAS is a very rare condition, estimated to have an incidence of 0.5 per 1 million births. The incidence of other forms of congenital asplenia is higher than that of ICAS, but still low, approximately 1 in 10,000 to 1 in 20,000 live births. Some researchers, however, think that the condition is underdiagnosed because newborns with congenital asplenia have high mortality rates and may not be autopsied.

More males are affected with the condition than females. Asplenia also accounts for 1%–3% of all congenital heart defects and 30% of newborns who die of malformations of the heart. Congenital asplenia appears to occur with equal frequency in all races and ethnic groups.

Signs and symptoms

Almost all individuals with congenital asplenia have an abnormal or absent spleen. The most common symptom of isolated congenital asplenia or ICAS is primary immunodeficiency. Most affected individuals die in early childhood of severe bacterial infections.

In the various heterotaxy syndromes, however, organ systems in addition to the spleen and the immune system are commonly affected.

Abdominal organs

SPLEEN. As the name of the condition implies, the spleen is always affected in asplenia. The spleen in individuals with asplenia either is absent or does not develop completely (hypoplastic spleen). Because the spleen is involved in the body's immune system, these infants can have an abnormal immune system, which increases their risk for developing an infection.

DIGESTIVE TRACT DISORDERS. There are several abnormalities that can occur with the digestive tract in individuals with asplenia. The most common digestive tract disorder associated with asplenia is malrotation of the intestine. Sometimes a digestive tract problem will present with symptoms of an obstruction in the digestive system, requiring emergency surgery.

STOMACH. Most individuals with asplenia have their stomach located on the right side or in the center of the body instead of the left. In addition, individuals with asplenia can have a “twisted” stomach that could result in an obstruction in their digestive system and impair the blood supply to the stomach (gastric volvulus).

LIVER. Normally, the liver is located on the right side of the body and the shape of the liver is not symmetrical. In asplenia, there can be isomerism of the liver—it may be located in the middle of the body, or located on the left side with the larger half of the liver located in the upper left side of the abdominal area.

GALLBLADDER. The gallbladder may also be located in the middle of the body in individuals with asplenia.

Heart

Many infants with asplenia first present with cyanosis and severe respiratory distress. These are symptoms often seen in individuals who have a heart defect. Most

individuals with asplenia have a defect in the structure and/or the position of their heart.

Typically, the heart is divided into two sides, a left and right, with each side containing two chambers, called ventricle and atrium. The left and right sides of the heart are different from each other in their structure and function. The right side of the heart pumps blood through the pulmonary artery to the lungs to receive oxygen. The left side of the heart receives the oxygenated blood from the lungs and pumps it to the rest of the body. In congenital asplenia, the affected individual may have a heart with two left sides or two right sides.

A common heart defect often seen in asplenia is anomalous pulmonary venous return, which occurs when the pulmonary veins are connected to the right atrium instead of the left atrium. This malformation causes the oxygenated blood to be pumped back to the lungs instead of the body. Sometimes there is a hole between the right and left atria (called atrial septal defect or ASD) that allows some of the oxygenated blood into the left atrium and pumped to the rest of the body.

Other heart defects frequently seen in individuals with asplenia include: common atrioventricular canal, common atrial canal, persistent truncus arteriosus, pulmonary stenosis or atresia, single ventricle in the heart, and transposition of the great arteries. Often there is more than one heart defect present. Furthermore, in many individuals with asplenia, the heart is located on the right side of the body instead of the left.

Lungs

Normally, the lungs are divided into lobes. The lung on the right side of the body usually has three lobes, and the left lung typically has two lobes. In asplenia, each lung usually has three lobes.

There can be abnormalities in other systems of the body as well, but they are not often seen in most individuals with asplenia. Other abnormalities associated with asplenia include kidney anomalies, extra fingers and toes, scoliosis, facial abnormalities, and central nervous system anomalies.

Diagnosis

The diagnosis of asplenia is typically made by imaging studies. There is no single radiographic study that is best for all types of asplenia. An echocardiogram of the heart can help identify any structural abnormalities and its exact position within the body. A chest x-ray can also be used to locate the position of the heart and some of the other organs in the body. Ultrasound is preferred for diagnosing ICAS. Ultrasound and CT examinations can also help determine whether there are any malformations in the abdominal organs, the position of the stomach, and

QUESTIONS TO ASK YOUR DOCTOR

- What type of congenital asplenia does my child have? Is it treatable?
- Is there a specific gene or inheritance pattern associated with my child's form of asplenia?
- What are the risks and benefits of heart surgery?
- What are the risks and benefits of digestive tract surgery?
- What specific structural abnormalities are present in my child's heart?
- Will my child's activity be restricted throughout life?

the number of lobes in the lungs. These exams can also determine the presence, appearance, and number of spleens. While an MRI can also detect the presence and position of organs inside the body, it is less commonly used because of the need for sedation and the high cost of the test, especially in children.

Testing for the presence of Heinz and Howell-Jolly bodies in the blood has been suggested as a method to screen for an absent spleen. Howell-Jolly bodies are unique cells that tend to be present in the blood of individuals who do not have a spleen, but they can also be found in the blood of individuals who have certain types of anemia. Therefore, this test should not be used as the sole diagnostic test for an absent spleen.

Some of the abnormalities seen in asplenia can be detected prenatally. Often the position of the heart and some of the heart defects can be diagnosed by fetal echocardiogram (an ultrasound examination of the fetal heart) in the late second and third trimesters of pregnancy. A fetal echocardiogram should be performed during pregnancy when a couple already has a child with asplenia. In addition, a level II ultrasound examination can detect some digestive system anomalies, such as the position of the stomach.

Treatment and management

ICAS is presently treated with prophylactic antibiotics to lower the risk of bacterial infections. The child should continue to receive antibiotic therapy as long as he or she lives.

In children with Ivemark syndrome or other forms of congenital asplenia associated with heart defects, surgery can sometimes be performed on the heart to repair the defect or defects. There are limitations to heart surgery, and it

cannot always be performed. Moreover, heart surgery is not always successful. Surgery can also be used to correct many of the digestive tract disorders.

Because the spleen is involved in the body's immune system, it is also recommended that all patients with the diagnosis of asplenia be given prophylactic antibiotics as well as pneumococcal and meningococcal vaccination. In addition, they are usually required to take prophylactic antibiotics prior to even minor surgery or dental procedures, and to be restricted from traveling to countries with high levels of infectious disease.

Prognosis

As of 2015, all known patients with ICAS died of sepsis within 23 months of birth, most of them within 12 months.

Without treatment, the prognosis of an infant diagnosed with asplenia is poor, with approximately 80% of these infants dying within the first year of life. The cause of death is usually complications from the heart defects, although many infants with congenital asplenia also die of overwhelming bacterial infections. However, with advances in heart surgery and improvements in correcting many of the digestive tract anomalies, infants with asplenia are living much longer.

Resources

BOOKS

Abuhamad, Alfred Z., et al., eds. *A Practical Guide to Fetal Echocardiography: Normal and Abnormal Hearts*, 4th ed. Riverwoods, IL: Wolters Kluwer, 2021.

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Lee, Grace M. "Preventing Infections in Children and Adults with Asplenia." *Hematology, ASH Education Program* (2020). DOI: 10.1182/hematology.2020000117.

WEBSITES

"Asplenia." AMBOSS. October 19, 2020. <https://www.amboss.com/us/knowledge/Asplenia> (accessed May 21, 2021).

ORGANIZATIONS

American Academy of Pediatrics (AAP), 141 Northwest Point Blvd., Elk Grove Village, IL 60007-1098, (847) 434-4000, (800) 433-9016, (847) 434-8000, <http://www2.aap.org/guestbook/contactus-form.cfm><https://www.aap.org/en-us/Pages/Default.aspx>

American Society of Hematology (ASH), 2021 L St. NW, Suite 900, Washington, DC 20036, (202) 776-0544, (202) 776-0545, <http://www.hematology.org/>

National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Dr., MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, (301) 402-2218, <http://www.genome.gov/10005049>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>
 Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

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 and Rebecca J. Frey, PhD

Asplenia/polysplenia complex see **Asplenia**

Asthma

Definition

Asthma is a chronic and inherited disease resulting from an overactive immune system that causes inflammation of the lungs, coughing, wheezing, and shortness of breath. “Asthma” comes from the Greek word for “panting.” The disease results from an over-responsiveness of the respiratory system to stimulating factors like allergens. It is characterized by repeated, temporary episodes of constriction and inflammation of the airways and lungs, along with excess mucous production. Asthma attacks are characterized by severe difficulty breathing, especially when exhaling. Severe attacks that are left untreated may become fatal. An individual with asthma may be completely without symptoms between attacks.

Description

Asthma is a chronic, lifelong disease that affects the complex network of air passageways of the respiratory system. People with asthma may experience a range of symptoms from mild discomfort to life-threatening attacks that require immediate emergency treatment. The respiratory system is made up of bronchial tubes (airways) and the lungs. Asthma involves the inflammation of the bronchial tubes and lining of the lungs. The inflammation causes the airways to be overly sensitive to irritating factors, which cause constriction and obstruction to the passage of air into the lungs. People with asthma also produce excess amounts of mucus in the respiratory tract. Mucus is a normal component of respiratory function that aids in carrying irritating particles up and out of the respiratory system to be expectorated (coughed up) from the body. People with asthma produce excessive, abnormally thick mucus that interferes with breathing and contributes to the problem. Severe asthma attacks can be fatal. Persistent or chronic inflammation of the airways can cause permanent damage, which is also called airway “remodeling.” This will reduce lung function so that breathing becomes less efficient even outside of asthma attacks. People with

asthma may experience chronic wheezing, coughing, shortness of breath, and a feeling of a tightening of the chest. Medication and careful management of the disease are often necessary for maintaining normal function.

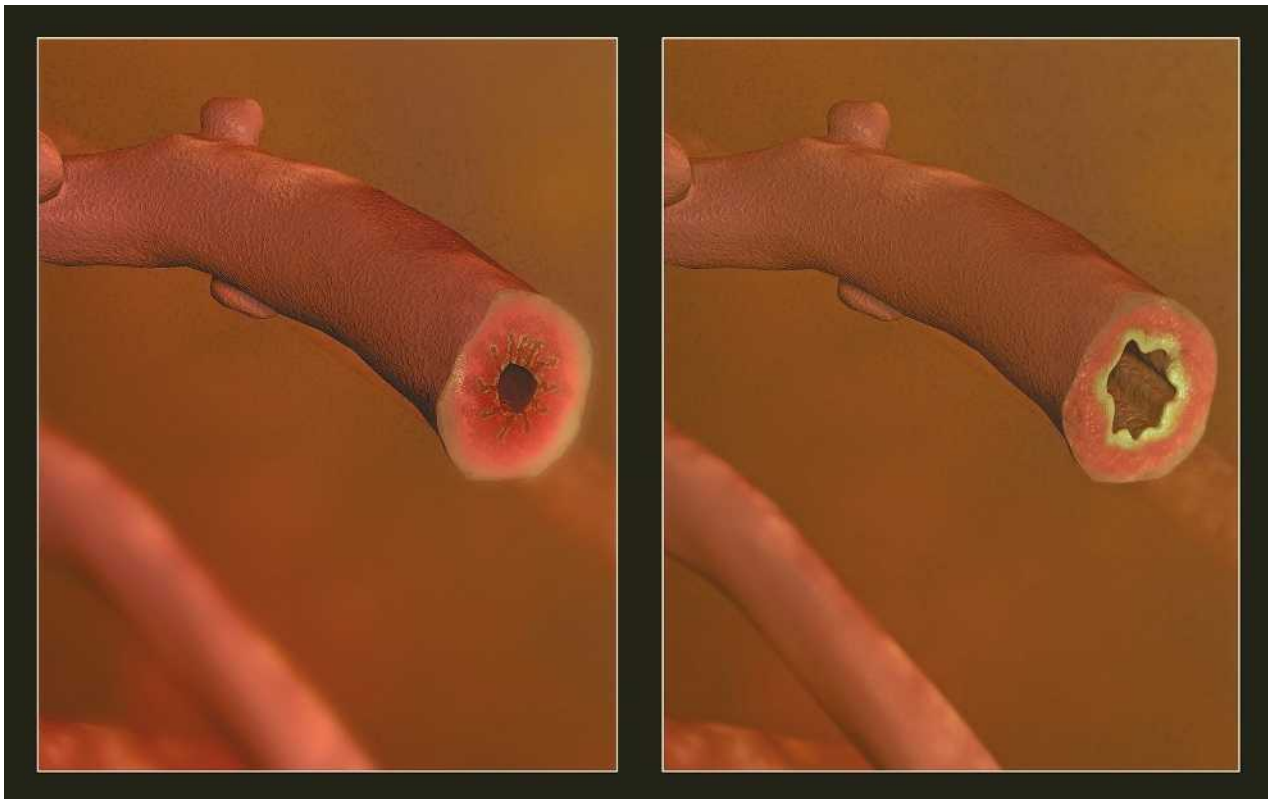
Some individuals inherit a genetic predisposition to asthma that can be triggered by a variety of environmental factors. Stimuli for triggering asthmatic symptoms include repeated exposure to irritants, such as dust mites, pet hairs, and tobacco smoke. These types of stimuli are considered allergens, or particles that trigger an allergic response. Asthma may also be induced by exercise, especially in cold climates where the respiratory system has to work harder to warm and moisten inhaled air. Some people with asthma only experience symptoms during viral infections. Both physical and psychological factors may precipitate an asthma attack.

Genetic profile

Asthma is a complex inherited disease in which a number of different genes and environmental triggers contribute to asthmatic predisposition. Children who have one parent with asthma have a 25% of having asthma, and children who have two parents with asthma have around a 50% risk. Variations in some genes influence how likely someone will be to develop asthma, while other variations influence the severity or response to treatment. In some cases, variations in different genes can cause the same symptoms. More commonly, variations in multiple genes and factors in the environment affect the risk of asthma in each person. While genes may cause a predisposition, asthma attacks are triggered by stimulating environmental factors. Variants in some asthma genes can also increase risk for other diseases, such as cardiovascular disease, cancer, or autoimmune diseases. Some researchers have postulated that asthma is an autoimmune disease. An autoimmune disease is a condition in which the immune system attacks the body because it mistakes parts of it as foreign. Similar genes can influence the risk of both allergies and asthma. Variations in some genes can decrease the risk of asthma.

Variations in over 100 different genes have been associated with asthma, although not all associations have been confirmed. Variations in the *ORMDL3*, *GSDMB*, and *GSDML* genes appear to be associated with an increased risk for childhood-onset asthma. Variations in some of the interleukin genes may increase the risk of asthma triggered by allergens. Variations in some genes, such as the *TSLP* gene, may decrease the risk of cancer.

Research studies suggest that specific symptoms experienced by asthma patients, such as the inflammation of the airways and lungs, are initiated by the action of genes that regulate the activity of the immune system. In other words, these genes control how the immune system



Asthma is a chronic disease of the respiratory system in which the airway occasionally constricts and become inflamed. An inflamed bronchus (left) and a normal one (right) are shown. (MedicalRF/Science Source)

responds to the presence of substances that can potentially trigger asthma symptoms.

Like a microscopic army, the immune system consists of a wide array of specialized cells that work together to neutralize threats to the system. Antigens are any foreign agents that invade the body and trigger such an immune response. They include disease-producing organisms, such as viruses, toxic chemicals in the environment, or allergens, such as animal dander and dust mites. In response to the identification of specific foreign antigen particles, some immune cells produce antibodies to attack them. This immune response occurs after an initial encounter with an antigen and is known as a primary immune response. The immune system recognizes past contact with specific antigens by maintaining specific levels of the antibodies that are customized to attack specific antigens. When the same antigen is encountered again, the specific antibodies that have been maintained in the body multiply and mount a stronger immune response than the primary response. This process is known as the secondary immune response.

One of the specific antibodies produced in response to allergens is a protein known as immunoglobulin E (IgE). In a normal inflammatory response, IgE recognizes

foreign antigens and initiates immune reactions against the antigen by binding to other immune cells, such as mast cells. Mast cells release chemical mediators that contribute to inflammation directly but also recruit more immune cells to the site of inflammation. The recruited immune cells also release mediators of inflammation, such as histamine, that amplify the response and cause inflammation. In people with asthma, the IgE mast cells are highly excitable, making them hypersensitive to stimulation. When foreign antigens are breathed into the respiratory system, the entire inflammatory process, including the recruitment of other immune cells that release histamine, becomes exaggerated, resulting in asthma.

People with asthma seem to produce higher levels of IgE antibodies, more hyperactive mast cells, and higher levels of consequent histamine than the general population. Histamine is a type of chemical signal that initiates the inflammatory response. It stimulates the dilation of blood vessels' walls and makes them more porous. As a result, blood fluid and proteins leak out of the blood vessels and into surrounding tissue, causing the swelling and reddening that are typical of inflammation. Inflammation involves increased blood flow to affected tissues to allow

the passage of the recruited immune cells from the blood into them. The immune cells may then dispose of the foreign particles. While this response is designed to defend the tissue from foreign invasion of harmful particles, an exaggerated response can be dangerous. In asthma, the resultant inflammation, along with the reactive constriction of the muscles in walls of the bronchial airways, narrows the air passages and causes an asthma attack.

Overactive T helper 2 (Th2) immune cells can increase the amount of IgE produced by the body. Overactive TH2 cells are linked to 80% of childhood cases and 60% of adult asthma cases. In people who are predisposed to asthma, allergens activate the Th2 cells, which produce proteins that can increase the amount of IgE antibody produced. The Th2 proteins and IgE stimulate the immune system to overact, which results in asthma symptoms. Interestingly enough, lack of exposure to childhood illnesses can contribute to the increased response of Th2 cells found in asthma. In the absence of exposure to illness, the immune system seems to produce more of these Th2 cells, which ultimately increases the production of the IgE antibody.

Another component of the immune defense is the production of nitric oxide gas (NO) by an enzyme called inducible nitric oxide synthase (iNOS). Cells lining the bronchial tubes contain this enzyme that produces NO in response to chemical signals released from immune cells. People with asthma produce an abnormally higher level of iNOS in their respiratory cells than the general population does, and they have higher levels of NO in their lungs and bronchial tubes that contribute to the disease.

Demographics

In the United States, almost 10%, or 25 million people, have asthma. In 2012, asthma resulted in approximately 1.6 million emergency visits. It affects individuals of all ages but often starts in childhood. Asthma is the most prevalent childhood chronic disease. In children, more boys than girls have asthma. Boys have a 30% higher prevalence of asthma compared to girls. In adults, the trend is reversed, with more women having asthma than men. Women have a 30% higher prevalence of asthma than men do. Within ethnic groups, non-Hispanic blacks have more asthma attacks. Furthermore, they are more likely to be hospitalized and die from asthma than are non-Hispanic whites. Asthma is distinct from, but closely linked to, allergies. Most, but not all, people with asthma also have allergies.

Asthma attack prevalence is a crude indicator of how many individuals have uncontrolled asthma and are at



A young girl is using an inhaler to facilitate breathing.
(Bikeriderlondon/Shutterstock)

risk for hospitalization. According to the Asthma and Allergy Foundation of America, each day in America, 44,000 people have asthma attacks. Asthma attack prevalence decreases with age, being most prevalent in children. Puerto Ricans have the highest asthma attack prevalence, a full 100% higher than non-Hispanic whites. The prevalence of an asthma attack is about 30% higher in non-Hispanic blacks than in non-Hispanic whites. Based on current data, Non-Hispanic blacks are the most likely to die from asthma, with an asthma death rate more than 200% higher than that of non-Hispanic whites. Women have an asthma death rate approximately 40% higher than men. Differences in male and female hormones may cause this disparity.

Asthma has been described as the fastest-growing chronic disease and a worldwide epidemic. According to Global Initiative for Asthma (GINA), an asthma research and education program, asthma accounts for about one in every 250 deaths worldwide. Many of the deaths are believed to be preventable and are caused by poor medical care.

The World Health Organization (WHO) estimates that there are 235 million people with asthma worldwide. In most countries, asthmatic cases are increasing by 20% to 50% every decade. The United States is one of the top countries for prevalence of asthma, along with England, Australia, parts of South America, and Canada. In Australia, the incidence of asthma is very high in Caucasian children but much lower in aboriginal children.

It is speculated that lifestyle factors, such as a lack of physical activity, increased obesity, and more time spent indoors, may contribute to higher rates of asthma in highly developed countries. It is also possible that environmental irritants, such as poor indoor and outdoor air quality, along with the presence of potent irritants such

as cockroach allergens, may contribute to higher rates of childhood asthma in poorer communities. Other factors that may prompt the onset of asthma include viral respiratory infections, low birth weight, and smaller-than-average air passageways in asthmatic patients.

Signs and symptoms

People with asthma may experience coughing that is often worse at night or early in the morning, making sleep difficult. Wheezing is a common symptom, creating a whistling or squeaky sound when breathing. People with asthma experience tightness in the chest region, as if their chest feels it is being compressed. Shortness of breath and the feeling of breathlessness are common symptoms. There is difficulty getting enough air into or out of the lungs, especially during exhalation. If airflow to the lungs is inadequate, a lack of sufficient oxygen to the tissues causes the body to breathe more rapidly in an attempt to get more oxygen. People with asthma often breathe more rapidly as a result.

People with asthma often have wheezing during a cold, flu, or other illness. Emotional stress may also result in asthmatic symptoms, such as coughing or wheezing from prolonged crying or laughing. Many indoor and outdoor factors can trigger or initiate typical symptoms of asthma, including allergies, viral respiratory infections, weather changes, and exercise. Medications containing aspirin also act as asthma triggers in about 10% to 20% of adults with asthma.

When allergies stimulate an asthma attack, it is known as allergic asthma. Allergic asthma is stimulated when an affected individual is physically near an allergen or irritant. Research has confirmed that allergies cause the majority of childhood asthma cases. Allergic asthma is the most common form of asthma and tends to run in families. Common allergens that may contribute to allergies and asthmatic reactions include dust mites, dust particles, animal dander, animal hair, bird feathers, mold, plant pollen, and substances found in food. Food products containing peanuts, eggs, dairy products, or seafood can cause asthma attacks in some children with allergies to these foods. Food additives, such as sulfites, can also act as asthma triggers. Synthetic (manmade) products like the latex material used in surgical gloves can also trigger asthmatic episodes in susceptible individuals. Non-allergic factors that can stimulate or aggravate asthmatic symptoms include tobacco smoke, chalk dust, talcum powder, car exhaust, and fumes from chemicals such as household cleaners. Auto pollution is a major factor in asthma prevalence.

Exercise is a common trigger for asthma in about 80% of asthmatic individuals. Some people with asthma have exercise-induced symptoms precipitated

by brisk activity such as running, especially during cold weather. Pretreatment medications, such as short-acting bronchodilators, quickly widen air passages and thus help prevent the onset of asthma while an asthmatic individual participates in physical activities. Activities that allow for frequent breaks, rather than prolonged endurance, are most suitable. Asthma does not have to be a barrier to participating in athletic activities. Many Olympic athletes have exercise-induced asthma that is controlled by medication.

Changes in the weather, such as temperature and humidity variations, can also negatively affect asthma patients. Cold climates also may exacerbate asthma, because the lungs have to work harder to warm and moisten inhaled air. People with asthma who exercise in such conditions could wear a surgical mask that can trap the warm, moist air exhaled with each breath. Viral infections of the respiratory system, which tend to increase in number during winter months, may trigger severe asthma attacks. Additionally, unclean and poorly maintained forced-air heating systems release many pollutants that further aggravate asthmatic symptoms.

Every asthma patient is unique. Because there are so many environmental conditions that affect individuals with a genetic predisposition for asthma, it is often difficult to pinpoint the primary cause of the disease in individual cases.

A person with asthma may have any combination of symptoms, which may vary from one asthma attack to another. Symptoms may exhibit a range of severity, from mildly irritating to life-threatening. They occur with varying frequency from once every few months to every day. Asthma classifications are based on symptom levels in the absence of medication. Mild intermittent asthma is defined as symptoms of wheezing, coughing, or breathing difficulty less than twice per week or less, with night symptoms twice per month or less. Mild persistent asthma is defined as symptoms of wheezing, coughing, or breathing difficulty once per day or less, but more than twice per week. Symptoms occur at night more than twice per month.

Moderate persistent asthma is defined as daily symptoms that require daily medication. Symptoms at night occur more than once per week. They may be severe enough to interfere with normal physical activity.

Severe asthma is described as ongoing, persistent symptoms with more serious asthma attacks. Symptoms may occur throughout the day, with night symptoms occurring often. In severe asthma, physical activity is likely to be limited.

All people with asthma may have severe asthma attacks. However, with appropriate treatment and

KEY TERMS

Allergen—A substance or organism foreign to the body; allergens stimulate the immune system to produce antibodies.

Allergy—A condition in which the immune system is hypersensitive to contact with allergens; an abnormal response by the immune system to contact with an allergen; a condition in which contact with an allergen produces symptoms such as inflammation of tissues and production of excess mucus in the respiratory system.

Antibody—A protein produced by the mature B cells of the immune system that attach to invading micro-organisms and target them for destruction by other immune system cells.

Antigen—A substance or organism that is foreign to the body and stimulates a response from the immune system.

Autoimmune disease—A condition in which the immune system attacks the body because it mistakes parts of it as foreign.

Bronchi—Branching tube-like structures that carry air into and out of the lungs. The walls of the bronchi contain circular muscles that can constrict (tighten up to make airways narrower) or dilate (relax to make airways wider). The bronchi divide into smaller bronchioles within the lung tissue.

Biologic—A medication that is made from a plant, animal, or micro-organism, such as bacteria.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein. It is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Genetic disease—A disease that is (partly or completely) the result of the abnormal function or expression of a gene; a disease caused by the inheritance and expression of a genetic mutation.

Histamine—A substance released by immune system cells in response to the presence of an allergen. Histamine stimulates widening of blood vessels and increased porousness of blood vessel walls so that fluid and protein leak out from the blood to surrounding tissue, causing inflammation.

Hypersensitive—Referring to a process or reaction that occurs at above-normal levels; over-reacting to a stimulus.

IgE—An antibody composed of protein; specific forms of IgE produced by cells of the immune system in response to different antigens that contact the body; a major factor that stimulates the allergic response.

Immune system—A major system of the body that produces specialized cells and substances that interact with and destroy foreign antigens that invade the body.

Inflammation—Swelling and reddening of tissue; usually caused by the immune system's response to the body's contact with an allergen.

avoidance of asthma stimulators, most people with asthma can achieve a general condition of minimal or no symptoms. People with asthma are encouraged to learn to recognize their own specific asthma stimulators and avoid them, and they are recommended to recognize their specific pattern of early warning signs that signal the start of an attack. The first signs of a mild or moderate attack may be a slight tightening of the chest, coughing or wheezing, and spitting up mucus. Severe attacks can bring on a feeling of extreme tightening of the neck and chest, making breathing increasingly difficult. People with asthma may struggle to speak or breathe. In advanced stages of severe attacks, lips and fingernails may take on a grayish or bluish tinge, indicating declining oxygen levels in the blood. Such attacks can be fatal in the absence of prompt medical attention. Fortunately, asthma symptoms are usually reversible with medication.

Diagnosis

The first stage of asthma diagnosis is from a history of asthmatic symptoms. These symptoms include periods of coughing, wheezing, shortness of breath, or chest tightness that come on suddenly in response to specific stimulants or time periods. A history of head colds that evolve into chest congestion or take more than 10 days to recover from is pertinent. Family history of asthma or allergies may also be part of the diagnosis.

A physical exam may reveal wheezing in the chest that can be heard with a stethoscope. A device called a spirometer may be used to check the function of the airways in children over five years of age and in adults. The test measures the volume of air and the speed with which it can be blown out of the lungs after a deep breath. If the airways are narrowed from inflammation and the muscles around the airways tightening up from asthma,

the results will be lower than normal. If spirometry results are normal, but asthma symptoms are present, other tests are performed. A bronchial challenge test involves inhalation of a substance such as methacholine, which causes narrowing of the airways in asthma. The effect is measured by spirometry to determine whether asthma is present. Children under five years of age usually cannot use a spirometer successfully. In such cases, asthma medications are often attempted as part of the diagnosis to determine whether they are able to alleviate the symptoms.

Allergy testing may be performed to determine whether there are specific allergens to which the individual is reactive. A device called a peak flow meter may be used every day for several weeks to measure breathing efficiency. Tests may be performed to determine the reaction of the airways to exercise. In some cases, a chest x-ray or an electrocardiogram may be used to determine whether a foreign object, other lung disease, or heart disease could be causing asthma-like symptoms. The results of the medical history, physical exam, and lung function tests are used to diagnose the severity of asthma and determine treatment.

Treatment and management

Asthma is treated by avoiding stimulating factors and by medication. There are two main types of asthma medication. Acute medications give rapid, short-term treatment but are only used when asthma symptoms require immediate relief. These medications are bronchodilators that may be inhaled and take effect within minutes to dilate the airways and allow normal breathing. Bronchodilators may be used at the beginning of an asthma attack to provide relief. They also may be used before exercise to prevent exercise-induced asthma symptoms. Long-term control medications are taken daily over long periods of time to control chronic symptoms and prevent asthma attacks. The full effect of these medications requires several weeks of use. Individuals with persistent asthma require long-term control medications.

The most effective, long-term control medication for asthma is an inhaled corticosteroid. Corticosteroids work by suppressing inflammation caused by overactive Th2 cells. They can reduce the swelling of airways and help to prevent asthma attacks from occurring. Inhaled corticosteroids are preferred for treatment of all levels of persistent asthma. In some cases, steroid tablets or liquid medications are used temporarily to control asthma. Other types of asthma medications inhibit the inflammatory mediators released in the asthma response. Some of these long-term control medications may be used in combination with inhaled corticosteroids to treat moderate persistent and severe persistent asthma. Long-term control medications are used in a preventative manner and

QUESTIONS TO ASK YOUR DOCTOR

- What are the causes of asthma?
- Is stress likely to increase the frequency and severity of my asthma attacks?
- Are there lifestyle changes I can make to reduce the frequency and severity of my asthma attacks?
- Is my asthma condition likely to improve or get worse over time?
- Are there any new treatments I should try?

will not stop an asthma attack in progress. Many people with asthma require both a short-acting bronchodilator to use when symptoms worsen and a long-term daily asthma control medication to treat ongoing inflammation.

Uncontrolled asthma during pregnancy can be very dangerous. Lowered oxygen levels to the fetus may cause damage. Many asthma treatments are considered safe to use during pregnancy. Older adults may need adjustments in asthma treatment because of other present diseases or conditions. Some medications, such as beta-blockers used for hypertension, aspirin, and nonsteroidal anti-inflammatory drugs such as ibuprofen, can interfere with some asthma medications or cause asthma attacks. The use of corticosteroids may also adversely affect bone density in adults.

People with asthma can monitor the function of their respiratory system with the aid of peak flow meters and spirometers. These devices measure the amount of air exhaled with each breath. They are used to regularly monitor the severity of asthma symptoms and to evaluate and manage treatment procedures for individual patients. Maintaining control over asthma symptoms and keeping a healthy lifestyle are key components of asthma treatment.

Emergency care may become necessary during a severe asthma attack. Emergency care takes place in a hospital setting and may include treatment with high levels of bronchodilators and corticosteroids, additional medications, and oxygen administration in an attempt to restore normal respiratory activity. Delayed access to emergency treatment can lead to complete respiratory failure, where the patient simply stops breathing and cannot be revived.

Allergen Desensitization

Allergen immunotherapy, also called desensitization, decreases symptoms in people with allergies to

environmental allergens like plants and animals. During these treatments, people with asthma are given shots of increasing amounts of the allergen. This treatment can take three to five years but can significantly reduce the severity of asthma and lower the amount of medication required. The benefits of this treatment can last for seven to 12 years after it is stopped. This treatment seems to improve the Th2 response.

Biologics

There are a number of biologic medications (biologics) that target specific aspects of the overactive immune response caused by Th2 cells and help treat severe asthma. Some biologics, such as Omalizumab, decrease the amount of IgE and make cells less sensitive to stimulation by allergens. Other biologics, including Mepolizumab, Reslizumab, Benralizumab, and Dupilumab, reduce the activity of proteins produced by the Th2 cells, which decreases the body's response to allergens. Still other biologics, like Tezepelumab, decrease the amounts of certain proteins that stimulate Th2 cells.

Prognosis

There is currently no cure for asthma, but proper treatment and management have dramatically improved the quality of life for individuals with asthma. When medication is used properly, the prognosis for most people with asthma is excellent. An improvement in environmental conditions can reduce the number and severity of asthma attacks and improve the prognosis. Such improvement is also believed to affect the overall prognosis for a society, simply by decreasing the number of individuals who are sensitized to environmental triggers.

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ORGANIZATIONS

- Allergy and Asthma Network. Mothers of Asthmatics, Inc, 8229 Boone Boulevard, Suite 260, Vienna, VA 22182, (800) 878-4403, (703) 288-5271, <http://www.allergyasthmanetwork.org/main>
- American Academy of Allergy, Asthma & Immunology, 555 East Wells Street, Suite 1100, Milwaukee, WI 53202, (414) 272-6071, (414) 272-6070, <http://www.aaaai.org/default.stm>
- American Lung Association, 55 W. Wacker Drive, Suite 1150, Chicago, IL 60601, (800) 586-4872, (202) 452-1805, <http://www.lungusa.org>
- Asthma and Allergy Foundation of America (AAFA), 8201 Corporate Drive Suite 1000, Landover, MD 20785, (800) 727-8462, <http://www.aafa.org>
- Global Initiative for Asthma (GINA), <http://www.ginasthma.com>
- National Asthma Education and Prevention Program (NAEPP). School Asthma Education Subcommittee, http://www.nhlbi.nih.gov/health/dci/Diseases/Asthma/Asthma_WhatIs.html

National Center for Environmental Health, Centers for Disease Control and Prevention, Mail Stop F-29, 4770 Buford Highway NE, Atlanta, GA 30341-3724, <http://www.cdc.gov/asthma>

National Heart, Lung and Blood Institute, Division of Lung Diseases, NHLBI Health Information Center, P.O. Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, <http://www.nhlbi.nih.gov/index.htm>

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Astrocytoma

Definition

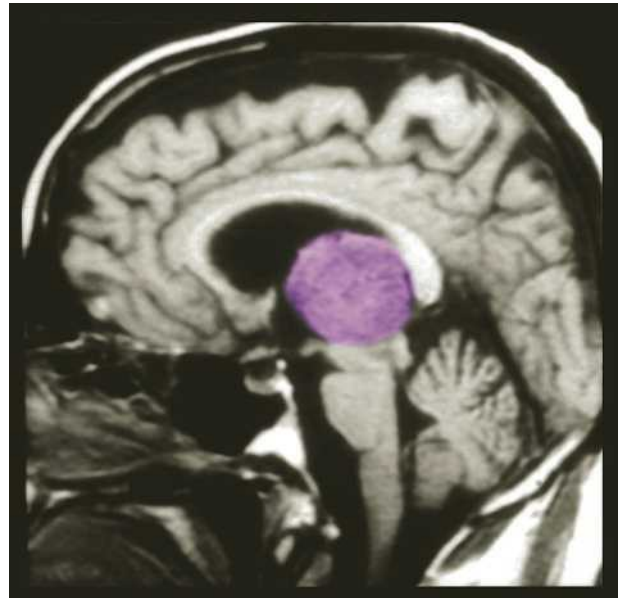
Astrocytoma is a tumor that arises from astrocytes, star-shaped cells that play a supportive role in the brain.

Description

The brain acts as a computer that controls all of the functions of the body. It stores information, regulates behavior, and sends instructions to the rest of the body. Because of the brain's importance, cancers in the brain can affect many of the body's functions. The location of a tumor within the brain determines which effects it will have. Astrocytomas may occur in the cerebrum, the cerebellum, or the brainstem. The cerebrum is the site of thought and language. The cerebellum is the area responsible for movement and muscle co-ordination. The brainstem is the location that regulates critical activities like breathing and heartbeat. Astrocytomas in children are most commonly located in the cerebellum. Astrocytomas in adults usually develop in the cerebrum.

Astrocytomas rarely metastasize (spread) outside the brain to other parts of the body. However, they may grow and spread within the brain. Because there is no extra room in the skull, the presence of a brain tumor causes an increase in intracranial (within the skull) pressure. This leads to headaches. Furthermore, normal brain function is affected possibly by compressing delicate brain tissue.

Astrocytomas are a type of glioma. The glioma classification identifies a tumor of glial cells that are specialized cells giving physical support and electrical insulation between neurons. They are sometimes called gliomas, anaplastic astrocytomas, or glioblastoma multiforme. Oligoastrocytomas are a type of mixed glioma similar to astrocytomas. They are usually low grade tumors containing cells that originate from oligodendrocytes as well as astrocytes. Grading is an estimate of the tumor's malignancy and aggressiveness; lower-grade tumors require less drastic therapy than high-grade tumors.



This MRI image of the brain shows a large, rounded mass (purple), which is a tumor. (Living Art Enterprises/Science Source)

Genetic profile

Researchers are still learning about the many possible genetic and hereditary causes of astrocytomas. They have made some progress. Recent findings include the connection between neurofibromatosis type 1 and astrocytoma in the visual pathway. Neurofibromatosis type 1 is an inherited condition caused by changes to the *NF1* gene. Children with this condition tend to develop a type of astrocytoma in the visual pathway. Inherited mutations of the phosphatase and tension homolog, or *PTEN*, gene are found in many astrocytomas. The *PTEN* gene is involved in making a protein that is found in nearly all of the body's tissues. In addition, mutation of the "deleted in malignant brain tumors 1" (*DMBT1*) gene likely is involved in formation of astrocytomas and glioblastoma multiforme tumors. Presence of a certain alternative type of the peroxisome proliferator-activated receptor gamma (*PPARG*) gene has been associated with a type of glioma called glioma 1 (GLM1). The *PPARG* gene provides coding for an important protein. Other mutations associated with astrocytomas include alterations in the B-raf proto-oncogene (*BRAF*) gene and that can lead to pilocytic astrocytoma or low-grade gliomas.

Demographics

Astrocytoma occurs slightly more often in boys and men than in girls and women. It is also slightly more common in Caucasians than in those of African or Asian descent. Although it affects both adults and children,

children usually develop a less serious form with a better prognosis. The total incidence of all types of brain cancer, including astrocytomas, is approximately 13 people out of every 100,000.

Signs and symptoms

The cause of astrocytoma is not known. Brain cancer may occasionally be caused by previous radiation treatments. However, x-rays are not believed to play a role. Some studies suggest that brain tumors may occur more frequently in people who have occupational exposure to certain chemicals, including some pesticides, formaldehyde, vinyl chloride, phenols, acrylonitrile, N-nitroso compounds, polycyclic aromatic hydrocarbons, lubricating oils, and organic solvents. The greatest risk is associated with exposure before birth or during infancy.

There is a slightly higher incidence of astrocytoma in the siblings and parents of people with this tumor. However, only one type of astrocytoma is known to have a genetic cause. The rare subependymal giant cell astrocytoma occurs in conjunction with tuberous sclerosis, a hereditary disorder.

A wide variety of symptoms develop as a result of astrocytoma including the following:

- headache
- nausea and vomiting
- neck stiffness or pain
- dizziness
- seizures
- unsteadiness in walking or unusual gait
- lack of coordination, decreased muscle control
- visual problems such as blurring, double vision, or loss of peripheral vision
- weakness in arms or legs
- speech impairment
- altered behavior
- loss of appetite

Because there are several different types of astrocytoma, not all patients will show the same symptoms. The location of the tumor within the brain will determine which symptoms a patient will experience. Because the tumor causes an increase in intracranial pressure, most people with astrocytoma will develop headaches and nausea and vomiting.

Diagnosis

In the first stage of diagnosis, the doctor will take a history of symptoms and perform a basic neurological exam. Diagnosis will also include an eye exam and tests

of vision, balance, coordination and mental status. The doctor will then require a computerized tomography (CT) scan and magnetic resonance imaging (MRI) of the patient's brain. During a CT scan, x-rays of the patient's brain are taken from many different directions. These are combined by a computer, producing a cross-sectional image of the brain. For an MRI, the patient relaxes in a tunnel-like instrument while the brain is subjected to changes of magnetic field. An image is produced based on the behavior of the brain's water molecules in response to the magnetic fields. A special dye may be injected into a vein before these scans to provide contrast and make tumors easier to identify.

If a tumor is found, it will be necessary for a neurosurgeon to perform a biopsy on it. This simply involves the removal of a small amount of tumor tissue, which is then sent to a neuropathologist for examination and staging. The biopsy may take place before surgical removal of the tumor or the sample may be taken during surgery. Staging of the tumor sample is a method of classification that helps the doctor to determine the severity of the astrocytoma and to decide on the best treatment options. The neuropathologist stages the tumor by looking for atypical cells, the growth of new blood vessels, and indicators of cell division called mitotic figures. The diagnosis, staging, and classification of an astrocytoma often include molecular markers as well. These are identified genetic associations with tumors, which help doctors better target treatment.

Treatment and management

Treatment of astrocytoma often involves a neurosurgeon to remove the tumor, a neuropathologist to examine the tumor sample, and an oncologist to monitor the patient's health and coordinate radiation therapy and chemotherapy if necessary. Nurses and radiation therapists also play a role. After treatment, the patient may be followed up by a neurologist to monitor the patient for signs that the tumor has grown or recurred. There are several different systems for staging astrocytomas. The World Health Organization (WHO) system is the most common. It has four grades of increasing severity based on the appearance of the astrocytoma cells. Other methods of staging correspond fairly closely to the WHO system. Grades I and II are sometimes grouped together and referred to as low-grade astrocytomas. Over time, tumors may progress from a low-grade form with a relatively good prognosis to a higher-grade form and poorer prognosis. Additionally, tumors may recur at a higher grade.

Grade I Pilocytic Astrocytoma

This is also sometimes referred to as juvenile astrocytoma because it occurs more frequently in

KEY TERMS

Anaplastic—Undifferentiated, appearing to have an immature cell type.

Biopsy—A sample of tissue taken from the tumor.

Glioma—A tumor of the brain's glial cells.

Primary tumor—An original tumor, not a metastatic tumor resulting from cancer's spread.

children than adults. Under a microscope, the astrocytes, known as pilocytes, are thin and elongated. They are accompanied by Rosenthal fibers. The tumor mass does not invade surrounding tissues and is sometimes enclosed in a cyst. In children, pilocytic astrocytoma often occurs in the cerebellum, but may also occur in the cerebrum.

Treatment of this grade depends on the patient's age and the location of the tumor. Surgery is the preferred treatment for this type of astrocytoma. The surgical procedure is known as a craniotomy. An incision is made in the skin and an opening is made in the skull. After the tumor is removed, the bone is normally replaced and the incision closed. The neurosurgeon may also insert a shunt (drainage system) to relieve intracranial pressure. This involves inserting a catheter into a cavity inside the brain called a ventricle, then threading the other end under the skin to a drainage area where the fluid is absorbed.

If the tumor can be completely surgically removed, the patient may not need further therapy and may be monitored only for recurrence. If the tumor cannot be completely removed, patients may be given chemotherapy as well. If the tumor is not completely resected or if it continues to grow after chemotherapy, radiation therapy may be necessary. Radiation therapy is not normally given to children under the age of three, because it can cause permanent damage to the child's healthy brain tissue. Radiation treatment may cause swelling in the brain. Steroids may be prescribed to reduce the swelling.

The best indicator for prognosis is complete removal of the tumor. With complete tumor removal, 80% of patients are alive 10 years later. Location of the tumor in the cerebellum also suggests a better prognosis than other locations.

Grade II Low-Grade Diffuse Astrocytoma

These astrocytomas spread out and invade surrounding brain tissues but grow very slowly. Under the

microscope, fibrous structures are present. Grade II astrocytomas may occur anywhere in the brain, in the cerebellum and brain stem, or in the cerebrum, including the optic pathways. Genetic studies indicate that mutations of the tumor suppressor gene *p53* occur frequently in these tumors.

Surgical removal of the tumor is the first choice for treatment, but it may not be possible due to the tumor's location. Surgery is usually followed by radiation. Patients under 35 years of age have a better prognosis than older patients. In older patients, low-grade tumors progress to higher grades more rapidly. Overall median survival is four to five years.

Pleomorphic xanthoastrocytoma, a tumor originating in cells of a mixture of glial and neuronal origin, is often considered a grade II astrocytoma. It is relatively benign and treated only with surgery.

Grade III Anaplastic Astrocytoma

Anaplastic astrocytoma occurs most frequently in people aged 50 to 60. The term "anaplastic" means that the cells are not differentiated. They have the appearance of immature cells and cannot perform their proper functions. Researchers believe this is due to a gradual accumulation of genetic alterations in these cells. These tumor cells invade surrounding healthy brain tissue.

Anaplastic astrocytomas may be inoperable because of their location and their infiltration into normal tissue. When this occurs, radiation therapy is recommended. Chemotherapy may include various combinations of alkylating agents and other drugs, including carmustine, cisplatin, lomustine, procarbazine and vincristine. These tumors tend to recur more frequently than grade I and II tumors. Following treatment, median survival is 12 to 18 months. The five-year survival rate for these patients is approximately 10% to 35%.

Grade IV Glioblastoma Multiforme

Glioblastoma Multiforme (GBM) is the most common primary brain tumor in adults. These tumors aggressively invade adjacent tissue and may even spread throughout the central nervous system. They frequently occur in the frontal lobes of the cerebrum. Tumor biopsies may show large areas of necrosis, or dead cells, surrounded by areas of rampant growth. There may also be a mixture of cell types within the biopsy. Genetic studies show that a number of different types of mutations can take place in genes for tumor suppressor *p53* and other proteins that play a role in controlling the normal growth of cells.

Often GBM cannot be entirely surgically removed because it affects large areas of the brain. Radiation

therapy will be given regardless of whether surgery is possible, except to very young children. Conventional radiation may be performed, but more specialized types may also be used. One of these specialized types, stereotactic radiosurgery, uses imaging and a computer to treat the tumor very precisely. Another, interstitial radiation, delivers radiation by placing radioactive material directly on the tumor. Chemotherapy will follow radiation; it may include carmustine, lomustine, procarbazine, and vincristine.

GBM is most common in patients over 50 years of age and rarely occurs in patients under 30. Increasing age is associated with a poorer prognosis. Median survival is 9 to 11 months following treatment. Fewer than 5% of patients are alive five years later. Because of the poor prognosis of GBM, it is treated more aggressively than low-grade astrocytomas. Many clinical trials take place to test new treatments.

Alternative and complementary therapies

No specific alternative therapies have been noted as effective for this particular type of brain cancer, but patients interested in pursuing complementary therapies should discuss the idea with their doctor. A doctor may be able to provide information about how helpful certain techniques can be at relieving symptoms or improving quality of life. An important concern is whether they may interfere with conventional treatment.

Patients may experience unpleasant side effects from treatment. Patients should discuss any side effects they experience with their doctors. Occasionally an effect may be unexpected or dangerous and dosages may need to be adjusted. Doctors can help alleviate nausea with anti-nausea medications and may prescribe antidepressants to help the patient deal with the cancer on a psychological level. Joining support groups will also help patients deal with the psychological effects of treatment. Cancer survivors can help provide encouragement and offer advice for coping with cancer on a day-to-day basis.

Clinical trials are an important treatment possibility, especially for patients who have tumors that are inoperable or who do not respond well to treatment. Participation in clinical trials also gives patients an opportunity to make contributions to the search to find a cure for their cancer. A wide variety of clinical trials are available, particularly for the higher-grade astrocytomas. Trials for higher-grade astrocytomas may test new drugs, new combinations of drugs, drug implants, and higher doses of drugs, possibly in combination with different methods of radiation therapy. Some studies may examine the use

QUESTIONS TO ASK THE DOCTOR

- Where inside my brain is the cancer located and where will it spread?
- What types of treatment are recommended?
- What are the possible side effects of this treatment?
- How can the side effects be minimized?
- Am I eligible for any clinical trials?
- Are there any alternatives to this treatment?
- What are the chances that the cancer will return?
- Will this cause any disabilities?
- How will this affect my daily life?

of gene therapy. Others analyze immune therapy, including vaccines.

Trials for lower-grade astrocytomas focus on finding chemotherapy that causes fewer side effects. Some studies may also feature new combinations of drugs while others may attempt to treat the tumor by using lower dosages of drugs spread out over a longer period of time.

Currently, scientists do not know what causes most brain cancers. There may be a slight genetic predisposition as family members of astrocytoma patients have a slightly increased incidence of the disease. Clinical studies show that a large number of genetic alterations take place in the higher grade astrocytomas. Although this helps to explain what is going wrong in the cells, it does not explain what is causing these genetic mutations to take place or how to prevent them.

While it is known that ionizing radiation can cause brain tumors, most people are not exposed to this type of radiation unless they are being treated for cancer. Ongoing studies are examining the long-term risks of other types of radiation, but neither x-rays, electromagnetic fields, nor cell phones appear to increase the likelihood of brain cancers.

Although evidence is not yet conclusive, some studies suggest that brain tumors may be caused by environmental exposure to certain organic chemicals. Exposure is most harmful to the developing fetus and infants, so pregnant women may wish to consider whether they have any occupational exposure to organic chemicals. Parents of infants should be aware of pesticides and any other potentially harmful chemical their child could come into contact with.

Prognosis

Children who develop astrocytoma should be monitored regularly by their physicians to ensure that the tumor does not recur. A follow-up schedule should be discussed with the doctor. The child may be examined twice a year initially and then tested annually afterwards. In addition to the possibility of recurrence, other health problems from treatment may arise in the child. The child may have lower levels of growth hormone or thyroid hormone. They may experience delayed growth as a result of radiation. There may also be intellectual, learning, or physical disabilities that can be detected during follow-up. Parents can then arrange for rehabilitation or special needs education for their child.

Adults may also experience permanent negative effects as a result of their treatment. Radiation damage to healthy tissue may occasionally cause delayed effects such as decreased intellect, impaired memory, changes in personality, and confusion. These types of side effects should be reported to a health professional. The patient can be referred to rehabilitation specialists who can help with regaining abilities.

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ORGANIZATIONS

American Brain Tumor Association, 8550 W. Bryn Mawr Ave., Suite 550, Chicago, IL 60631, (773) 577-8750, (800) 886-2282, 773-577-8738, info@abta.org, <http://www.abta.org>

National Brain Tumor Society, 55 Chapel Street, Suite 200, Newton, MA 02458, (617) 924-9997, (617) 924-9998, <http://braintumor.org>

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Ataxia-Telangiectasia

Definition

Ataxia-Telangiectasia (A-T) is a rare, genetic neurological disorder that progressively affects various systems in the body. Children affected with A-T appear normal at birth; however, the first signs of the disease—usually a lack of balance and slurred speech—often appear between one and two years of age.

Description

The onset of cerebellar ataxia (unsteadiness and lack of coordination) marks the beginning of progressive degeneration of the cerebellum, the part of the brain responsible for motor control (movement). This degeneration gradually leads to a general lack of muscle control and eventually confines the patient to a wheelchair. Children with A-T become unable to feed or dress themselves without assistance. Because of the worsening ataxia, children with A-T lose their ability to write, and speech also becomes slowed and slurred. Even reading eventually becomes impossible, as eye movements become difficult to control.

Soon after the onset of the ataxia, an individual usually exhibits another symptom of the disease—telangiectases, or tiny red spider veins (dilated blood vessels). These telangiectases appear in the corners of the eyes—giving the eyes a bloodshot appearance—or on the surfaces of the ears and cheeks exposed to sunlight.

In about 70% of children with A-T, another symptom of the disease is present: an immune system deficiency that usually leads to recurrent respiratory infections. In many patients, these infections can become life threatening. Because of deficient levels of IgA and IgE immunoglobulins—the natural infection-fighting agents in the blood—children with A-T are highly susceptible to lung infections that are resistant to the standard antibiotic treatment. For these patients, the combination of a weakened immune system and progressive ataxia can ultimately lead to pneumonia as a cause of death.

Children with A-T tend to develop malignancies of the blood circulatory system almost 1,000 times more frequently than the general population. Lymphomas (malignant tumors of lymphoid tissues) and leukemias (abnormal overgrowth of white blood cells, causing tumor cells to grow) are particularly common types of cancer, although the risk of developing most types of cancer is high in those with A-T. Another characteristic of the disease is an increased sensitivity to ionizing radiation (high-energy radiation such as x-rays), which means that

patients with A-T frequently cannot tolerate the radiation treatments often given to cancer patients.

Genetic profile

Ataxia-Telangiectasia is called a recessive genetic disorder because parents do not exhibit symptoms; however, each parent carries a recessive (unexpressed) gene that may cause A-T in offspring. The genetic path of A-T is therefore impossible to predict. The recessive gene may lie dormant for generations until two people with the defective gene have children. When two such A-T carriers have a child together, there is a 25% risk of having a child with A-T. Every healthy sibling of a child with A-T has a 50% risk of being a carrier, like his or her parents.

The A-T gene (called *ATM*, or A-T Mutated) was discovered by Tel Aviv researchers in 1995. The ATM protein is thought to prevent damaged DNA from being reproduced. However, the cells of patients with A-T lack the ATM protein, although the cells of those with the mild form of the disorder contain small amounts of it. It is thought that ATM is involved in sending messages to several other regulating proteins in the body. The absence of ATM severely disrupts the transmission of these messages, thereby affecting many different systems of the body.

Scientists have discovered that the *ATM* gene is often found with the *p53* gene, which is defective in the majority of cancerous tumors. Tumor biologists, therefore, view A-T as one of the most explicit human models for studying inherited cancer susceptibility. In children who have A-T, the defective *A-T* gene blocks the normal development of the thymus, the organ most important for the development of the immune response. Understanding how immunodeficiencies develop in children with A-T may have relevance to research on other immunodeficiency disorders.

Demographics

Both males and females are equally affected by A-T. Epidemiologists estimate the frequency of A-T as between 1 in 40,000 and 1 in 100,000 live births worldwide. However, it is believed that many children with A-T, particularly those who die at a young age, are never properly diagnosed. Thus, the disease may occur much more often than reported.

According to the National Cancer Institute (NCI), about 1% (2.5 million) of the American population carry a copy of the defective *A-T* gene. According to some researchers, these gene carriers may also have an increased sensitivity to ionizing radiation and have a

significantly higher risk of developing cancer—particularly breast cancer in female carriers.

Signs and symptoms

Although there is much variability in A-T symptoms among patients, the signs of A-T almost always include the appearance of ataxia between the ages of two and five. Other, less consistent symptoms may include neurological symptoms, cutaneous (skin) symptoms, and a variety of other conditions.

Neurological

Neurological symptoms of A-T include:

- progressive cerebellar ataxia (although ataxia may appear static between the ages of two and five)
- cerebellar dysarthria (slurred speech)
- difficulty swallowing, causing choking and drooling
- progressive apraxia (lack of control) of eye movements
- muscle weakness and poor reflexes
- initially normal intelligence, sometimes with later regression to mildly retarded range

Cutaneous

Cutaneous symptoms include:

- progressive telangiectases of the eye and skin develop between two to ten years of age
- atopic dermatitis (itchy skin)
- café au lait spots (pale brown areas of skin)
- cutaneous atrophy (wasting away)
- hypo- and hyperpigmentation (under-pigmented and over-pigmented areas of skin)
- loss of skin elasticity
- nummular eczema (coin-shaped inflammatory skin condition)

Other symptoms

Other manifestations of A-T include:

- susceptibility to neoplasms (tumors or growths)
- endocrine abnormalities
- tendency to develop insulin-resistant diabetes in adolescence
- recurrent sinopulmonary infection (involving the sinuses and the airways of the lungs)
- characteristic loss of facial muscle tone
- absence or dysplasia (abnormal development of tissue) of thymus gland
- jerky, involuntary movements
- slowed growth

- prematurely graying hair

Diagnosis

For a doctor who is familiar with A-T, the diagnosis can usually be made on purely clinical grounds and often on inspection. But because most physicians have never seen a case of A-T, misdiagnoses are likely to occur. For example, physicians examining ataxic children frequently rule out A-T if telangiectases are not observed. However, telangiectases often do not appear until the age of six and sometimes appear at a much older age. In addition, a history of recurrent sinopulmonary infections might increase suspicion of A-T, but about 30% of patients with A-T exhibit no immune system deficiencies.

The most common early misdiagnosis is that of static encephalopathy—a brain dysfunction, or ataxic cerebral palsy—paralysis due to a birth defect. Ataxia involving the trunk and gait is almost always the presenting symptom of A-T. And although this ataxia is slowly and steadily progressive, it may be compensated for—and masked—by the normal development of motor skills between the ages of two and five. Thus, until the progression of the disease becomes apparent, clinical diagnosis may be imprecise or inaccurate unless the patient has an affected sibling.

Once disease progression becomes apparent, Friedreich ataxia (a degenerative disease of the spinal cord) becomes the most common misdiagnosis. However, Friedreich ataxia usually has a later onset. In addition, the spinal signs involving posterior and lateral columns along the positive Romberg's sign (inability to maintain balance when the eyes are shut and feet are close together) distinguish this type of spinal ataxia from the cerebellar ataxia of A-T.

Distinguishing A-T from other disorders (differential diagnosis) is ultimately made on the basis of laboratory tests. The most consistent laboratory marker of A-T is an elevated level of serum alpha-fetoprotein (a protein that stimulates the production of antibodies) after the age of two years. Prenatal diagnosis is possible through the measurement of alpha-fetoprotein levels in amniotic fluid and the documentation of increased spontaneous chromosomal breakage of amniotic cell DNA. Diagnostic support may also be offered by a finding of low serum IgA, IgG, and/or IgE. However, these immune system findings vary from patient to patient and are not abnormal in all individuals.

The presence of spontaneous chromosome breaks and rearrangements in lymphocytes in vitro (test tube) and in cultured skin fibroblasts (cells from which connective tissue is made) is also an important laboratory marker of A-T. And finally, reduced survival of lymphocyte

KEY TERMS

Alpha-fetoprotein (AFP)—A chemical substance produced by the fetus and found in the fetal circulation. AFP is also found in abnormally high concentrations in most patients with primary liver cancer.

Atrophy—Wasting away of normal tissue or an organ due to degeneration of the cells.

Cerebellar ataxia—Unsteadiness and lack of coordination caused by a progressive degeneration of the part of the brain known as the cerebellum.

Dysarthria—Slurred speech.

Dysplasia—The abnormal growth or development of a tissue or organ.

Immunoglobulin—A protein molecule formed by mature B cells in response to foreign proteins in the body; the building blocks for antibodies.

Ionizing radiation—High-energy radiation such as that produced by x-rays.

Leukemia—Cancer of the blood-forming organs, which results in an overproduction of white blood cells.

Lymphoma—A malignant tumor of the lymph nodes.

Recessive gene—A type of gene that is not expressed as a trait unless inherited by both parents.

Telangiectasis—Very small arteriovenous malformations, or connections between the arteries and veins. The result is small red spots on the skin known as “spider veins.”

(cells present in the blood and lymphatic tissues) and fibroblast cultures, after exposure to ionizing radiation, will confirm a diagnosis of A-T, although this technique is performed in specialized laboratories and is not routinely available to physicians.

When the mutated A-T gene (ATM) has been identified by researchers, it is possible to confirm a diagnosis by screening the patient's DNA for mutations. However, in most cases the large size of the ATM gene and the large number of possible mutations in patients with A-T seriously limit the usefulness of mutation analysis as a diagnostic tool or method of carrier identification.

Treatment and management

There is no specific treatment for A-T because gene therapy has not become an option. Also, the disease is

QUESTIONS TO ASK YOUR DOCTOR

- Are my child's symptoms likely to be caused by some condition other than Ataxia-Telangiectasia?
- What course of action is available for dealing with this condition?
- Based on the signs and symptoms of the condition at this point, what is the prognosis for the disorder in my child?

usually not diagnosed until the individual has developed health problems. Treatment is therefore focused on the observed conditions, especially if neoplasms are present. However, radiation therapy must be minimized to avoid inducing further chromosomal damage and tumor growth.

Supportive therapy is available to reduce the symptoms of drooling, twitching, and ataxia, but individual responses to specific medications vary. The use of sunscreens to retard skin changes due to premature aging can be helpful. In addition, early use of pulmonary physiotherapy, physical therapy, and speech therapy is also important to minimize muscle contractures (shortening or tightening of muscles).

Although its use has not been formally tested, some researchers recommend the use of antioxidants (such as vitamin E) in patients with A-T. Antioxidants help to reduce oxidative damage to cells.

Clinical trials

Clinical trials for the treatment or prevention of A-T are currently sponsored by the National Institutes of Health (NIH) and other agencies. In 2015, NIH reported 18 ongoing studies.

A few examples include:

- The evaluation of antibody responses to a pneumococcal vaccine for the treatment of A-T. (NCT00656409)
- A study on the treatment of A-T in children with cancer. (NCT00187057)
- The evaluation of whether Baclofen, a medicine that is often used for the treatment of abnormal stiffness, might also be useful to treat some of the neurologic problems caused by A-T. (NCT00640003)

Clinical trial information is constantly updated by NIH and the most recent information on A-T trials

can be found at <http://clinicaltrials.gov/search/open/condition=%22Ataxia+Telangiectasia%22>

Prognosis

A-T is an incurable disease. Most children with A-T depend on wheelchairs by the age of ten because of a lack of muscle control. Children with A-T usually die from respiratory failure or cancer by their teens or early twenties. However, some patients with A-T may live into their forties, although this is extremely rare.

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ORGANIZATIONS

A-T Children's Project, 5300 W. Hillsboro Blvd., Suite 105, Coconut Creek, FL 33073, (800) 543-5728, (954) 481-6611, info@atcp.org, <http://www.communityatcp.org>

A-T Ease Foundation, 217 Thompson Street, Suite 404, New York, NY 10012, (212) 529-0622, (212) 505-8031, info@ateasefoundation.org, <http://www.ateasefoundation.org>

National Ataxia Foundation (NAF), 2600 Fernbrook Lane, Suite 119, Minneapolis, MN 55447, (763) 553-0020, <http://www.ataxia.org>

National Institute for Neurological Disorders and Stroke (NINDS), PO Box 5801, Bethesda, MD 20824, (800) 352-9424 or (301) 496-5751, <http://www.ninds.nih.gov>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Genevieve T. Slomski, PhD

Attention deficit hyperactivity disorder

Definition

Attention deficit hyperactivity disorder (ADHD) is a neurological disorder that presents in various forms, with no two ADHD disorders having exactly the same characteristics. ADHD is classified as a disruptive behavior disorder characterized by ongoing difficulty with attention span, hyperactivity, and/or impulsivity. These difficulties occur more frequently and severely than is typical for individuals in the same stage of development.

Description

ADHD is a neurological condition, frequently familial, that affects specific types of brain functioning. The term ADHD is further divided into presentations (subcategories) that describe the type of ADHD. The three



Students diagnosed with attention deficit hyperactivity disorder find it difficult to concentrate for long periods of time. (Suzanne Tucker/Shutterstock)

presentations recognized by the scientific community are ADHD inattentive type, ADHD impulsive-hyperactive type, and ADHD combined type. Some individuals, including many professionals, still refer to the condition as ADD (attention deficit disorder). However, this term is no longer in widespread use. For individuals who have been diagnosed with ADD in the past, the corresponding current terminology is most likely to be predominantly ADHD, inattentive type.

It is possible to meet the accepted diagnostic criteria for ADHD without displaying any symptoms of hyperactivity or impulsivity. Each ADHD individual will display a unique combination of symptoms. They will not necessarily have all of the symptoms associated with ADHD. Furthermore, the levels of severity or impairment vary from individual to individual. There are mild forms of ADHD in addition to the severe forms that result in significant impairment. Symptoms of ADHD usually begin before age seven. In later life, these symptoms can cause problems in school, work, family life, and relationships. ADHD can be managed through behavioral or medical interventions or a combination of the two. Despite public controversy over the legitimacy of the disorder's existence, the National Institutes of Health (NIH), the Surgeon General of the United States, and the international community of clinical researchers and physicians have affirmed that ADHD is a valid disorder that may result in severe, lifelong consequences if left untreated. The U.S. Senate designated September 7, 2004, as National Attention Deficit Disorder Awareness Day.

Genetic profile

The exact cause of ADHD is unknown, although abnormal neurotransmitter levels, genetics, and complications occurring around the time of birth have been implicated. According to the National Resource Center on ADHD, heredity makes the largest contribution to the prevalence of ADHD in the population, and evidence for heritability comes from family, twin, and adoption studies. Genetic influences are estimated to account for 70% to 80% of the risk. Inheritance is an important risk factor as ADHD occurs frequently in families. Between 10% and 35% of children diagnosed with ADHD have a first-degree relative with ADHD. Approximately 50% of parents who have ADHD have a child with the disorder. ADHD is significantly more likely to be present in an identical (monozygotic) twin than in a fraternal (dizygotic) twin.

Genome-wide association studies (GWASs) have found that ADHD is associated with many rare and common genetic variants. As of 2021, at least 21 gene variants have been associated with ADHD risk. Among these are *FOXP2*, which has been implicated in speech

and language disorders as well as adult ADHD, and *DUSP6*, which governs the balance of neurotransmitters by regulating dopamine levels in the synapses, the gaps between neurons across which impulses are conveyed by a neurotransmitter. Because symptoms of ADHD respond well to treatment with stimulants that increase the availability of the neurotransmitter dopamine, the dopamine hypothesis has gained acceptance. It suggests that ADHD is due to inadequate availability of dopamine in the central nervous system. Dopamine plays a key role in initiating focused movement, increasing motivation and alertness, and preventing sleepiness in response to boredom. Multiple genes have been implicated in ADHD, including genes affecting dopamine usage by the brain.

The GWAS also demonstrated that much of the heritability of ADHD is due to the polygenic effects of many common variants, each having very small effects. In addition, some genetic syndromes, such as the 15q11.2 BP1-BP2 and fragile X, Turner syndrome, tuberous sclerosis, neurofibromatosis, Klinefelter syndrome, and Williams syndrome have ADHD as a symptom.

The male-to-female ratio is 8:1. Despite the strong genetic linkage, research also suggests that non-genetic factors may play a role in ADHD. Hyperactivity and inattention are more common in children who have had exposure to toxins such as lead, alcohol, or cigarette smoke, or episodes of fetal oxygen deprivation during complications of pregnancy. These factors may adversely affect dopamine-rich areas of the brain.

In addition to dopamine, research has shown that glucose usage may be involved in ADHD. Brain-imaging studies, using magnetic resonance imaging (MRI), have demonstrated differences between the brains of children with and without ADHD. A link has been established between an individual's ability to pay continued attention and the brain's use of glucose as a fuel. In adults with ADHD, the brain areas that control attention span may use less glucose and be less active, suggesting that a lower level of activity in this part of the brain may cause the inattention symptoms associated with ADHD.

By 2002, the NIMH Child Psychiatry Branch concluded a decade-long controlled study that demonstrated ADHD children having 3% to 4% smaller brain volumes in multiple critical brain regions affecting the types of behaviors associated with ADHD. The study also demonstrated that ADHD children receiving medication had developed a volume of white matter that was the same as in normal children. Individuals who had ADHD, but were never medicated, had an abnormally small volume of white matter.

Demographics

ADHD is the most commonly diagnosed behavioral disorder of childhood, affecting an estimated 8% to 12% of school-aged children. Males are considered up to eight times more likely to have ADHD than females, although the difference between the numbers of males and females may be due in part to males having a higher rate of hyperactivity symptoms that are easier to detect and diagnose. ADHD often occurs in conjunction with other problems, such as depressive and anxiety disorders, conduct disorders, drug abuse, and antisocial behaviors. Among children ages three to 10, The 2016-2018 National Health Interview Survey found that non-Hispanic black children (16.9%) were more likely than white (14.7%) or Hispanic children (11.9%) to have been diagnosed with ADHD. Children with untreated ADHD have increased rates of injury and co-morbid psychiatric disorders. Approximately 70% to 80% of children with ADHD continue to exhibit significant symptoms into adolescence and adulthood.

An estimated 2% to 6% of adolescents and 2% to 4% of adults have ADHD. Adults who had untreated ADHD in childhood have more severe symptoms and adverse risk factors later in life. Adverse factors both influence the expression of ADHD and increase the risk for associated disorders reducing overall adjustment throughout life. ADHD is considered a lifelong disorder that requires accurate diagnosis and appropriate treatment.

Signs and symptoms

Symptoms of ADHD often become apparent by age seven, but many adults remain undiagnosed. The three presentations of ADHD recognized by the scientific community include a predominantly hyperactive-impulsive type that does not display significant symptoms of inattention, a predominantly inattentive type that does not display significant symptoms of hyperactive-impulsive behavior, and a combined type that displays both the inattentive and hyperactive-impulsive symptoms associated with ADHD. The predominantly inattentive type is sometimes still referred to as ADD, but this is an outdated term for the disorder.

Symptoms of inattention tend to persist through childhood into adulthood. The symptoms of inattention may include difficulty in observing details, easy distractibility, inability to concentrate, procrastination of tasks requiring sustained mental effort, frequent careless mistakes, disorganization, difficulty maintaining conversations, and difficulty completing appointed tasks. The symptoms of hyperactivity and impulsivity are nearly always present before the seventh year and tend to diminish with age. Hyperactivity symptoms may include

restlessness, excessive verbosity, and frequent inappropriate social interactions. Hyperactive behavior is often associated with the development of other disruptive behavioral disorders. It has been proposed that the impulsivity and inattention associated with ADHD may interfere with social learning in a way that predisposes the individual to the development of these disorders.

While many of these symptoms may sometimes occur in other children, those with ADHD experience these behaviors more intensely and across several settings. Both children and adults with ADHD may experience these symptoms to a degree that interferes with normal functioning. Some individuals with moderate to severe ADHD may also experience periods of anxiety or depression. Individuals whose predominant symptom is inattention are most prone to depression. It follows that ADHD rarely occurs alone. It has been demonstrated that many people with ADHD also are subject to one or more comorbid (co-occurring) conditions such as depression, anxiety disorders, learning disabilities, or substance abuse disorders. Many conditions may have symptoms similar to, and be mistaken for, ADHD. It is critical that comorbid disorders be diagnosed and treated, so that efforts to treat the ADHD will succeed. When ADHD symptoms are present as secondary to another psychiatric disorder, the individual may be incorrectly treated for ADHD. However, when ADHD is the primary disorder, treating it often eliminates or ameliorates other dysfunctions.

There are many ADHD websites available to the public. Many offer various questionnaires and descriptions of symptoms on the subject of ADHD. These websites are not standardized or scientifically validated and should never be used to diagnose ADHD. A valid diagnosis can only be provided by a qualified, licensed professional.

Diagnosis

Well-established and research-validated clinical guidelines for the diagnosis of ADHD are provided in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V). The DSM-V's criteria for diagnosis include multiple symptoms of inattention or hyperactivity-impulsivity that persist for at least six months across multiple settings such as school, work, or home. These symptoms must exist to a degree that is inconsistent with other individuals at the same developmental level. Some of the hyperactive-impulsive or inattentive symptoms must have been present before the age of twelve years. The symptoms must not occur exclusively during the course of another developmental disorder, schizophrenia, or psychotic disorder. Furthermore, the symptoms should not be diagnosed by

the description of any other mental disorder. Although fidgeting and inattentiveness are common childhood behaviors, the DSM-V criteria indicate a diagnosis of ADHD for children in whom such behavior occurs so frequently that it produces continuing, pervasive dysfunction. A diagnostic evaluation requires histories from multiple sources, a medical evaluation of general and neurological health, and a full cognitive assessment. In practice, the diagnosis is often made in individuals who meet only some of the criteria established by the DSM-V.

Treatment and management

The American Academy of Child and Adolescent Psychiatry (AACAP) established treatment as the support and education of family members, appropriate school placement, and pharmacology. Both pharmacological treatment and psychosocial treatment such as behavioral modification may be used.

Pharmacological treatment

Pharmacological treatment with psychostimulants is the most widely researched treatment for ADHD. This treatment has been used for childhood behavioral disorders since the 1930s. Psychostimulants are highly effective for approximately 75%–90% of children with ADHD. There are four psychostimulant treatments that have been demonstrated by hundreds of randomized controlled trials to consistently reduce the primary symptoms of ADHD: methylphenidate, dextroamphetamine, pemoline, and a mixture of amphetamine salts. These medications are only effective for one to four hours and so must be administered with the individual's school or work schedule. The medications are most effective for symptoms of hyperactivity, impulsivity, inattention, and the associated features of rebelliousness, aggression, and argumentativeness. They promote improved overall performance. Individuals who do not respond to one stimulant may respond to another. Those in whom psychostimulant treatment has been indicated require an assessment to determine which, if any, psychostimulant may improve their symptoms with the fewest side effects. According to guidelines established by the AACAP, stimulants are usually started at a low dose and adjusted weekly. According to the NIMH, the stimulants most commonly prescribed for ADHD include methylphenidate (Ritalin), dextroamphetamine (Dexedrine), and amphetamine (Adderall).

In December 1999, the National Institutes of Mental Health (NIMH) began the ongoing Multimodal Treatment Study of Children with ADHD (MTA), a landmark study that was one of the largest clinical studies ever conducted by the National Institutes of Health. The MTA

utilized 18 nationally recognized authorities in ADHD at six different university medical centers and hospitals to evaluate the leading psychosocial and pharmacological treatments for ADHD. The MTA indicated that long-term combination treatments and pharmacological treatment alone are both significantly superior to intensive behavioral treatments and routine community care in reducing most ADHD symptoms. Combined treatment was equal in efficacy to medication alone in modifying the core ADHD symptoms of inattention, hyperactivity, impulsivity, and aggression. Combined treatment was superior to medication alone in treating anxiety symptoms and in improving academic performance and social skills. Combined treatment also allowed children to be successfully treated with lower doses of medication. The NIH ADHD Consensus Conference of 1998 reported that several decades of research have established behavioral therapies to be very effective. However, the NIMH MTA study demonstrated that carefully monitored medication management is even more effective for the treatment of ADHD symptoms.

Some common side effects of psychostimulant therapy include insomnia, decreased appetite, stomachaches, headaches, and jitteriness. There may be rebound activation (a sudden increase in attention deficit and hyperactivity) after medication levels drop. Most side effects are mild; they tend to diminish over time and respond to changes in dosage. There is no evidence that height or weight is affected by psychostimulant treatment, but precautionary monitoring of growth for children taking stimulants is still recommended. Atomoxetine (Strattera) is the only nonstimulant medication approved for the treatment of ADHD. It has effects on the neurotransmitter norepinephrine, which may also play a role in ADHD. When Strattera has been prescribed to children with ADHD, more than 70% have shown significant improvement in their symptoms. A 2020 study conducted comparing methylphenidate and atomoxetine found comparable efficacy and compliance, and slightly higher satisfaction with methylphenidate.

Between 10% and 30% of individuals with ADHD do not respond to stimulant medication. For them and for those who cannot tolerate the side effects, there are other useful medications. The antidepressant bupropion has been shown to be effective for a lower percentage of patients than stimulant medication. Certain types of antidepressants are sometimes used to augment psychostimulant treatment.

Psychosocial treatment

Psychosocial treatments may be used alone or in conjunction with pharmacological treatment to manage ADHD symptoms. Behavioral treatment for children

KEY TERMS

Magnetic resonance imaging (MRI) scan—Noninvasive analysis of organs, large blood vessels, and soft tissues using magnetization without exposure to ionizing radiation.

White matter—The part of the brain that consists of fibers that establish long-distance connections between brain regions. It normally thickens as a child grows older, and the brain matures.

typically involves using time-out, point systems, and contingent attention (adults reinforcing appropriate behavior by paying attention to it).

Children with ADHD can present a challenge that places significant stress on the family. Skills training in psychosocial treatment for parents can help reduce this stress. Systematic programs conducted in specialized classrooms or summer camps by highly trained individuals may be highly effective for some children. Adults may need treatment designed to train them in coping skills for management of ADHD symptoms. These skills may include list-making systems or other such reminders to assist in the completion of important tasks. Psychosocial treatment of ADHD symptoms has been proven to be less effective than pharmacological treatment when used alone. Furthermore, psychosocial treatment must be consistently applied across multiple settings to be fully effective. Behavioral interventions focus on improving targeted behaviors or skills, but they are not as useful in reducing the core symptoms of inattention, hyperactivity, or impulsivity.

Educational accommodations for children with ADHD are federally mandated. Two federal laws that impact ADHD individuals are the Rehabilitation Act of 1973 and the Americans with Disabilities Act of 1990, which prohibit discrimination against individuals with disabilities in higher education and the workplace. Adults with ADHD are sometimes eligible for both protection and accommodation in higher education and the workplace under these laws. Organizations such as Children and Adults with Attention Deficit Disorder (CHADD) and the National Attention Deficit Disorder Association can provide information and support for individuals with ADHD.

Treatment controversies

Antidepressants known as selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, are not effective treatments for ADHD. Elimination diets, vitamin

QUESTIONS TO ASK YOUR DOCTOR

- My child has just been diagnosed with ADHD. How is that different, if at all, from the condition known as attention deficit disorder (ADD)?
- Can you tell me what causes my child's ADHD?
- Are there other medical conditions often associated with ADHD?
- What is the prognosis for my child's ADHD?

supplements, and dietary changes have also been proven to be ineffective. Rigorous controlled studies have failed to demonstrate that sugar exacerbates the symptoms of children with ADHD. Alternative therapies such as homeopathy, biofeedback, and hypnotherapy have not been shown to be effective. Similarly, there is no evidence to support the popularly held views that ADHD can be caused from excessive sugar intake, food additives, excessive television, poor parenting, or social and environmental factors such as poverty.

One highly controversial issue is whether there is over-diagnosis of ADHD and resultant over-prescription of stimulant medications. Special education legislation in the early 1990s increased general awareness of ADHD as a handicapping condition and provided the legal basis for accommodating ADHD-impaired students in the school setting. These legal mandates increased awareness of ADHD within the school system and may have inadvertently led to the inaccurate conclusion that ADHD is a new disorder or that it is overdiagnosed. Despite the increased awareness, the Executive Summary on Mental Health, a supplement to the Surgeon General's Report in 2001, indicated that 75% to 80% of youths with mental health illnesses do not receive the needed treatments. Any increased use of stimulants in the 1990s is thought to reflect better diagnosis and more effective treatment of this prevalent disorder, which is still underdiagnosed. Most underdiagnosis is thought to be due to inadequate information supplied to the healthcare provider.

Prognosis

When properly diagnosed and treated, ADHD can be well managed. Treatment often leads to increased satisfaction in life and significant improvement in daily functioning. Many people with ADHD lead highly successful and happy lives. With proper treatment, the prognosis for ADHD can be very good. However, medications do not cure ADHD; they only temporarily control

the symptoms. Although medications improve the prognosis and assist with symptom control, they cannot improve academic skills. The medications only help people to use those skills they already possess. Behavioral therapy and emotional counseling help individuals with ADHD to cope with their disorder.

Treatment may also mitigate risk factors for ADHD. A review of all long-term studies on stimulant medication and substance abuse, conducted by researchers at Massachusetts General Hospital and Harvard Medical School, determined that teenagers with ADHD who remain on medication have a lower probability of substance abuse than those who do not. Medications used properly at a young age may prevent additional later-onset emotional problems. People with ADHD who do not receive any form of treatment, either pharmacological or psychosocial, have a much poorer prognosis.

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Children and Adults with Attention/Hyperactivity Deficit Disorder {CHADD}, 4221 Forbes Boulevard, Suite 270, Lanham, MD 20706, <http://www.chadd.org>

National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892, (301) 496-4000, <http://www.nih.gov>

Attention Deficit Disorder Association, P.O. Box 103, Denver, PA 17517, (800) 939-1019, <http://www.add.org>

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Atypical Singleton-Merten syndrome

Definition

Atypical Singleton-Merten syndrome is a newly discovered variant of a very rare multisystem genetic disorder characterized by calcifications (calcium deposits) in the major blood vessels near the heart, glaucoma, and

dental and skeletal abnormalities. The major difference between atypical Singleton-Merten syndrome (SGMRT2) and the typical form of the disorder (SGMRT1) in terms of clinical features is the absence of dental abnormalities in SGMRT2.

Both forms of the syndrome are named for the two American radiologists, Edward Singleton and David Merten, who first described the disorder in 1973. Other names for the typical form of the syndrome include Merten-Singleton syndrome, Singleton-Merten dysplasia, SM syndrome, and syndrome of widened medullary cavities of the metacarpals and phalanges, aortic calcification, and abnormal dentition. The name of the variant, “atypical Singleton-Merten syndrome,” was given by the discoverer of its causative gene in 2015.

Description

In order to understand why SGMRT2 is considered atypical, it is helpful to look first at the typical form of the disorder. SGMRT1 is characterized by abnormalities in several body systems: cardiovascular, musculoskeletal, ocular, and dental:

- **Cardiovascular:** Calcifications in the aorta, the mitral and aortic valves of the heart, and the pulmonary artery gradually narrow the diameter of these vessels and valves (stenosis), slowing the flow of oxygenated blood to body tissues. By late adolescence, a child with Singleton-Merten syndrome has high blood pressure, abnormal transmission of the electrical impulses that regulate the activity of cardiac muscle (a condition known as heart block), abnormal enlargement of the heart, and the risk of heart failure.
- **Musculoskeletal:** Musculoskeletal abnormalities begin to appear as early as four months of age. The infant’s muscles waste away (atrophy) and the remaining muscle tissue loses its tone (hypotonia). The child’s overall growth is often slowed, resulting in short stature, delayed motor development, and muscle contractures. Skeletal abnormalities include widening of the medullary cavities in the bones (phalanges) of the hands; scoliosis and kyphosis; displacement of the hips, high risk of tendon rupture, and a waddling gait as a result of muscular weakness; and osteoporosis by late adolescence.
- **Ocular:** Glaucoma develops in late childhood or early adolescence and may result in complete blindness.
- **Dental:** Abnormal mineralization of the jawbones leads to late eruption and early loss of both baby and permanent teeth. The permanent teeth may be malformed and have an unusually large number of cavities.

Some patients with SGMRT1 also develop a skin rash that resembles psoriasis, with thick, red, scaly patches that are most noticeable on the fingers.

KEY TERMS

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a nonsex chromosome is required for a disease or inherited trait to develop in an individual.

Autosome—One of the 22 chromosomes that are not involved in determining gender (chromosomes 1 through 22 and not the X or Y chromosome).

Calcification—The process by which tissue becomes hardened by the depositing of calcium in the tissue.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Gain-of-function mutation—A mutation that changes the gene's product such that it acquires a new and abnormal function.

Genetic heterogeneity—The occurrence of the same or similar disease, caused by different genes among different families.

Hyperkeratosis—Abnormal thickening of the outermost layer of the skin, the stratum corneum.

Interferon—Any of a group of cells signaling proteins that are made and released by cells in

response to the presence of viruses, bacteria, and other disease organisms. The name is derived from the way in which these proteins interfere with the replication of viruses by protecting cells from virus infections.

Kyphosis—Abnormal outward curvature of the spine resulting in a hunchback.

Medullary cavity—The marrow-filled cavity inside of a long bone (such as the femur).

Osteoporosis—Loss of bone density that can increase the risk of fractures.

Phenotype—An observable characteristic or trait of an organism as determined by its genetic makeup (genotype) and its interactions with the environment.

Scoliosis—Abnormal curvature of the spine, usually defined as greater than 10 degrees to the right or left as the doctor faces the patient.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

Stenosis—The constricting or narrowing of an opening or passageway.

Genetic profile

The identification of SGMRT2 confirmed previous researchers' identification of the Singleton-Merten syndrome as marked by genetic heterogeneity, that is, that the same phenotype (an organism's visible features or traits) can result from different genetic mechanisms or from mutations in different genes. Although SGMRT1 was (and still is) considered to have an autosomal dominant inheritance pattern, a few cases of it appear to be sporadic (occurring at random for no apparent reason). SGMRT1 is associated with a mutation in the *IFIH1* gene (also known as the *MDA5* gene) on the long arm of chromosome 2 at 2q24.2. In early 2015, this *IFIH1* mutation was identified as a gain-of-function mutation, which means that the gene's product acquires a new and abnormal function. The *IFIH1* mutation triggers the production of an interferon that heightens the body's inflammatory response to a viral infection.

SGMRT2, in contrast, is associated with mutations in the *DDX58* gene located on the short arm of chromosome 9 at 9p21.1. This gene is involved in the recognition of viral proteins and plays a role in activating the immune system's response to the presence of a virus. Like SGMRT1, SGMRT2 is inherited in an autosomal dominant pattern.

Demographics

Both forms of Singleton-Merten syndrome are very rare; the prevalence is estimated at less than one person per million. As of 2015, only eleven cases of SGMRT1 from seven unrelated families had been reported worldwide. Males and females are equally affected, although in one of the families, all three patients were males.

SGMRT2 was identified in a Korean family in which eight members over four generations had the characteristic signs and symptoms of atypical Singleton-Merten syndrome. As with SGMRT1, males and females are equally affected. The pattern of inheritance is clearly autosomal dominant. It would be premature, however, to conclude from this initial case series of SGMRT2 that the disorder is more common among east Asians in general or Koreans in particular. Further research is required to determine whether the disorder is more common in some populations than in others.

Signs and symptoms

On the basis of the initial case series, the characteristic signs and symptoms of SGMRT2 are as follows:

- Cardiovascular: calcifications in the aorta, coronary arteries, and aortic valve; stenosis of the aortic valve
- Musculoskeletal: short stature, contractures in the joints of the hands, abnormalities in the bones of the hands and feet, deterioration of the end joints of the fingers, and calcifications in the tendons and ligaments
- Ocular: glaucoma and blindness in adolescence
- Dermatological: skin rash resembling psoriasis, abnormal thickening of the outermost layer of the skin (hyperkeratosis)
- Dental: no abnormalities of teeth or jaws

Diagnosis

The diagnosis of both forms of Singleton-Merten syndrome is based on observation of the symptoms that appear at various points in early childhood, later childhood, and adolescence. Infants and toddlers with the syndrome will usually show signs of muscle weakness, loss of muscle tissue, difficulties in walking, hip displacement, and other skeletal abnormalities. Those with *SGMRT1* will also show late eruption and/or premature loss of baby teeth, frequent dental cavities, and possible early loss of permanent teeth.

These signs, along with high blood pressure or abnormally frequent bone fractures in the patient's teenage years, warrant specialized tests to confirm or rule out Singleton-Merten syndrome. X-ray studies can be used to reveal the presence of calcium deposits in the valves and aorta of the heart. X-ray imaging can also be used to look for signs of osteoporosis and abnormalities in the medullary cavities in the bones of the hands and feet. Another test that can be performed is cardiac catheterization, which involves threading a long, thin, hollow tube called a catheter through the blood vessels leading to the heart. This procedure is done to evaluate the presence and extent of stenosis in these blood vessels and to determine the rate of blood flow through the chambers of the heart.

As of 2015, there were two laboratories in the United States that offered testing for mutations in the *IFIH1* gene as part of a panel for diagnosing Aicardi-Goutières syndrome, a rare genetic disorder characterized by inflammation of the brain and skin, with symptoms resembling those of systemic lupus erythematosus (SLE). There were, however, no laboratories offering genetic testing for mutations in the *DDX58* gene as of 2015.

Treatment and management

There is no cure for either form of Singleton-Merten syndrome. Treatment is directed at the specific symptoms in each individual. While children with atypical Singleton-Merten syndrome do not need the specialized

QUESTIONS TO ASK YOUR DOCTOR

- Do you think other families with the atypical form of Singleton-Merten syndrome will be identified? Is it possible that it might turn out to be the more common form of the disorder?
- Do you think there will soon be a molecular genetic test for *SGMRT2*?
- Do you think prenatal testing should be offered for this syndrome?

dental treatments required for those with *SGMRT1*, they do require medical and surgical care from several different types of specialists, including cardiologists, dermatologists, ophthalmologists, physical therapists, and orthopedic surgeons. Those with severe calcifications in the heart may require surgery to remove the calcium deposits, replace damaged valves, and prevent complete heart failure.

Children diagnosed with the syndrome should have regular eye examinations from early childhood to monitor for signs of glaucoma. Glaucoma surgery has been shown to be beneficial in preventing blindness in the patients.

Children with either form of Singleton-Merten syndrome will also need a range of special education programs and other social services. Their families should be offered genetic counseling.

Prognosis

The initial case series that led to the identification of atypical Singleton-Merten syndrome indicates that patients can live well into their reproductive years. The oldest person in the series was 56, and two other patients were in their mid-30s at the time of the study. It is possible that the cardiovascular abnormalities may shorten some patients' lifespans, but long-term follow-up of the affected family is necessary to clarify the prognosis of the disorder.

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ORGANIZATIONS

American Academy of Oral & Maxillofacial Pathology, 214 North Hale Street, Wheaton, IL 60187, (630) 510-4552 or (888) 552-2667, (630) 510-4501, info@aaomp.org, <http://www.aaomp.org>

American College of Radiology (ACR), 1891 Preston White Dr., Reston, VA 20191, (703) 648-8900, info@acr.org, <http://www.acr.org>

Developmental Delay Resources (DDR), 5801 Beacon Street, Pittsburgh, PA 15217, (800) 497-0944, (412) 422-1374, devdelay@mindspring.com, <http://www.devdelay.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

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Autism spectrum disorders

Definition

Autism spectrum disorders (ASD) encompass a wide range of complex neurological and developmental disorders. ASD varies from mild to debilitating and is characterized by impairment in social functioning, communication, learning, reasoning, and behaviors. Signs and symptoms of ASD are evident from early childhood and often last throughout life.

Description

ASD is a variable neurological disorder that affects the structure and function of the brain and nervous system. It can interfere with communication, social interactions, understanding, and learning. It is a spectrum disorder because of the wide range in symptoms and severity. Although 15%–20% of people with ASD have severe intellectual impairment, 46% have average or above-average intellectual ability. For example, some children with ASD teach themselves to read before they are able or choose to talk. Some people with ASD have extraordinary talents in various areas, such as math, art, or music, and are termed “savants.”

People with ASD usually have problems interacting verbally and nonverbally and are often described as “being in their own world.” Those who develop speech often use pronouns—such as “I,” “me,” and “you”—incorrectly and may have difficulty understanding the purpose of speech. They may echo the comments of others (echolalia) or use phrases inappropriately. They often have problems recognizing social cues such as facial expressions and tone of voice. About one-third of children with ASD develop seizures in early childhood or adolescence.

Individuals with ASD may have hyperacute senses. They may be overly sensitive to bright lights, loud noises, or rough textures. Self-stimulating or repetitive behaviors—such as head banging, hand flapping, or rocking—may be attempts at self-calming when overstimulated. Other characteristic behaviors can include temper tantrums, fixations, or obsessions. Many people with ASD require strict routines and have difficulty adapting to any type of change.

Origins

The term “autism,” from the Greek word *autos* meaning “self,” was first used by the Swiss psychiatrist Eugen Bleuler for “isolated self,” indicating removal from social interaction. In the 1940s, the Austrian-American psychiatrist Leo Kanner used the term “early infantile autism” to describe children with a pattern of symptoms, but with some unique abilities, who did not appear to be emotionally disturbed or mentally retarded. At about the same time, the Austrian pediatrician Hans Asperger described children with a similar behavioral profile that became known as Asperger syndrome.

In 2013, the fifth edition of the American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* significantly—and controversially—altered ASD classifications, defining it as a single spectrum disorder regardless of the symptoms or their severity. Previously, ASD was defined as a category consisting of four types:

- autistic disorder or “classic” autism
- Asperger syndrome, with well-developed language skills and milder symptoms primarily involving social behaviors
- childhood disintegrative disorder, in which children initially appear to develop normally, but lose language, movement, coordination, and other neurologic functions and develop autistic behaviors between the ages of three and ten years
- pervasive developmental disorder not otherwise specified (PDD-NOS) or “atypical” autism, with some symptoms of classic autism or Asperger syndrome.



Autistic teenager working with a speech therapist in a music workshop. (Amelie Benoist/Bsip SA/Alamy)

These terms are no longer used. Rather, patients are all described as having ASD.

Genetic profile

Studies strongly suggest the existence of a genetic predisposition to ASD, but the genetic profile is extremely complicated. If one identical twin has ASD, the risk that the other twin (who has inherited identical genes) is also affected may approach 90%. In contrast, the risk is much lower that a second non-identical twin is also affected. Likewise, in families with one child with ASD, the risk of having a second affected child is somewhere between 2% and 18%. Sometimes a parent or other relative of a child with ASD exhibits mild social or communicative impairment or repetitive behaviors. Some mental disorders, such as bipolar disorder, appear to occur more frequently in families affected by ASD. Nevertheless, most people with ASD have no family history of the disorder.

About 100 genes and 50 chromosomal abnormalities have been associated with ASD. However, another 500 to 1,000 genes appear to contribute to the risk of ASD. The potential involvement of so many different genes and

gene variants probably accounts for the range of symptoms seen in ASD. Most people with ASD have different combinations of gene variants or mutations (changes) in different genes. The largest study to date of genes that contribute to ASD, published in 2014, strongly implicated 33 different genes. Those conferring the most significant risk of ASD were genes involved in the formation of communications between brain cells, genes that controlled the expression of other genes, and genes that were regulated by environmental factors. The greatest risk factors for ASD were rare mutations in 107 different genes. The researchers identified gene mutations that increased the risk for ASD in boys by more than 20-fold. Another study published in 2014 reported that about 60% of the risk for ASD was due to both common and rare versions of genes inherited from the parents, with only about 2.6% of the risk attributable to spontaneous mutations that were not inherited from a parent. A study published in 2015 reported that, among siblings with ASD, only one-third had inherited similar gene variants from a parent, again indicating that genetic and environmental interactions are responsible. Furthermore, many people with some of the ASD-associated gene mutations have no symptoms of ASD. Some researchers have suggested

that every case of ASD is caused by a set of genetic and environmental factors unique to the individual.

ASD-associated genetic syndromes

Despite the large number of gene variations that appear to be associated with ASD—ranging from single point mutations in the DNA sequence of a gene to deletions or duplications of sections of DNA to large chromosome abnormalities—fewer than 20% of ASD cases have specific genetic causes. There are known genetic disorders that carry a risk for ASD and that can usually be detected with genetic testing. About 10% of children with ASD have Down syndrome, fragile X syndrome, tuberous sclerosis, or other known genetic disorders.

Fragile X syndrome—the most common cause of inherited intellectual disability—accounts for about 2% of ASD cases. Fragile X syndrome is caused by a defect in the *FMR1* gene located on the X chromosome. It almost exclusively affects males, since they have only one X chromosome inherited from their mother. Females have two X chromosomes, so they are unlikely to be affected even if they inherit one fragile X gene.

Tuberous sclerosis is caused by mutations in the *TSC1* and *TSC2* genes. It is a variable disorder characterized by under-pigmented skin patches, tumors, seizures, and mental retardation in some affected individuals. Up to 25% of patients with tuberous sclerosis have symptoms of ASD.

Phenylketonuria (PKU) is an inherited metabolic disorder in which the enzyme that breaks down the amino acid phenylalanine is defective or absent. Protein in the diet causes the buildup of phenylalanine in the body leading to mental retardation and autistic symptoms. In the United States, most newborns are tested for PKU and are treated with a phenylalanine-free diet, which prevents intellectual impairment and ASD.

Rett syndrome is a progressive neurological disorder that is caused by mutations in the *MECP2* gene and almost exclusively affects females. Girls with Rett syndrome develop normally until 18 months of age and then undergo a period of regression with loss of speech and motor skills. Girls with Rett syndrome have mental retardation and often exhibit autistic behaviors including constant hand wringing or hand washing.

Other risk factors

Researchers are attempting to identify other factors that interact with genetic susceptibility to cause ASD. These include other problems with connections in the brain, problems in the growth or overgrowth of brain regions, or metabolic or immune system problems that are

not caused by identified genetic factors. Among people with ASD, 89% are diagnosed with at least one other developmental disorder, such as learning disabilities or attention deficit disorder (ADD), and 10% are diagnosed with at least one psychiatric disorder. Other co-existing disorders may include Tourette syndrome or epilepsy. A small percentage of children born prematurely or with low birth weight are at higher risk for ASD. Children born to older parents are also at higher risk. Researchers have reported that pregnant women who took common antidepressants called selective serotonin reuptake inhibitors (SSRIs), especially during the first trimester, were at two–three times greater risk of having a child with ASD. Assisted reproductive technology (ART) has been reported to increase the risk of ASD, especially ART that injects sperm directly into the cytoplasm of the egg cell. The risk also appears to depend on the type of infertility being treated with ART. Other possible risk factors for ASD include infection or exposure to environmental chemicals, such as pesticides.

Demographics

It is difficult to determine the true incidence of ASD, particularly with recent changes in diagnostic criteria. However, ASD diagnoses have increased significantly in recent years. Some of this increase is due to improved awareness of ASD on the part of healthcare professionals and parents. In the past, children now diagnosed with ASD may have been diagnosed with developmental delay or mental retardation at one end of the spectrum or simply labeled as unusual or quirky at the other end of the spectrum. However, the increase in ASD cannot be explained by increased awareness or diagnoses alone. In the United States, ASD affects about one in 68 children, and recent North American, European, and Asian studies have reported an average incidence of 1%. A South Korean study reported a prevalence of 2.6%.

ASD occurs in all ethnic, racial, socioeconomic, and age groups. In the United States, it affects almost five times more males than females: one in 42 boys compared with one in 189 girls. However, some researchers believe that ASD is underdiagnosed in females because they are better than males at masking their symptoms, particularly symptoms involving social interactions.

Although the causes of ASD are unknown, there are clearly multiple factors contributing to symptoms that fall along the autism spectrum. These symptoms are believed to result from the interaction of multiple genes, termed multifactorial inheritance, and environmental factors that appear to occur during prenatal development. Studies have found irregularities in several brain regions in people with ASD, as well as abnormal levels of serotonin and other neurotransmitters. Such studies suggest a

KEY TERMS

Antipsychotics—Medications for reducing symptoms of a severe mental disorder such as schizophrenia; sometimes used for behavioral ASD symptoms.

Asperger syndrome—A term previously used to describe mild autism in individuals with normal intelligence and language skills; now classified as an ASD.

Assisted reproductive technology (ART)—Infertility treatments, including fertility drugs, artificial insemination, and in vitro fertilization.

Attention deficit disorder (ADD); attention deficit/hyperactivity disorder (ADHD)—Condition characterized by diverse symptoms including age-inappropriate attention span, hyperactivity, and impulsive behavior.

Catatonia—Psychomotor disturbances that can include stupor, rigidity, muteness, purposeless, or bizarre movements; may occur with a severe ASD.

Childhood disintegrative disorder—A type of ASD in which children develop normally until about age three or four and then, over a period of a few months, lose their previously learned motor, language, social, and other skills.

Down syndrome—A genetic disorder characterized by development delay, intellectual deficits, distinctive facial characteristics, and sometimes ASD.

Epilepsy—Recurrent seizures that temporarily affect awareness, movements, sensations or consciousness; sometimes associated with ASD.

Fragile X syndrome—A genetic disorder usually affecting males, caused by a defective gene on the X chromosome, and associated with mental retardation and often ASD.

Neurotransmitter—Any of a variety of molecules that facilitate nerve impulses throughout the nervous system with the purpose of influencing and balancing thought, movement, and other body functions.

Off-label—The decision to prescribe a drug for purposes other than those specifically approved by the U.S. Food and Drug Administration.

Pervasive developmental disorder not otherwise specified (PDD-NOS)—A term previously used to describe individuals who met some but not all of the criteria for classic autism or Asperger syndrome; now classified as an ASD.

Phenylketonuria (PKU)—A genetic disorder of amino acid (phenylalanine) metabolism that, if left untreated, causes mental retardation and possibly ASD.

Rett syndrome—An inherited progressive neurodevelopmental disorder that affects females, usually beginning in infancy, and characterized by slow brain growth, cognitive and motor deterioration, and possibly ASD.

Savants—People with ASD who have unusual abilities in areas such as art, math, or music.

Tuberous sclerosis—A genetic disorder of the skin and nervous system involving the formation of small tumors in various organs and sometimes causing ASD.

possible disruption in early prenatal brain development. Increased head size or rapid head growth can be an early sign of ASD. Brain-imaging studies have suggested that abnormal brain development during the first few months of infancy may play a role. This suggests that defects in growth factors may be involved. It has been conclusively demonstrated that ASD is not caused by either parental behaviors or childhood vaccines.

Signs and symptoms

Just as the causes of ASD appear to be unique to each individual, so are the signs and symptoms. Although differences in brain growth may be evident by six months-of-age, and ASD symptoms are always present by at least 12–18 months-of-age, signs are frequently not recognized until children fail to begin speaking. Furthermore, some children with ASD appear to develop

normally and then regress, usually between the ages of one and two years—they stop using language or previously acquired social or play skills.

Impaired social interaction is a hallmark of ASD. Infants may not respond to being held or may focus intently on one item to the exclusion of everything else. Children with ASD may:

- fail to respond to their name
- avoid eye contact
- be unresponsive to social cues such as facial expressions or tone of voice
- fail to attach to parents or caregivers
- demonstrate a lack of empathy
- have little or no interest in human contact or making friends

- display inappropriate laughing or giggling
- fail to engage in imaginative or pretend play
- avoid group play
- engage in repetitive movements
- engage in self-abuse such as biting or head banging

Communication signs of ASD may include:

- language delay or absence, such as no babbling or pointing by 12 months and no single words by 16 months or two-word phrases by two years
- impaired speech
- meaningless repetition of words or phrases
- use of gestures instead of words
- concrete or literal interpretations of words or phrases
- inability to initiate or conduct conversations
- referring to oneself by name rather than a personal pronoun
- speaking in a sing-song voice

Other signs of ASD can include:

- rigid or flaccid muscles when being held
- repetitive motions such as hand flapping
- temper tantrums or screaming fits
- resistance to change
- hyperactivity
- fixations or obsessive interest in an activity, idea, or person
- overreaction to sensory stimuli such as noise, lights, or textures

Diagnosis

Early diagnosis of ASD and early intervention greatly improve outcomes. However, children with ASD often go undiagnosed until after age three, when they are examined because of speech delays and may undergo assessment for hearing impairment. It can be particularly difficult to recognize ASD in children who are only mildly affected or who have other serious conditions that mask ASD symptoms. Initial screening is often based on parental questionnaires or a combination of parent and physician observations. Children showing signs of ASD should undergo comprehensive evaluations that include neurologic assessment and cognitive and language testing by a team of specialists, usually over a period of time. The team may include a psychologist, neurologist, psychiatrist, speech therapist, and other specialists. Other diagnostic work may include chromosome analysis and DNA testing for specific genetic disorders, brain-imaging scans for any structural anomalies, and electroencephalography (EEG) for brain electrical activity and evidence of epilepsy.

The *DSM-5* standardized criteria for ASD diagnosis include:

- persistent deficits or impairments in social communication and interaction, including “social-emotional reciprocity” such as initiating and responding to interactions, conversations, and sharing of interests or emotions; nonverbal communicative behaviors; and developing, maintaining, and understanding relationships
- “restricted, repetitive patterns of behavior,” including stereotyped or repetitive movements, object use, or speech; inflexible insistence on routines, sameness, or ritualized patterns of behavior; abnormal highly restrictive or fixated interests; and over- or under-reactions to sensory input
- symptoms that are present during early development, even if these are not obvious until later on or are masked by learned strategies
- symptoms that cause significant social or occupational impairment or other serious impairment of functioning
- symptoms that are not better explained by intellectual disability or global development delay, although these may co-exist with ASD

Individuals who were previously diagnosed under *DSM-4* criteria with autistic disorder, Asperger syndrome, or PDD-NOS are now diagnosed with ASD. Patients with deficits only in social (pragmatic) communication disorder. Under *DSM-5*, ASD is further specified as:

- with or without intellectual impairment
- with or without language impairment
- with or without an associated medical or genetic condition or known environmental factor
- with or without an associated neurodevelopmental, mental, or behavioral disorder
- with or without associated catatonia

Treatment and management

Language and behavioral therapies form the cornerstones of ASD treatment and management, although interventions depend on the individual’s specific problems and their severity and any unique abilities. Intensive interventions beginning as early as possible have the best outcomes. Healthcare professionals, therapists, educators, and families must work as a team for the effective treatment and management of ASD.

Interventions include:

- highly structured, specialized education programs tailored to individual needs
- speech, language, and communication therapy

QUESTIONS TO ASK YOUR DOCTOR

- How is ASD diagnosed?
- How severe is my child's ASD?
- Are there genetic tests for ASD?
- What treatments and interventions do you recommend for my child?
- What is my child's prognosis?

- occupational therapy and skills training for developing fine motor skills and basic self-help and functional skills such as grooming
- intensive, highly structured skills training, such as applied behavior analysis for social and language skills
- behavior modification using positive reinforcement
- various other behavioral therapies
- auditory and other sensory integration training
- vision therapy
- physical therapy
- music therapy
- dietary interventions, which can be helpful for some children
- family counseling for parents and siblings

Drugs

As of 2015, the only drugs specifically approved by the U.S. Food and Drug Administration (FDA) for treatment of ASD in children aged 5 to 16 are the antipsychotics risperidone and aripiprazole for reducing symptoms such as temper tantrums, aggression, or self-harm. However, many medications are prescribed off-label (not specifically approved by the FDA for ASD or for children of a certain age) for reducing problems at home and school:

- antipsychotics for reducing repetitive behaviors, hyperactivity, and attention problems, as well as aggression and other serious behaviors
- antidepressants, such as fluoxetine or sertraline, for depression, anxiety, reducing repetitive behaviors, and possibly controlling aggression, although it is unclear whether these drugs are effective
- stimulants such as methylphenidate (Ritalin) for hyperactivity, although children with ASD are less likely to respond to methylphenidate than those with attention deficit/hyperactivity disorder (ADHD) and also have more side effects from the drug
- anticonvulsants for seizures

- other medications for anxiety, depression, ADHD, or obsessive-compulsive disorder

Clinical trials

As of 2015, there were more than 200 open clinical trials for ASD. Current listings are available at <https://clinicaltrials.gov/search/open/condition=%22Autistic+Disorder%22> Examples of clinical trials include:

- computer-based training for appropriately creating and responding to facial expressions
- social interventions for classroom use
- parental interventions for reducing and preventing ASD-related disability in high-risk children
- a new medication for improving functioning in children with fragile X syndrome

Prognosis

Although there is no cure for ASD, behaviors can and do moderate over time. ASD symptoms in many children improve with age and treatment, although some children with ASD develop depression or behavioral problems during adolescence. Prognosis ultimately depends on the individual's intellectual and communicative abilities and the severity of behavioral problems. Children whose language skills regress before the age of three appear to be at higher risk for epilepsy or other seizure-like brain activity. Nevertheless, interventions have improved considerably in recent years and—especially with early, intensive intervention—many children with ASD can become independent, highly functioning adults. Nevertheless, many adults with ASD require lifelong services and supports.

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ORGANIZATIONS

Association for Science in Autism Treatment, PO Box 1447, Hoboken, NJ 07030, info@asatonline.org, <http://www.asatonline.org>

Autism Society, 4340 East-West Hwy., Suite 350, Bethesda, MD 20814, (301) 657-0881, (800) 3AUTISM (328-8476), info@autism-society.org, <http://www.autism-society.org>

Autism Speaks, 1 E. 33rd St., 4th Floor, New York, NY 10016, (212) 252-8584, (888) 288-4762, (212) 252-8676, familyservices@autismspeaks.org, <https://www.autismspeaks.org>

Eunice Kennedy Shriver National Institute of Child Health and Human Development, NICHD Information Resource Center, PO Box 3006, Rockville, MD 20847, (866) 760-5947, (800) 370-2943, NICHDInformationResourceCenter@mail.nih.gov, <http://www.nichd.nih.gov>

Kathleen A. Fergus, MS, CGC
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Autologous germline mitochondrial transfer

Definition

Autologous germline mitochondrial transfer (AUGMENT) is an experimental procedure used to enhance fertility. It involves transferring mitochondria from a woman's own egg cells into eggs used for in vitro fertilization (IVF). Mitochondria are structures found in the cells that produce most of the energy needed to power the cells. This procedure can make it easier for women with infertility problems to have children, especially older women who have fewer mitochondria in their eggs.

Description

What is AUGMENT?

As women age, the DNA (genetic material) in their mitochondria (mtDNA) has acquired more mutations,

KEY TERMS

Cells—Building blocks that provide structure to the body and perform all of the functions of the body. Cells contain genetic information and can copy themselves. There are many different types of cells in the body.

In vitro fertilization (IVF)—A procedure that involves creating embryos in the lab by mixing eggs and sperm and transferring the embryos to the uterus.

Mitochondria—Structures found in the cell (organelles) surrounded by two layers of membrane. Mitochondria turn energy from food into energy that powers the cell. They also help the cell produce heat and store calcium, and they help choose which damaged cells need to be destroyed.

Mitochondrial DNA (mtDNA)—The DNA (genetic material) found in the mitochondria. MtDNA contains the instructions for about 37 genes. These genes produce proteins that help the mitochondria function. MtDNA is only passed from the mother to her offspring.

Mitochondrial Mutation—Variation in the mitochondrial DNA that can affect how well the mitochondria functions.

Stem cells—Cells that can transform into any different type of cell and can make copies of themselves indefinitely.

Oogonial stem cells—Cells that develop into mature eggs.

which can interfere with the normal functioning of the mitochondria and reduce the number of them in a cell. Mutations in the mtDNA of an egg can interfere with fertilization. Normally, mitochondria in the egg increase from 6,000 in the immature egg to 300,000 to 400,000 or more in the mature egg. The number of mitochondria increases because of the increased need for energy during fertilization and embryo development.

Older women who are experiencing infertility typically have a decreased number of mitochondria in their eggs, and the fewer mitochondria present do not function as well. The result can be problems with embryo development and infertility. The idea behind AUGMENT is that increasing the number of mitochondria in an egg could improve fertilization and embryo development.

QUESTIONS TO ASK YOUR DOCTOR

- Could AUGMENT help me overcome my fertility problems.?
- What are the limitations of the treatment?
- Is this treatment available in your clinic?

How AUGMENT is Done

The AUGMENT procedure uses oogonial stem cells from the ovaries. Oogonial stem cells are egg precursor cells that can develop into eggs. These stem cells possess the same mitochondria as egg cells. The advantages of these stem cells are that their mtDNA has fewer mutations, and the mitochondria appear to function better than in regular eggs, likely because the stem cells are dormant cells and have a lower rate of age-related DNA damage.

During AUGMENT, a piece of the ovary is removed and grown in a test tube that contains ovarian tissue. The stem cells are then identified and isolated, and mitochondria are removed from these cells. The isolated mitochondria and sperm are injected into an egg. Like in conventional IVF, embryos that develop from this procedure are implanted in the uterus. Two limitations of AUGMENT are that it can be a challenge to find ovarian tissue to grow the stem cells, and it is difficult to evaluate the quality of eggs produced.

Mitochondrial Replacement Using Donors

Mitochondrial replacement therapy can also be done using mitochondria from other women (donors). This procedure is sometimes called ‘three-person IVF.’ In addition to improving fertility, mitochondrial replacement therapy from donors with normal mtDNA can help prevent disease. In this case, mitochondria from donors with normal mtDNA can be used for women who have mutations in their mtDNA that could cause disease in their offspring. Mitochondrial replacement therapy could prevent mitochondrial abnormalities in children. Using donors for mitochondrial transfer is banned in the U.S., because it is considered a modification that could affect future generations and have unintended consequences. AUGMENT, which is legal in the U.S., solves the potential problem of having “foreign” mitochondria present in the resulting embryos. It can also decrease the expense and difficulty of finding donor mitochondria. However, it cannot be used to prevent mitochondrial disorders in children.

AUGMENT Clinical Trials

At least three fertility centers have had successful clinical trials using AUGMENT on women who have previously had poor outcomes using IVF. Ninety-three patients recruited from The Toronto Centre for Assisted Reproductive Technologies (TCART) (Toronto, Canada) and FAKIH IVF (Dubai, United Arab Emirates) were treated with AUGMENT through the OvaScience Global Registry program. At TCART, the pregnancy rates before treatment with AUGMENT were around 1.3% and after treatment they were 35%. At FAKIH IVF, the pregnancy rates before treatment with AUGMENT were around 2% and after treatment they were around 22%. Eleven other patients from GenArt Women’s Health and Reproductive Biotechnology Centre in Turkey were also treated with AUGMENT with a pregnancy rate that increased to around 40%.

Measuring Mitochondrial DNA for Embryo Selection

Interestingly, although poorer-quality eggs tend to have lower amounts of mtDNA, poorer-quality early embryos tend to have higher amounts of mtDNA. Some researchers have found that embryos will not implant in the uterus if their levels of mtDNA are too high. However, not all research supports this claim, and further research is necessary before it is used by fertility centers to help select embryos.

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Resolve, The National Infertility Association, 7918 Jones Branch Drive, Suite 300, McLean, VA 22102, (703) 556-7172, (703) 506-3266, info@resolve.org, <https://resolve.org/>

Reproductive Facts.org From American Society for Reproductive Medicine, 726 7th Street, SE, Washington, D.C. 20003, (202) 863-4985, (205) 978-5005, asrm@asrm.org, <https://www.reproductivefacts.org/>

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Autosomal dominant multiple pterygium syndrome

Definition

Autosomal dominant multiple pterygium syndrome refers to a rare genetic disorder that belongs to a group of congenital musculoskeletal disorders characterized by abnormal webs of skin or soft tissue called pterygia on the neck and other body locations, in addition to other abnormalities. This group of disorders is called multiple pterygium syndrome, or MPS, and is marked by genetic heterogeneity. Most known forms of MPS are inherited in an autosomal recessive pattern; autosomal dominant MPS is distinguished by the gene associated with it as well as by its autosomal dominant pattern of inheritance.

Description

MPS in general is a syndrome in which infants are born with webs of skin called pterygia around the base of the neck, between the fingers, inside the elbows, and behind the knees. These webs may become large enough to restrict the movement of the fingers and limbs. In addition to pterygia, children with MPS also have arthrogryposis (joint contractures in two or more regions of the body), camptodactyly (permanent bending of the middle joint of one or more fingers), short stature, a small rib cage, abnormal curvature of the spine (scoliosis), humpback (kyphosis), fusion of some of the vertebrae in the spine, and unusual or malformed facial features.

The contractures and pterygia in MPS are thought to be the result of fetal akinesia, a condition in which the fetus's movements in the mother's uterus slow down as the result of structural abnormalities of the uterus, genetic mutations in the fetus, or an inadequate amount of amniotic fluid. The musculoskeletal abnormalities found in MPS are nonprogressive, which means that they do not become worse over time.

Genetic profile

The two most common forms of MPS have an autosomal recessive inheritance pattern, which means that both parents must have a genetic mutation in order for the offspring to develop MPS. One form is called MPS, lethal type because the affected fetus dies before or shortly after birth. Lethal-type MPS is caused by mutations in any of three genes, all on the long arm of chromosome 2: the *CHRNA1* gene at 2q31.1, the *CHRNA2* gene at 2q37.1, and the *CHRNA3* gene, also at 2q37.1.

The nonlethal type of autosomal recessive MPS is also known as Escobar syndrome. It is also caused by mutations in the *CHRNA3* gene. Children with Escobar syndrome have the pterygia, arthrogryposis, fusion of spinal vertebrae, short stature, and facial deformities associated with MPS. Their knee joints may lack kneecaps. Boys may have an unusually small penis and undescended testicles (cryptorchidism), and females may lack the labia majora (external genital folds). The facial deformities of Escobar syndrome include epicanthal folds around the eyes, drooping eyelids (ptosis), an abnormally small jaw (micrognathia), low-set ears, abnormally widely set eyes (hypertelorism), cleft palate, an unusually small mouth, an abnormally long philtrum, and a flat, expressionless face. This form of MPS is named for the clinician who first reported it in 1978.

There have been occasional reports of autosomal dominant forms of MPS in the medical literature from 1980 onward. In 1988, a pair of British researchers reported on a family with four members affected by an autosomal dominant form of MPS, although they did not identify a specific gene associated with the syndrome. In 1996 a group of researchers in Utah suggested renaming this autosomal dominant form of MPS distal arthrogryposis type 8 or DA8. They also did not link the syndrome to a specific gene.

In May 2015, an international team of researchers reported that they had traced autosomal dominant MPS to a mutation in the *MYH3* gene on the short arm of chromosome 17 at 17p13.1. This gene codes for a muscle protein called embryonic skeletal muscle myosin heavy chain 3. Myosin plays a role in cell movement, as well as the composition of muscle fibers. The form of myosin encoded by the *MYH3* gene is active during fetal development and is critical to normal muscle development in the fetus.

Mutations in the *MYH3* gene are associated with two other congenital arthrogryposis syndromes, Freeman-Sheldon syndrome and Sheldon-Hall syndrome. Both of these syndromes are associated with multiple congenital contractures. A major difference between the mutations

KEY TERMS

Arthrogryposis—A congenital musculoskeletal condition in which the infant has contractures of the joints in two or more areas of the body.

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a nonsex chromosome is required for a disease or inherited trait to develop in an individual.

Camptodactyly—Abnormal bending of the middle joint of the finger. It is most often found in the little finger but may affect any finger.

Congenital—Refers to a disorder that is present at birth.

Contracture—An abnormal and usually permanent shortening and contraction of a muscle or tendon that causes a deformity or subnormal range of movement.

Epicanthal fold—A wrinkle in the skin extending from the nose up to the eyebrow; it is sometimes associated with genetic anomalies.

Fetal akinesia—A condition in which lack of fetal movement (akinesia) during pregnancy results in musculoskeletal abnormalities, underdevelopment of the lungs, and/or misshapen facial features. Fetal akinesia can result from a variety of conditions, ranging from abnormalities in the structure of the mother's uterus to infections or genetic disorders that affect fetal development.

Genetic heterogeneity—The production of apparently identical genetic disorders by different genetic mechanisms or by different genes at different positions on the chromosomes.

Kyphosis—Abnormal outward curvature of the spine resulting in a hunchback.

Micrognathia—The medical term for an undersized or underdeveloped jaw.

Philtrum—The center part of the face between the nose and lips that is usually depressed.

Ptosis—Drooping of the upper eyelid.

Scoliosis—Abnormal curvature of the spine, usually defined as greater than ten degrees to the right or left as the doctor faces the patient.

in the *MYH3* gene that underlie these two disorders and those associated with the autosomal dominant form of MPS, however, is that the mutations occur in different portions of the gene. All myosin genes have three

domains known as the head, neck, and tail; each domain has different functions. The tail domain, which is the most important for the present discussion, determines the role of a particular myosin. The mutations linked to the Freeman-Sheldon and Sheldon-Hall syndromes are found in the head and neck of the *MYH3* gene, whereas the mutations linked to MPS were found in the tail. This finding means that the autosomal dominant form of MPS results from a different developmental mechanism than the congenital arthrogryposis syndromes. The researchers also suggest that the location of the *MYH3* mutation in the tail of the gene indicates that embryonic myosin is important in fetal skeletal as well as muscle development.

Demographics

All forms of MPS are very rare; fewer than 70 cases have been reported in the medical literature since the 1970s. Many cases of autosomal recessive MPS were found in consanguineous families, meaning that the parents of the affected children were closely related by blood as well as marriage.

The demographics of the autosomal dominant form of MPS are difficult to establish at present because the disorder was reported only in 2015, and the findings are based on only four families. More case studies will be required to obtain a clearer understanding of the demographics of the disorder.

Signs and symptoms

According to the authors of the 2015 article, the major signs and symptoms of autosomal dominant multiple pterygium syndrome are musculoskeletal: the characteristic pterygia, camptodactyly of the hands, scoliosis, and fusion of some of the spinal vertebrae. Facial deformities or abnormalities were not mentioned.

Diagnosis

Diagnosis of MPS and the congenital arthrogryposis syndromes can be made before birth by fetal ultrasound. The ultrasound images will reveal such features as scoliosis of the spine, clenched fingers, bent legs, and other evidence of contractures. Ultrasound imaging can also detect fetal akinesia.

Molecular genetic testing is available for the genes associated with the lethal form of MPS and with Escobar syndrome. Genetic testing is also available for mutations in the *MYH3* gene at a number of different laboratories in the United States and Europe.

QUESTIONS TO ASK YOUR DOCTOR

- Have you ever seen or treated a patient with any form of MPS?
- Do you think more cases of the autosomal dominant form of MPS will be identified?
- What treatments would you recommend for a child with MPS?
- Would you recommend genetic testing for other family members when a child is diagnosed with MPS?

Treatment and management

Treatment of the contractures, skeletal abnormalities, and pterygia associated with MPS usually involves a team of specialists, including a pediatrician, orthopedic surgeon, and plastic surgeon. Correction of the spinal abnormalities should be undertaken before five years of age to prevent permanent scoliosis. Children with unusually small rib cages should be monitored carefully for pneumonia and other respiratory disorders, as they are at increased risk of these infections.

Correction or removal of pterygia is usually performed by a plastic surgeon. Great care must be taken when removing the excess soft tissue to ensure that any blood vessels or nerves in the webbing are not damaged. Plastic surgery may also be performed to repair cleft palate or other facial deformities associated with the Escobar type of autosomal recessive MPS.

As children with MPS grow older, they should receive appropriate physical therapy for their musculoskeletal problems. They may also need counseling to help them cope with social difficulties resulting from their physical limitations or facial features. Intellectual disability, however, is not usually associated with MPS, and children with either the autosomal recessive or autosomal dominant form should be able to complete their schooling.

Prognosis

The Escobar type of MPS and the autosomal dominant form of the disorder are not life-threatening. Most patients are thought to have normal life expectancy. Follow-up studies of the known cases of the autosomal dominant form of MPS will be needed, however, to provide a more specific prognosis.

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ORGANIZATIONS

- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), Information Clearinghouse, 1 AMS Circle, Bethesda, MD 20892-3675, (301) 495-4484 or (877) 226-4267, (301) 718-6366, NIAMSinfo@mail.nih.gov, <http://www.niams.nih.gov>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>
- Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS), 6701 Democracy Blvd., Suite 1001, MSC 4874, Bethesda, MD 20892, (301) 402-4336, (301) 480-9655, ordr@nih.gov, <https://rarediseases.info.nih.gov>

Rebecca J. Frey, PhD

AUTS2 syndrome

Definition

AUTS2 syndrome is a genetic disorder presently classified as an autism spectrum disorder or ASD. Children diagnosed with these disorders are characterized by abnormal behaviors and difficulties interacting socially

with others, problems with spoken as well as nonverbal communication, and stereotypy (repetitive gestures, behaviors, or utterances). In fact, one alternate name for AUTS2 syndrome is autism spectrum disorder with AUTS2 deficiency. The *AUTS2* gene was identified as the cause of the syndrome in 2013. Another alternate name for AUTS2 syndrome is mental retardation, autosomal dominant 26.

Description

Patients diagnosed with AUTS2 syndrome have many of the same characteristics as patients with other ASDs; however, they have more severe developmental delays, intellectual disability and other learning disabilities, feeding difficulties, and deformities of the face and skeleton less often found in other ASDs. These additional characteristics help to explain not only why one of the alternate names for the disorder is mental retardation, autosomal dominant 26, but also why an alternate name for the *AUTS2* gene itself is *MRD26*.

In addition to AUTS2 syndrome, mutations in the *AUTS2* gene have been associated with such other neurological disorders as dyslexia, epilepsy, visual impairments, bipolar disorder, and alcohol addiction. As of 2015, however, the mechanisms and genetic pathways of the gene were not well understood. It is possible that further research will clarify not only the role of the *AUTS2* gene in human neurological development, but also the relationship of AUTS2 syndrome to other ASDs and other single-gene disorders.

Genetic profile

The *AUTS2* gene was first identified in 2002 when researchers were examining a pair of identical twins diagnosed with ASD. The gene had been disrupted by a balanced translocation, which is a chromosomal abnormality caused by an exchange of material between two nonhomologous chromosomes. In a balanced translocation, the genetic material is evenly exchanged between the two chromosomes, with no extra or missing genetic material. The *AUTS2* gene was mapped to the long arm of chromosome 7 at 7q11.22. The gene is sometimes referred to as the *KIAA0442* or *MRD26* gene, but *AUTS2* has become the most common identifier. It stands for “autism susceptibility candidate 2.” The gene codes for a protein that is strongly expressed in the human central nervous system, which would account for its association with neurodevelopmental disorders; however, there is much that is still unknown about the function of the *AUTS2* gene.

The gene is inherited in an autosomal dominant pattern, which means that only one copy of the

KEY TERMS

Autism spectrum disorder (ASD)—A general term for a group of neurodevelopmental disorders characterized by difficulties in social interactions, significant abnormalities in speech patterns, and limited but repetitive interests and activities. AUTS2 syndrome is classified as an autism spectrum disorder.

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a nonsex chromosome is required for a disease or inherited trait to develop in an individual.

Autosome—One of the 22 chromosomes that are not involved in determining gender (chromosomes 1 through 22 and not the X or Y chromosome).

Dysmorphic—Referring to a malformed or misshapen body part.

Hypotonia—Low or poor muscle tone, resulting in floppy limbs.

Kyphosis—Abnormal outward curvature of the spine resulting in a hunchback.

Microcephaly—Abnormal smallness of the head; it often is associated with intellectual disability.

Nonhomologous—Referring to chromosomes that are not members of the same pair.

Ptosis—Drooping of the upper eyelid.

Scoliosis—Abnormal curvature of the spine, usually defined as greater than 10 degrees to the right or left as the doctor faces the patient.

Stereotypy—A repetitive movement, gesture, or utterance; examples include head banging, rocking, or repeatedly crossing and uncrossing the legs. Stereotypy is found in persons with intellectual disabilities and some forms of schizophrenia, as well as autism spectrum disorders.

Translocation—A chromosomal abnormality that occurs when two nonhomologous chromosomes exchange genetic material. A translocation is said to be balanced if the genetic material is evenly exchanged, with no missing or extra genes. In an unbalanced translocation, the genetic material is not evenly exchanged, and there may be extra or missing genes.

mutation is required for the disorder to appear. As of 2015, it was thought that AUTS2 syndrome is a single-gene disorder, which distinguishes it from other ASDs.

Demographics

The prevalence of AUTS2 syndrome is unknown, largely because the disorder was first described in the medical literature only in 2013. The first report consisted of a case series of 17 patients, all Europeans. Later reports were of single patients identified in China and the United States, respectively, and two additional patients in Belgium and the Netherlands. The frequency of the disorder is estimated to be less than one person per million.

AUTS2 syndrome has been diagnosed in patients of various ages, ranging from 11 months to 32 years of age at the time they were examined. It is not yet known, however, whether the syndrome is more common in some racial or ethnic groups than in others.

Signs and symptoms

The major characteristics of AUTS2 syndrome, which vary somewhat in severity from patient to patient, are as follows:

- autistic behaviors, including difficulties in social interactions and delayed speech
- significant intellectual and learning disabilities
- low birth weight and feeding difficulties
- microcephaly (unusually small head) and unusually short stature
- dysmorphic facial features: unusually widely spaced eyes (hypertelorism), drooping eyelids (ptosis), a prominent tip on the nose, and a narrow mouth
- cerebral palsy
- skeletal abnormalities: scoliosis and kyphosis

Some patients diagnosed with AUTS2 syndrome have the following additional symptoms:

- attention deficit hyperactivity disorder
- hypotonia (poor muscle tone)
- structural abnormalities in the brain

Diagnosis

ASDs in general are diagnosed in late infancy or early childhood on the basis of such symptoms as absence of recognition of parents and other familiar persons, abnormal reactions to sounds or objects in the environment, stereotyped behaviors, delayed speech or abnormal use of language, and resistance to change. There are several checklists that can be administered to the child's parents or used by the pediatrician to screen young children for signs of an ASD. The Centers for Disease Control and Prevention (CDC) recommends that screening should be done twice, when the child is

QUESTIONS TO ASK YOUR DOCTOR

- Have you ever seen or treated a patient with any form of MPS?
- Do you think more cases of the autosomal dominant form of MPS will be identified?
- What treatments would you recommend for a child with MPS?
- Would you recommend genetic testing for other family members when a child is diagnosed with MPS?

18 months old and again at 24 months of age. There are two reasons for early screening: to begin treatment as early as possible if the child has a high score on the checklist and to evaluate other children in the family for possible ASDs, since the disorders are known to be at least partly heritable.

Children who are thought to show signs of an ASD on the basis of the checklist are then given a follow-up comprehensive evaluation by a team of several different specialists (typically a neurologist, a psychiatrist, a speech therapist, and a child psychologist). As of 2015, there was no evidence that MRIs or other neuroimaging studies are useful in diagnosing ASDs, although electroencephalography is sometimes used to rule out seizure disorder. In addition, the child's hearing is usually tested to make sure that delayed speech is not the result of a hearing impairment.

In the specific case of AUTS2 syndrome, the diagnosis can be confirmed by genetic testing, as the syndrome is presently considered a single-gene disorder.

Treatment and management

There is no cure for AUTS2 syndrome or for any other ASD. Treatment is highly individualized and tailored to the patient's specific symptoms and their severity. Patients with AUTS2 syndrome are presently treated with a combination of special education, speech therapy, and antiseizure medications for those with epilepsy. It is possible that follow-up studies of the patients who have been identified since 2013 will lead to more detailed treatment recommendations.

Prognosis

The prognosis for patients with AUTS2 syndrome depends on the severity of their intellectual disability. Those less severely affected may be able to complete

some schooling and live by themselves, but most will require home or residential care throughout their lives. At present, AUTS2 syndrome is not thought to affect patients' life expectancy; however, since the *AUTS2* gene has been linked to acute lymphoblastic leukemia and certain other cancers as well as AUTS2 syndrome, it is possible that patients diagnosed with the syndrome are at increased risk of cancer. More research is required to investigate this question.

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American Academy of Child and Adolescent Psychiatry (AACAP), 3615 Wisconsin Ave. NW, Washington, DC 20016-3007, (202) 966-7300, (202) 966-2891, <http://www.aacap.org>

Association for Science in Autism Treatment, PO Box 1447, Hoboken, NJ 07030, info@asatonline.org, <https://asatonline.org>

Autism Society, 4340 East-West Hwy., Suite 350, Bethesda, MD 20814, (301) 657-0881 or (800) 328-8476, info@autism-society.org, <http://www.autism-society.org>

Autism Speaks, 1 E. 33rd St., Fourth Floor, New York, NY 10016, (212) 252-8584 or (888) 288-4762, (212) 252-8676, familyservices@autismspeaks.org, <https://www.autismspeaks.org>

Rebecca J. Frey, PhD

B

Bardet-Biedl syndrome

Definition

Bardet-Biedl syndrome (BBS) is a condition that primarily affects vision, kidney function, limb development, growth, and intelligence.

Description

BBS is a genetic condition that most often involves visual loss, obesity, polydactyly, learning delays, problems with the genitourinary system, and kidney problems, although there may be other clinical features as well. BBS expresses itself differently from person to person, even among members of the same family.

Genetic profile

BBS is a genetically heterogeneous condition; this means that it has more than one known genetic cause. There are fourteen genes known to be associated with the condition and another four that are likely associated. The gene *BBS1* is located on chromosome 11 and is found in 23% of those that have a clinical diagnosis of BBS. *BBS10* is located on chromosome 12 and is found in 20%. The other genes are found in 8% or fewer cases. The 18 associated mutations are found in 70%–80% of people with BBS. Therefore, it is likely that additional genes that have not yet been identified account for the remaining cases. Research suggests that the *BBS1* gene may be associated with milder visual loss, and those with *BBS10* may have more difficulty with diabetes and obesity. Research suggests that various types of cilia are affected by the *BBS* genes and result in the clinical features. For example, defects in the movement of proteins important in the retina lead to cell death and cause retinitis pigmentosa. Regardless of the gene involved, BBS displays an autosomal recessive inheritance pattern. This means that the condition occurs when an individual inherits two mutated copies of a *BBS* gene. If one copy is normal, the individual does not have BBS. This individual is

called a carrier of BBS and can pass the gene on to the next generation.

Research indicates that people who inherit one abnormal *BBS* gene and one normal gene may be at risk for some of the health problems seen in BBS. Compared to the general population, these *BBS* gene carriers are more likely to develop high blood pressure, diabetes mellitus, and kidney disease, including kidney cancer. Some research indicates that about 5% of cases of BBS may be caused by the combination of three genes rather than just two, but little is known about this type of inheritance for BBS yet.

Demographics

BBS affects people around the world. However, it is most common in the Middle East, especially in the Arab and inbred Bedouin populations of Kuwait. In these groups, it may affect as many as 1 in 13,500 individuals. The incidence is almost as high in Newfoundland, where as many as 1 in 17,500 individuals has BBS. Outside of these areas, researchers estimate that BBS affects only 1 in 100,000 to 160,000 people.

The specific genetic cause of BBS differs by family and geographic location. For example, in the Middle East, BBS appears to be associated with *BBS1*, 3, and 4 located on chromosomes 11, 3, and 15 respectively. However, in patients of European descent, BBS appears to be associated with *BBS1* and 10 located on chromosomes 1 and 12.

Signs and symptoms

Due to the subtlety of outward clinical features in some cases, medical care providers may not immediately suspect BBS. It becomes a consideration in children with polydactyly, although this condition has many other causes. BBS is also suspected when additional abnormalities emerge as the child develops. In boys, genital abnormalities become evident soon after birth. In almost all patients, obesity and retinal degeneration begin in early

KEY TERMS

Brachydactyly—Abnormal shortness of the fingers and toes.

Cilium (plural, cilia)—A slender protuberance projecting from the body of a cell involved either in sensory functions or motility in the cell.

Electroretinogram (ERG)—A measurement of electrical activity of the retina.

Intravenous pyelogram—An x-ray assessment of kidney function.

Polydactyly—The presence of extra fingers or toes.

Retinitis pigmentosa—Degeneration of the retina marked by progressive narrowing of the field of vision.

Syndactyly—Webbing or fusion between the fingers or toes.

childhood. Learning disabilities, if present, are identified in school-aged children if not earlier. Failure to menstruate leads to diagnosis of some adolescent girls. Infertility brings some young adults to medical attention. Kidney disease is progressive and may not become obvious until adulthood.

Due to progressive degeneration of the rods and cones in the retina, vision damage occurs in all patients. Specific vision defects include poor night vision during childhood, severe myopia (nearsightedness), glaucoma, and cataracts. Ninety percent of patients suffer from retinitis pigmentosa, a condition in which the field of vision progressively narrows. This finding often leads to the diagnosis. Seventy-five percent of individuals with BBS will become legally blind. The average age of legal blindness is age 15–20 years.

Fifty-three to eighty-two percent of infants with BBS are born with a kidney defect affecting kidney structure, function, or both. The specific abnormality varies from patient to patient and may be aggravated by lifelong obesity. Obesity most often occurs in the truncal area and is found in 72%–92% of people with BBS. The complications of obesity, such as high blood pressure (hypertension) and insulin-resistant diabetes mellitus, contribute to kidney disease.

A majority of patients with BBS have extra fingers or toes (polydactyly). They may also have short fingers (brachydactyly) or broad, short feet. Some patients have a combination of all three of these features. Alternately, polydactyly may be limited to one limb, hands only, or feet only. Syndactyly, the fusion of two or more fingers or toes, may

also occur. In some BBS families, all affected members display at least some of these limb abnormalities.

Many individuals with BBS have genital abnormalities. Most boys with BBS have a very small penis, and some also have undescended testes. Men with BBS are usually unable to have children. In women with BBS, the genitalia, ovaries, fallopian tubes, and uterus may be underdeveloped. The vagina may not be completely formed. Though some women with BBS do not menstruate, others menstruate irregularly. Some women are able to have children. In both sexes, there may be birth defects in the urinary or gastrointestinal tract.

Research indicates that people with BBS have characteristic facial features, including a large head with a narrow forehead; short, narrow eye openings; large ears; flat nasal bridge; and a long, smooth area above the upper lip. Teeth are small and crowded. A high, arched palate is common. Still, facial features vary considerably.

Some individuals with BBS have liver disease and poor balance. About half have heart abnormalities.

In addition to the physical effects of the condition, intelligence is often affected. While some BBS patients show normal intelligence, others have mild to moderate learning disabilities. These patients are slower than most children to walk, speak, or reach other developmental milestones. Difficulty with language and comprehension may continue into adulthood. In a few people with BBS, more severe intellectual disability occurs. In some patients, vision handicaps and developmental delay appear to be related.

About a third of children with BBS have behavioral problems that continue into adulthood. These include lack of inhibition and social skills, emotional outbursts, and obsessive–compulsive behavior. Most people with BBS prefer fixed routines and are easily upset by a change in plans.

Diagnosis

Diagnosis of BBS is a challenge for medical professionals. Not only do the symptoms of BBS vary greatly from patient to patient, but some of these symptoms occur in other conditions, many of which are more common than BBS.

The diagnosis is based on clinical features. Genetic testing is available to identify causative mutations but does not rule out a diagnosis. Therefore, patients must have a thorough genetic evaluation. This provides a chance to rule out other disorders with similar symptoms. Some disorders confused with BBS include McKusick-Kaufman syndrome, Alstrom syndrome, Senior-Loken syndrome, Leber congenital amaurosis, and Biemond syndrome type II. McKusick-Kaufman syndrome is

caused by a mutation in the *MKKS* gene that can also be found in people with BBS. While people with this syndrome show some of the same symptoms as BBS patients, the specific *MKKS* mutation differs between the conditions. This explains how one gene can be responsible for two distinct yet similar disorders.

A clinical diagnosis is established when an individual either has four primary clinical features of BBS or three primary and two secondary features. The primary features are retinal degeneration, polydactyly, obesity, learning disabilities, kidney abnormalities, and genital defects (in males). The secondary features are speech delay, developmental delay, behavior problems, eye abnormalities other than retinal degeneration, brachydactyly, syndactyly, poor balance, mild hypertonia, diabetes mellitus, dental abnormalities, cardiovascular abnormalities, or liver problems. To aid in a diagnosis, the patient should receive three particular diagnostic tests. An eye exam called an electroretinogram is used to test the electric currents of the retina. An ultrasound is used to examine the kidneys, as is an intravenous pyelogram (IVP). An IVP is an x-ray assessment of kidney function.

Treatment and management

Treatment and management for those with BBS depends largely on which features of the condition are present. Obesity and kidney disease are major threats. If unchecked, obesity can lead to high blood pressure, diabetes mellitus, and heart disease. Untreated kidney disease can lead to renal failure, a frequent cause of early death in patients with BBS. Some patients require dialysis and kidney transplant. Therefore, it is very important to regularly monitor and manage patients with BBS and to promptly treat any complications. Affected individuals should eat a well-balanced low-calorie diet. They should also exercise regularly. Individuals with BBS should have cardiac, hearing, dental, and neurologic evaluations to detect and treat or manage any problems with these systems.

Because BBS carriers also appear prone to kidney disease, parents and siblings of patients with BBS should take extra precautions. These include baseline screening for kidney defects or cancer, as well as preventive health care on a regular basis.

In order to conserve vision to the extent possible, retinal degeneration should be carefully monitored. Therapy, education, and counselling help prepare the patient for progressive loss of vision. The Foundation Fighting Blindness, a support and referral group, offers help to BBS patients and their families.

Though not life-threatening, learning disabilities and reproductive dysfunction need attention in order to maximize the quality of life for patients with BBS. Affected

QUESTIONS TO ASK YOUR DOCTOR

- Can you tell me the cause of my child's Bardet-Biedl syndrome?
- What are the first treatments or other steps that should be taken to deal with this disorder?
- What long-term medical care will be required for the control of this condition?
- What kinds of symptoms should I watch for that might indicate changes in the progression of this disorder?

people benefit greatly from special or vocational education, speech therapy, social skills training, and community support services. Some adult patients may never be able to live independently and may remain with their families. In these cases, families should plan future living arrangements in case the patients outlive their caregivers.

Genital abnormalities may require hormonal treatment or surgical attention. Sometimes removal of undescended testes is necessary to prevent cancer. Patients with genital and reproductive dysfunction may need counseling to help them deal with the personal, familial, social, and cultural impacts of the condition. The Bardet Biedl Syndrome Foundation and Family Association (<http://www.bardetbiedl.org>) is a support organization for those with the condition and their families. Genetic counseling is available to help fertile BBS patients address their reproductive choices. Affected individuals have a low chance of having an affected child unless their partner also has BBS.

Prognosis

The outlook for people with BBS depends largely on the extent of the birth abnormalities, prompt diagnosis, and follow-up care. Unless they have severe birth defects involving the heart, kidneys, or liver, patients with BBS can have a normal lifespan. There is no treatment for the extensive retinal damage caused by BBS. However, good health care beginning in childhood can help many people with BBS avoid other serious effects of this disorder. Researchers are actively exploring genetic causes, treatment, and management of BBS.

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ORGANIZATIONS

Bardet Biedl Syndrome and Family Association, darla.mansker@bardetbiedl.org, <http://www.bardetbiedl.org>
Foundation Fighting Blindness, 6925 Oakland Mills Road, #701, Columbia, MD 21045, (800) 683-5555, <https://www.fightingblindness.org/>

Sonja E. Higgins

Base editing

Definition

Base editing is a technology that changes a specific DNA base into another. A DNA base is one unit in a DNA sequence. Base editing can be used to fix an error in a DNA sequence. A base editor is a protein that can make this change in the DNA. Prime editing is an updated version of base editing. Currently, base and prime editing are only used in research.

Description

Point mutations are errors in the DNA sequence where one DNA base is substituted for another or inserted or deleted. They are some of the most common causes of genetic disease in humans. A DNA base is one unit in a DNA sequence. The four DNA bases are adenine (A), guanine (G), thymine (T), and cytosine (C). The sequence of these DNA bases is the genetic code and contains the instructions for creating proteins. A three-base sequence in the DNA contains the instructions for making a particular amino acid. For example, CGC codes for the amino acid alanine. Proteins are made up of one or more amino acids strung together. The instructions for a particular protein are made up of a number of three-base sequences.

Because DNA is double-stranded, it has two complementary sequences where the bases pair up together. (C) always pairs with (G), and (A) always pairs with (T). One example of a double-stranded DNA sequence for alanine is GCG/CGC. Point mutations can sometimes cause the production of an abnormal protein or even the absence of a protein, which can result in a genetic disease. Around 31,000 point mutations are known to cause genetic diseases. The most common point mutation is the substitution of G–C for A–T.

Base editing can fix point mutations where one DNA base in the sequence is substituted by another. During base editing, the new base is changed back to the original one. Base editing tools are based on CRISPR–Cas technologies. CRISPR–Cas can be used to change an organism's DNA by making a cut in both strands of the DNA at a specific location and tricking the body's DNA repair mechanism to make the desired change. Base editing is a modified version of CRISPR–Cas, which enables the substitution of one DNA base pair for another without causing a double-strand DNA break. Base editing is better at correcting point mutations involving base pair substitutions than traditional CRISPR–Cas. Base editing techniques can fix point mutations almost 10 times more efficiently than traditional CRISPR–Cas technologies and with fewer errors.

There are two types of base editors: cytosine base editors and adenine base editors. Cytosine base editors change the C base in DNA to T, and T to C. Adenine editors change A to G, and G to A.

Base editing cannot fix transversion mutations (A or G) to (T or C) or vice versa. These types of point mutations are less common and usually do not cause a change in the protein or disease. Base editing is also unable to add a missing base pair or sequence of base pairs (deletion) or to remove an extra base pair or sequence of base pairs (insertion).

Prime editing

A new tool called prime editing can overcome some of the limitations of base editing. Prime editing, unlike base editing, can fix transversion mutations and small insertions and deletions. It also has a lower rate of unintentional mutations (0.86%) in other DNA locations than base editing (2.5%). Like base editing, prime editing only nicks one strand rather than cutting both strands.

Similar to CRISPR, both prime and base editing use a Cas enzyme-based editor and a piece of guide RNA, which guides the editor to a location on the DNA that will be changed. Both base and prime editors use the Cas enzyme called CAS9 nickase, which just cuts a strand of the DNA. CRISPR–Cas, on the other

KEY TERMS

Autosomal dominant condition—A disease or condition that results from a mutation in only one copy of a gene pair.

CRISPR–Cas —A tool that is used by researchers to examine and change DNA. CRISPR–Cas can be used to change an organism’s DNA by making a cut in the DNA at a specific location and tricking the body’s DNA repair mechanism to make the desired change. It is based on a tool found naturally in the immune system of bacteria.

Deletion—A mutation where a single base pair or sequence of base pairs is missing.

DNA base—One unit in a DNA sequence. The four DNA bases are adenine (A), guanine (G), thymine (T), and cytosine (C). The sequence of these bases is the genetic code, which contains the instructions for creating proteins.

DNA sequence—The sequence of DNA bases that contains the instructions for creating proteins.

Enzyme—A type of protein that speeds up chemical reactions in the body.

Insertion—A mutation where there is an extra single base pair or sequence of base pairs.

Point mutation (DNA)—An error in the DNA sequence where one DNA base is substituted for

another or inserted or deleted. This can sometimes cause the production of an abnormal protein or absence of a protein.

Proteins—Large complex biomolecules consisting of chains of amino acids that guide the development and functioning of the body. DNA contains the instructions for creating proteins.

Reverse transcriptase—An enzyme that makes DNA from an RNA template.

Ribonucleic acid (RNA)—The genetic material that is involved in creating proteins. During the creation of proteins, one of the strands of the double stranded DNA sequence is transcribed into single-stranded RNA, which is involved in creating proteins. In the RNA sequence, a base called uracil (U) replaces thymine (T) when it is found in the DNA sequence.

Tissue—A group of cells that have a common function.

Transversion mutation—A point mutation where an (A or G) base is changed to a (T or C) or vice versa.

Transition mutation—A point mutation where an (A) and (G) base are switched or a (C) and (T) base are switched.

hand, uses an enzyme like Cas9, which cuts both of the DNA strands.

DNA base editors include a Cas enzyme to bind to the DNA and a single-stranded DNA-modifying enzyme to make the change in the DNA base. The first cytosine base editor which changes the C base in DNA to T, and T to C, uses a naturally occurring enzyme called APOBEC1, which converts cytosine (C) to uracil (U). Uracil is the base found in RNA that is a complement to the thymine (T) base found in DNA. Adenine editors change A to G, and G to A, using a bacterial enzyme called Tada. Improved base editors are being developed by researchers around the world.

The editor used for prime editing is a fusion of the CAS9 nickase and reverse transcriptase. Reverse transcriptase is an enzyme that makes DNA from an RNA template. The guide RNA used in prime editing is called prime editing guide RNA (pegRNA). It is significantly larger than the standard guide RNA used in CRISPR–Cas. The pegRNA has a sequence of bases that will bind

to the target DNA (PBS) on one end and a template for the goal sequence of bases at its other end. The pegRNA combines with the prime editor to form a complex called the PE:pegRNA complex.

The editing process

Cytosine base editors convert GC to TA or vice versa. With cytosine base editors, the APOBEC1–Cas9 fusion editor is directed by the guide RNA to a target site on the DNA. Cas9 nickase cuts the G-containing strand. APOBEC1 converts cytosine (C) to uracil (U) in the target DNA. The cell has a system that repairs errors in the DNA sequence. This repair system changes uracil, which is not found in DNA, to thymine, which is found in DNA. This results in a GT mismatch, which the repair machinery fixes by converting the guanine to adenine. This ultimately results in an A–T pair.

Adenosine editors work in a similar way to cytosine editors. With adenine editors, Tada, which is fused to CAS9, turns adenosine into a base called inosine (I),

which is not found in the DNA from most species. Inosine is similar to guanine (G), which is normally found in DNA. The cell's DNA repair mechanism changes the inosine to guanine since guanine is the expected base. It then fixes the resulting mismatch of (T) paired to (G) by changing (T) to (C).

During prime editing:

1. The prime editor complex binds to the target DNA.
2. Cas9 cuts one strand of the double-stranded DNA, forming a flap, which exposes a section of the uncut DNA strand and a section of the cut DNA strand.
3. One side of the guide RNA binds to the DNA flap on the nicked DNA strand.
4. A new DNA sequence with the targeted change is transcribed from the RNA sequence on the guide using reverse transcriptase.
5. The newly created DNA sequence joins back with the other strand of DNA that has not been changed.
6. The original DNA sequence that was part of the nicked DNA is removed, leaving one strand with the changes joined to the other strand without the changes.
7. The sequence without the changes can be corrected to match the newly created sequence with the changes, using another guide RNA.

Uses for base and prime editing

Base and prime editing have been used in many different species, such as bacteria, yeast, rice, wheat, zebrafish, mice, rabbits, and monkeys. They have also been used to create animals with specific mutations in order to study genetic diseases and how to treat them. These techniques also have been used on very early human embryos in the lab. The hope is that one day they will be able to treat human diseases.

Base and prime editors have been used to create and fix models of human disease in animals (for example, muscular dystrophy; macular degeneration, an eye disorder that leads to blindness; and progeria, a rare genetic condition that leads to premature aging).

Base editing has also been used to correct mutations associated with cancer and Alzheimer's disease in both animal and human cells in the lab. Mutations that cause hereditary iron overload and sickle cell anemia have also been repaired using base editing. Prime editing has been used to fix sickle cell disease and Tay-Sachs, a childhood enzyme disorder, in human kidney cells.

Base and prime editing can also be used to improve crops to increase their yield or make them more disease resistant. For example, a single base change in the DNA

sequence could help rice plants use nitrogen more effectively and grow better.

Targeting autosomal dominant conditions

Autosomal dominant conditions are diseases that result from a mutation in only one copy of a gene pair. In order to treat some autosomal dominant conditions, the gene with the mutation must be silenced so it stops working. This can be done through base or prime editing. For example, retinitis pigmentosa (RP), an inherited autosomal dominant condition that causes blindness, could theoretically be cured in people who have RP because of a mutation in the P23H gene. By using one of these techniques, the sequence could be changed from CAC to CGC.

Future Uses

Currently, base and prime editing focus on editing DNA. Researchers are working on editors that can fix RNA sequences with mutations. They are also working on editors that might be able to fix mutations in the mitochondria. Mitochondria are energy-producing structures in cells, and they have their own DNA.

Challenges

One of the biggest challenges with base and prime editing is that, like CRISPR-Cas, they can make unintended changes in other parts of the DNA. It can also be challenging to deliver the editing complexes to the target tissue. Current base editors are too large to fit into the systems that are typically used to deliver editing tools to human cells. Researchers are working on making the editors smaller. Some researchers have solved the problem by splitting up the editor and delivering each piece separately.

Summary

CRISPR-Cas, base editing, and prime editing each work best in certain situations. CRISPR-Cas is best for adding or deleting large sequences of DNA. Base editing is best for fixing point mutations, since it has higher efficiency and causes fewer unintentional insertions and deletions. Prime editors are best when flexibility is needed; they offer the option to create insertions, deletions, point mutations, or a combination.

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Lisa L. Andres, MS, CGC

Beare-Stevenson cutis gyrata syndrome

Definition

Beare-Stevenson cutis gyrata syndrome is a serious, extremely rare genetic disorder affecting the skin, skull, genitals, navel, and anus. This condition often results in early death.

Description

Beare-Stevenson cutis gyrata syndrome is also known as Beare-Stevenson syndrome and cutis gyrata syndrome of Beare and Stevenson. This very rare inherited disease causes serious physical problems affecting many body parts. Cutis gyrata is characterized by an unusual ridging pattern in the skin

KEY TERMS

Acanthosis nigricans—A skin condition characterized by darkly pigmented areas of velvety wart-like growths. Acanthosis nigricans usually affects the skin of the armpits, neck, and groin.

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the early embryo. These cells are then tested for chromosome abnormalities or other genetic diseases.

de novo—A new mutation in a gene that is not inherited from either parent.

resembling corrugation in cardboard. This skin corrugation is present from birth and commonly occurs on the head and arms.

All people with Beare-Stevenson cutis gyrata syndrome have intellectual disabilities. The brain, skull, face, respiratory system, and genitals are often malformed. Death at an early age is common.

Genetic profile

Beare-Stevenson cutis gyrata syndrome is an autosomal dominant disorder, meaning that a person needs a change, or mutation, in only one of two copies of the gene involved to manifest the disorder. As of 2015, all reported cases of Beare-Stevenson syndrome have been due to *de novo* mutations (also called pathogenic variants). *De novo* mutations are changes or variations of the genetic code that occur only in the egg or sperm that become the affected individual; thus, they are genetic but not inherited. All cases of Beare-Stevenson to date have occurred in individuals with no family history of the

disease. This syndrome is associated with mutations (pathogenic variants) in *FGFR2*, a fibroblast growth factor receptor gene. The fibroblast growth factor receptor genes serve as blueprints for proteins important to the inhibition of cell growth during and after embryonic development. *FGFR2* is located on human chromosome 10 in an area designated as 10q26. There are several *FGFR* genes associated with genetic syndromes with craniosynostosis: *FGFR1*, *FGFR2*, and *FGFR3*.

Demographics

Beare-Stevenson syndrome is an extremely rare disorder. Both males and females are affected. The few cases documented in the medical literature (about 25 cases as of 2021) suggest that some cases of this disease might be associated with advanced paternal age. The affected children had older fathers.

Signs and symptoms

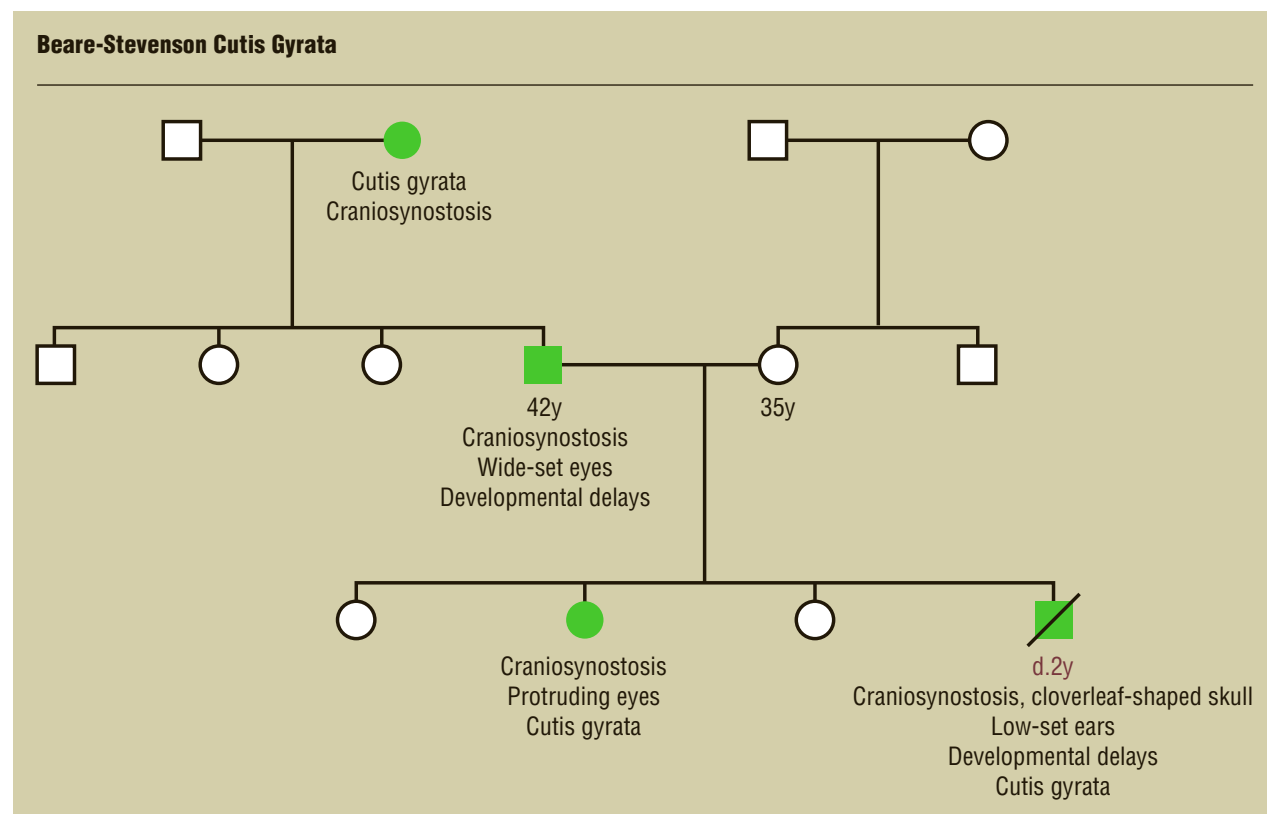
A cloverleaf-shaped skull is a very unusual birth abnormality that is common in infants with Beare-Stevenson cutis gyrata syndrome. Abnormalities in skull shape happen when some skull sutures (open seams

between the bony plates that form the skull) fuse before they typically would. Premature closure of the skull sutures is known as craniosynostosis. Growth of the brain pushes outward on skull plates that have not yet fused, causing characteristic bulges in those areas.

The face of someone with Beare-Stevenson cutis gyrata syndrome typically has prominent, bulging eyes that slant downward with droopy eyelids. The middle third of the face is underdeveloped and may appear somewhat flattened. The ears are positioned lower and rotated backward from where they would typically be. Skin ridges may be found in front of the ear. Infants with this condition may be born with teeth.

All people with Beare-Stevenson cutis gyrata syndrome have intellectual disabilities regardless of the degree of craniosynostosis. There may be excess fluid on the brain (hydrocephalus). Additionally, the nerve connection between the two halves of the brain (the corpus callosum) may be absent or underdeveloped.

The most recognizable physical symptom of this syndrome is the unusual ridging, or corrugation, of the skin. This cutis gyrata, usually evident at birth, affects the skin on the scalp, face, ears, lips, and limbs. Patches



Beare-Stevenson cutis gyrata syndrome: pedigree analysis chart (Gale)

QUESTIONS TO ASK YOUR DOCTOR

- What is the probability that a family that has one child with Beare-Stevenson cutis gyrata syndrome is likely to have a second child with the same condition?
- Do children with this condition usually survive infancy?
- What is the possible life expectancy?
- Are there prenatal tests for Beare-Stevenson cutis gyrata syndrome?
- Is there currently any research on this genetic disorder?
- How can I learn more about it?

of skin on the armpits, neck, and groin may also display acanthosis nigricans—unusually dark, thickened patches of skin with multiple delicate growths. Skin tags may be present on the surface of the skin and on the tissues lining the mouth. Affected children usually have a prominent navel and may have extra nipples.

People with this disorder may not be able to fully straighten their arms at the elbow. The skin of the palms of the hands and the soles of the feet often show deep ridging. Affected individuals may have small, underdeveloped fingernails.

Children with Beare-Stevenson cutis gyrata syndrome may have breathing problems and narrowing of the roof of the mouth (cleft palate). The anus may be positioned more forward than normal. The genitals are often malformed and surrounded by corrugated skin. An abnormal stomach valve may cause feeding problems.

Diagnosis

Diagnosis of Beare-Stevenson cutis gyrata syndrome is based on visible physical characteristics of the disease. As of 2015, the suspected diagnosis can be confirmed by DNA testing of the *FGFR2* gene. DNA testing for Beare-Stevenson syndrome starts with DNA sequencing of the coding regions of the *FGFR2* gene, which will detect differences (mutations) in the DNA base sequence of the gene. If no sequence mutations of the *FGFR2* gene are detected, other genetic testing methodologies may be used to detect deletions and duplications within the *FGFR2* gene. If a causative mutation (pathogenic variant) is identified by DNA testing, prenatal genetic testing can be performed in subsequent pregnancies. DNA testing may also

be done prenatally if the diagnosis of Beare-Stevenson cutis gyrata is suspected in an unborn fetus with the characteristic features, like a cloverleaf skull, visible on prenatal ultrasound.

Treatment and management

There is no cure for Beare-Stevenson cutis gyrata syndrome. Of the cases reported in the literature, many died early in life. So few people have been diagnosed with this disease that there is no published information regarding its treatment and management.

Prognosis

Early death is common in people with Beare-Stevenson cutis gyrata syndrome, especially among those with a cloverleaf skull.

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ORGANIZATIONS

Children's Craniofacial Association, 13410 Coit Road, Suite 517, Dallas, TX 75240, (214) 570-9099 or (800) 535-3643, contactcca@ccakids.com, <http://www.ccakids.com>
 FACES (The National Craniofacial Association), PO Box 11082, Chattanooga, TN 37401, (423) 266-1632 or (800) 332-2373, faces@faces-cranio.org, <http://www.faces-cranio.org>

Judy C. Hawkins, MS
 and Kathleen A. Fergus, MS, LCGC

Becker disease see **Myotonia congenita**

Becker muscular dystrophy see **Duchenne and Becker muscular dystrophy**

Beckwith-Wiedemann syndrome

Definition

Beckwith-Wiedemann syndrome (BWS) is a disorder of overgrowth. This condition is usually characterized by large body size (macrosomia), large tongue (macroglossia), enlarged internal organs (visceromegaly), the presence of an abdominal wall defect (umbilical hernia or omphalocele), and low blood sugar in the newborn period (neonatal hypoglycemia).

Description

Beckwith and Wiedemann initially described BWS in the 1960s. It is also known as Wiedemann-Beckwith syndrome and exomphalos macroglossia gigantism (EMG) syndrome.

BWS syndrome will frequently present prenatally with fetal macrosomia, enlarged placentas, and excessive amniotic fluid (polyhydramnios) that may lead to premature delivery (a baby being born more than three weeks before its due date). In the first half of pregnancy, the majority of amniotic fluid is made by the movement of sodium, chloride, and water, which cross the amniotic membrane and fetal skin to surround the fetus. During the second half of pregnancy, the majority of amniotic fluid is fetal urine that is produced by the fetal kidneys. Another major source of amniotic fluid is secretion from the fetal respiratory tract. This sterile fluid is not stagnant. It is swallowed and urinated by the fetus constantly and is completely turned over at least once a day. If the fetus has an enlarged tongue (macroglossia) and cannot swallow as usual, this can lead to buildup of excess amniotic fluid. Aside from swallowing difficulties in the newborn, macroglossia can also lead to difficulties with feeding and breathing.

Approximately 75% of infants who have BWS will have an omphalocele. An omphalocele occurs when the absence of abdominal muscles allows the abdominal contents to protrude through the opening in the abdomen. This is covered by a membrane into which the umbilical cord inserts. Omphaloceles are thought to be caused by a disruption of the process of normal body infolding at three to four weeks of fetal development. Although 25% of infants with BWS do not have omphaloceles, they may have other abdominal wall defects such as an umbilical hernia or even a less severe separation of the abdominal muscles called diastasis recti.

Fifty to sixty percent of newborns with BWS have low blood sugar levels within the first few days of life. This is called neonatal hypoglycemia and is caused by

having more than the usual number of islet cells in the pancreas (pancreatic islet cell hyperplasia). The islet cells of the pancreas produce insulin. This cluster of cells is called the islets of Langerhans and makes up about 1%–2% of the pancreas. These cells are the most important sugar (glucose) sensing cells in the body. When an individual eats a meal high in glucose or carbohydrates, this leads to a rise in blood sugar, which is then a signal for the increased insulin secretion by the islet cells of the pancreas. If too much insulin is produced, then the blood glucose levels drop too low. This is called hypoglycemia. Glucose is the primary fuel for brain function, so if hypoglycemia lasts too long, it can lead to brain damage. For this reason, detection and treatment of the hypoglycemia is extremely important. Any child born with features of this syndrome should be carefully monitored for hypoglycemia, especially during the first week of life. Occasionally, onset of hypoglycemia is delayed until the first month after birth. For this reason, the parents of a child with BWS should be taught to watch for the symptoms of hypoglycemia so that they can seek care as soon as possible.

Children with BWS have an increased risk of mortality associated with tumor development. These tumors begin development during fetal life (embryonal tumors). These malignant tumors develop in approximately 8% of children who have BWS. The most frequently seen tumors in individuals who have BWS include Wilms tumor (nephroblastoma) and hepatoblastomas. Wilms tumor is a tumor that arises in the kidney and consists of several embryonic tissues. Wilms tumor accounts for 80% of all kidney tumors in children. The peak incidence occurs between two and three years of age but can be present from infancy to adulthood.

Hepatoblastomas are tumors that arise in the liver during fetal development and are the most common primary liver tumor in infancy and childhood. A wide variety of other tumors, both malignant and benign, are also seen in individuals who have BWS and include, but are not limited to, nervous system tumors (neuroblastomas), adrenal gland tumors, and tumors that commonly occur in the head and neck (rhabdomyosarcoma). The increased risk for tumors appears to be concentrated in the first eight years of life, consistent with the embryonic nature of these tumors. In patients who have BWS, tumor development is not common after age eight.

Hemihyperplasia of a lower extremity or of the whole half of the body can be present. For example, one leg may be longer than the other leg. If hemihyperplasia is present, it may be recognized at birth and may become more or less obvious as a child grows. The risk of tumor development increases significantly when hemihyperplasia is present. While only 13% of affected individuals

have hemihyperplasia, 40% of those with neoplasms have hyperplasia. Most patients with BWS remain at or above the 95th percentile for length through adolescence. Advanced bone age can be identified on x-ray examination. Growth rate usually slows down at around age seven or eight. After nine years of age, the average weight remains between the 75th and 95th percentile. Although height, weight, skeletal, and dental maturity may be above average for years, growth rate gradually slows down and eventually children reach average height and normal proportions. Puberty occurs at the usual time.

Another feature includes unusual linear grooves within the ear lobes and/or a groove or pit on the top of the outer ear. Facial characteristics may include prominent eyes (exophthalmos), “stork bite” birth marks (telangiectatic nevi) on the upper half of the face, and “port wine stain” birth marks (facial nevus flammeus) on the face.

Genetic profile

The genetics of BWS is complex. Approximately 85% of individuals who have BWS have no family history of BWS and have a normal karyotype. BWS has been shown to specifically involve problems with a defined region on the short arm of chromosome 11 referred to as 11p15. Approximately 20% of BWS patients have paternal uniparental disomy for chromosome 11p15. Uniparental disomy occurs when an individual receives two copies of a chromosome, part of a chromosome, or a gene from one parent, as opposed to receiving one copy from each parent. In this situation, the amount of gene expression can be changed and cause a disease or disorder. Approximately 5%–10% of patients who have no family history and a normal karyotype have a gene change identified near 11p15 called p57(*KIP2*). This gene region, p57(*KIP2*), is a tumor suppressor region, meaning that its presence suppresses tumor development but that the loss of a normally functioning region could lead to tumor development and potentially lead to BWS. The *IGF2* (insulin-like growth factor-2) gene is also in this region. Both uniparental disomy and a gene mutation result in dosage changes of the normal functioning genes, resulting in overexpression and subsequently increased growth and tumor risk. When a gene change in the p57(*KIP2*) region is found in either of the parents of the affected child, the chance for a future child to have BWS could be as high as 50% with each future pregnancy. The remaining 70% of individuals who have BWS, no family history, and a normal karyotype have no identifiable cause for BWS. The chance for other family members to be affected in this case is expected to be low.

Approximately 10%–15% of individuals who have BWS have a positive family history and a normal karyotype. Of these families, up to 50% may have an identifiable

gene change in the p57 region. If a female carries this gene change, then she has a 50% chance with each pregnancy for having a child with BWS. If a male carries the gene change, the chance for having an affected child is increased, but specific risks are not yet available. Up to 50% of individuals with a positive family history and a normal karyotype do not have an identifiable gene change in the p57 region. In this situation, the chance for the parents to have another affected child is as high as 50%.

Approximately 1%–2% of patients with BWS have a detectable chromosomal abnormality. In patients who have a translocation or a duplication of 11p15 detected on their karyotype, the parents’ chromosomes should be analyzed. Depending upon the results of the parents’ chromosome analysis, there could be up to a 50% chance of having an affected child with BWS.

Demographics

As of 2015, the reported incidence for BWS was approximately 1 in 14,000 in the United States, although this is likely to be an underestimate because of undiagnosed cases. Worldwide frequency is estimated at 1 in 13,700 live births in other developed countries. Incidence is also higher in infants produced with in vitro fertilization. No race predilection has been reported.

Signs and symptoms

Major signs or symptoms include macrosomia, macroglossia, abdominal wall defect, visceromegaly, embryonal tumors, hemihyperplasia, ear lobe creases or ear pits, renal abnormalities, and, rarely, cleft palate.

Minor signs and symptoms include polyhydramnios, prematurity, neonatal hypoglycemia, advanced bone age, heart defects, hemangioma, facial nevus flammeus, and the characteristic facial features, which include underdeveloped midface and possible soft-tissue folds under the eyes.

Diagnosis

BWS is diagnosed primarily by the identification of clinical signs and symptoms. Although there is no official diagnostic criteria for BWS, most would agree that a diagnosis requires the presence of three major findings, or at least two major findings and one minor finding. For the purposes of diagnosis, a major finding would also include a family history of BWS.

When considering the diagnosis of BWS, several other syndromes should also be considered (differential diagnosis). These include, but are not limited to, infant of a diabetic mother, Simpson-Golabi-Behmel syndrome, Perlman syndrome, Sotos syndrome, and Costello syndrome.

If a couple has had a child affected with BWS and an identifiable gene change in the p57 region has been identified, or if a chromosome abnormality is detected by chromosome analysis, then prenatal testing through chorionic villus sampling (CVS) or amniocentesis is possible. If this is not possible, then a detailed ultrasound examination could help to reassure parents that the signs and symptoms of BWS are not present (such as omphalocele, macroglossia, and macrosomia). If any of these signs or symptoms are present, and the couple has had a previously affected child, then it would be very likely that the present pregnancy is affected as well.

If a couple has not had a previously affected child and has had an ultrasound examination that identifies an omphalocele, then chromosome analysis should be offered to rule out a chromosome abnormality and to look for the abnormal findings associated with BWS. If chromosome results are normal, BWS is still a possible cause for the ultrasound findings.

Treatment and management

Early treatment of hypoglycemia is important to reduce the risk of central nervous system damage. Most cases of hypoglycemia are mild and will resolve shortly with treatment; however, some cases may be more difficult. Treatment for hypoglycemia may include steroid therapy, which is usually required for only one to four months.

If an infant has an abdominal wall defect, such as an omphalocele, surgery is usually performed soon after birth to repair the defect. For very large omphaloceles, a multi-stage operation is performed. The treatment and management of the omphalocele depends upon the presence of other problems and is very specific to each individual.

A cardiac evaluation is recommended prior to surgery or if a heart defect is suspected by clinical evaluation. Cardiomegaly is frequently present but usually resolves without treatment.

Nonmalignant kidney abnormalities, including renal cysts and hydronephrosis, occur in approximately 25% of patients. A consult with a pediatric nephrologist would be recommended for patients who have structural renal abnormalities, including any evidence of renal calcium deposits on ultrasound examination.

To screen for tumors, a baseline MRI (magnetic resonance imaging) or CT (computed tomography) examination of the abdomen is recommended for individuals believed to have BWS. To screen for Wilms tumor and other embryonal tumors, abdominal ultrasound is recommended. Blood pressure should also be monitored, as approximately 50% of people with Wilms tumors may

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks of gestation. Under ultrasound guidance, a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the early embryo. These cells are then tested for chromosome abnormalities or other genetic diseases.

Hemihyperplasia—A condition in which overdevelopment or excessive growth of one-half of a specific organ or body part on only one side of the body occurs.

Neonatal—The first 28 days after birth.

Nevus flammeus—A flat blood vessel tumor present at birth, also known as a port wine stain.

have associated hypertension. Because tumor development may occur at any time, though usually before eight years of age, the screening recommendations are that abdominal ultrasound be performed every three to six months until eight years of age and then annually until growth is complete. In addition to ultrasound, screening for hepatoblastoma is accomplished by serial measurements of the serum alpha-fetoprotein (AFP) levels during these years as well. Elevated levels of serum AFP are present 80%–90% of the time when a hepatoblastoma is present. Alpha-fetoprotein is a protein produced by the fetal liver. Concentrations of this protein fall rapidly during the first few weeks after birth and reach adult levels by six months of age. These adult levels are approximately 2–20 ng/ml. Thus, the presence of elevated levels in children and adults usually indicates tumor development. Abnormal AFP levels should be followed with an abdominal CT examination looking for evidence of a tumor in the liver.

Surgical removal is the primary treatment for hepatoblastoma; however, in tumors that cannot be removed, chemotherapy is performed.

Treatment for Wilms tumor is often only surgical removal of the tumor; however, in some cases

QUESTIONS TO ASK YOUR DOCTOR

- What types of early treatment are needed for a child born with Beckwith-Wiedemann syndrome?
- What types of complications should we anticipate for a child with Beckwith-Wiedemann syndrome, and how can those complications be treated?
- Given my child's current condition, what is his or her long-term prognosis?

chemotherapy and radiation therapies are necessary, depending upon the stage of disease and the characteristics of the tumor.

Macroglossia may need to be addressed with the possibility of surgery. The large tongue may partially block the respiratory tract and lead to problems such as difficulty breathing and feeding. In most cases, the tongue growth slows over time and eventually the tongue can be accommodated. Dental malocclusion and a prominent jaw are secondary to the macroglossia. In rare cases, surgery to reduce tongue size is needed and is usually performed between two and four years of age.

Clinical trials

Two clinical trials for the treatment of BWS have been sponsored by the National Institutes of Health (NIH). The first study (NCT00773825) evaluated whether children born following assisted reproductive technologies exhibit an increased risk of genomic imprinting defects. The study has concluded, but as of 2015 no results had been published. The second trial (NCT00503893), in the recruitment stage, seeks to characterize the genetic events related to BWS.

Prognosis

After dealing with initial neonatal issues such as hypoglycemia, feeding, and respiratory problems, prognosis is usually good. Infants with BWS syndrome have an approximately 20% mortality rate, although recent studies indicate that it may be lower than 20%. Mortality is mainly because of complications stated above and also includes complications of prematurity and omphalocele. The prognosis with repaired omphalocele is good. The majority of deaths in cases of omphalocele are usually associated with other anomalies or respiratory insufficiency. Respiratory insufficiency can occur in patients

with omphaloceles if the omphalocele is so large that prenatal lung development cannot occur as usual. Respiratory insufficiency can also occur because of prematurity.

Tumor survival rates for Wilms tumor and for hepatoblastoma are as follows. In general, the four-year survival of all patients who have Wilms tumor with favorable histology approaches 90%. For hepatoblastomas, the combination of surgery and chemotherapy has achieved disease-free survival rates of 100% for stage I, 75% for stage II, and 67% for stage III hepatoblastomas.

In children who have BWS, development is usually normal if there is no history of significant, untreated hypoglycemia. After childhood, complications for patients with BWS are uncommon and prognosis is good.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06813, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Renee A. Laux, MS

Berlin breakage syndrome see **Nijmegen breakage syndrome**

Beta-galactosidase-1 deficiency see **Gm1 gangliosidosis**

Beta thalassemia

Definition

Beta thalassemia is an inherited disorder that affects the beta globin (protein molecules) chains in human

blood. These chains are required for the synthesis of hemoglobin A (a compound in the blood that carries oxygen to the cells and carbon dioxide away from the cells). A decrease in beta globin chains causes early destruction of the red blood cells. There are four types of the disorder; they range in severity of symptoms.

The thalassemias were first discovered by Thomas Cooley and Pearl Lee in 1975. Early cases of the disease were reported in children of Mediterranean descent. Therefore, the disease was named after the Greek word for sea, *thalassa*.

Description

Beta thalassemia results from a defect in the beta globin gene. Shortly after birth, the body converts from producing fetal hemoglobin (HbF), to producing beta globin chains. Fetal hemoglobin consists of gamma globin chains that pair with alpha globin chains. Beta globin chains pair with alpha globin chains to produce adult hemoglobin (HbA). Because of the decreased amount of beta globin chains in individuals with beta thalassemia, there is an excess of free alpha globin chains. The free alpha globin chains become abnormal components in maturing red blood cells. This process leads to destruction of the red blood cells in the spleen and a decreased number of red blood cells in the body. Individuals with beta thalassemia may continue producing gamma globin chains in an effort to increase the amount of HbF and compensate for the deficiency of HbA.

There are four subtypes of beta thalassemia: minima, minor, intermedia, and major. Beta thalassemia minima and beta thalassemia minor are less severe forms of the disorder and usually asymptomatic. Beta thalassemia minima is known as the silent form of the disorder. There are no major hematologic (blood and blood-forming tissue) abnormalities. The only notable abnormality is the decrease in beta globin production. Beta thalassemia minor is rare. A person with this type of the disorder inherits only one beta globin gene. Although children with beta thalassemia minor are usually asymptomatic, they do have abnormal hematologic (blood-related) findings.

Beta thalassemia intermedia and major often require medical treatment. Beta thalassemia intermedia is usually found during the toddler or preschool years. It is considered to be the mild form of thalassemia major and frequently does not require blood transfusions. Thalassemia major is typically diagnosed during the first year of life. There are two designations for beta thalassemia major: beta zero and beta positive. In beta zero, there is no adult hemoglobin (HbA) present as a result of the very small production of beta globin. In type beta

positive, there is a small amount of detectable HbA. In both forms of beta thalassemia major, individuals will experience severe fatigue due to the decrease or absence of HbA, which is needed to carry oxygen to the cells.

Other names for beta thalassemia include erythroblastic anemia, Mediterranean anemia, microcytemia beta type, and thalassemia beta type. Alternate names associated with beta thalassemia minor include thalassemia minor, minor hereditary leptocytosis, and heterozygous beta thalassemia. Alternate names associated with beta thalassemia intermedia include intermedia Cooley's anemia and thalassemia intermedia. Alternate names associated with beta thalassemia major include Cooley's anemia, erythroblastic anemia of childhood, hemoglobin lepreux syndrome, major hereditary leptocytosis, Mediterranean anemia, microcythemia, target cell anemia, and thalassemia major.

Risk factors

Beta thalassemia is a genetic disease originally found in Mediterranean populations. People of Mediterranean descent are at increased risk of thalassemia.

Demographics

Worldwide, beta thalassemia is a fairly common blood disorder. Beta thalassemia occurs more frequently in people from the Mediterranean area, North Africa, the Middle East, India, Central Asia, and Southeast Asia. Cooley's Anemia Foundation estimates that over 2 million people in the United States carry the genetic trait for thalassemia. The highest incidences occur in Cyprus, Sardinia, and Southeast Asia. As much as 10% of the populations in those areas may have the disorder. Population migrations have led to a global distribution of beta thalassemia, now also common in northern Europe, North and South America, the Caribbean, and Australia.

Signs and symptoms

Beta thalassemia is an autosomal recessive disorder caused by mutations in the *HBB* gene on chromosome 11 at 11p15.4. As of 2015, more than 250 mutations in this gene are known to cause beta thalassemia. In the autosomal recessive pattern, a person who is a carrier will not develop the disorder but may pass on the gene for the disorder to their child. There is a 25% chance for each pregnancy that the disorder will be passed on to the children if both parents are carriers of the trait and a 100% chance if both parents have the trait.

A parent who is a carrier of the beta thalassemia trait and has a child with someone who is a carrier of other abnormal hemoglobins is at risk of having children with blood disorders related to beta thalassemia. If one parent

carries the beta thalassemia trait and the other carries the hemoglobin E trait, their children have a 25% chance of having E beta thalassemia, a moderately severe anemia. Similarly, if one parent carries the beta thalassemia trait and the other parent carries the hemoglobin S trait, the children have a 25% chance of having sickle beta thalassemia, which can be almost as severe as sickle cell disease.

There are, however, a few families in which mutations in the *HBB* gene are transmitted in an autosomal dominant pattern. In the autosomal dominant pattern, only one copy of the mutated gene in each cell is sufficient to produce the symptoms of beta thalassemia.

Individuals with thalassemia minor are carriers of the beta globin gene. Therefore, these individuals possess only one of the genes necessary to express the disorder. These individuals are usually asymptomatic or have very few symptoms.

Individuals with thalassemia major express both abnormal genes for beta globin and therefore will have the disease. These individuals show severe symptoms for the disorder. The beta globin gene is found on chromosome 11. Mutations resulting in beta thalassemia are usually caused by substitutions, although some may be caused by deletions. Mutations involve inappropriate sequence of nucleotides, the building blocks of genes. Substitutions are the switching of one nucleotide for another. Deletions occur when part of a chromosome is missing. Substitutions occur within the nucleotide and deletions occur on the chromosome on which the beta globin gene is found.

Symptoms for beta thalassemia vary in severity according to the subtype of the disorder.

Beta thalassemia minima

There are no symptoms associated with this subtype. It is considered to be a “silent” form of beta thalassemia.

Beta thalassemia minor

Individuals with this type of beta thalassemia may be asymptomatic or experience very few symptoms. Symptoms may be worse in individuals who are pregnant, under stress, or malnourished. Symptoms may include:

- **Fatigue.** This may be the only symptom that an individual with beta thalassemia minor exhibits. Fatigue is caused by the decreased oxygen-carrying capacity of the red blood cells, resulting in lowered oxygenation of cells and tissues.
- **Anemia.** Anemia is a decrease in the amount of hemoglobin in the blood. Hemoglobin is needed to carry oxygen in the red blood cells. In beta thalassemia minor there is a decrease in adult hemoglobin (HbA) and

an increase in hemoglobin A2. Hemoglobin A2 is a minor hemoglobin that contains delta globin chains in the place of beta globin chains. Anemia is most likely to occur during pregnancy.

- **Splenomegaly.** Enlargement of the spleen may occur due to increased removal of defective red blood cells. This symptom is rarely seen in individuals with beta thalassemia minor and may be accompanied by pain in the upper left portion of the abdomen.
- **Pale skin.** The skin color of individuals with beta thalassemia minor may be pale due to oxygen deprivation in blood.

Beta thalassemia intermedia

Individuals with this form of beta thalassemia usually begin to show symptoms during the toddler or preschool years. These individuals present with many of the same symptoms as beta thalassemia major. Symptoms for beta thalassemia intermedia are less severe, however, and may include:

- **Anemia.** In individuals with beta thalassemia intermedia, hemoglobin levels are greater than 7g/dL but are lower than normal. Normal levels for hemoglobin are 13–18 for males and 12–16 for females.
- **Hyperbilirubinemia.** Bilirubin is a yellow pigment of bile that is formed by the breakdown of hemoglobin in the red blood cells. Excessive bilirubin in the blood is caused by the increased destruction of red blood cells (hemolysis) in the spleen.
- **Splenomegaly.** Enlargement of the spleen is caused by increased removal of defective red blood cells. Red blood cells are defective due to the increased amount of inclusion bodies caused by circulation of free alpha globin chains.
- **Hepatomegaly.** Enlargement of the liver may be caused by a build-up of bile due to increased amounts of bilirubin in the blood.
- **Additional abnormalities.** Individuals with beta thalassemia intermedia may have a yellow discoloration (jaundice) of the skin, eyes, and mucous membranes. This discoloration is caused by increased amounts of bilirubin in the blood. Individuals may also suffer from delayed growth and abnormal facial appearance.

Beta thalassemia major

Individuals with this form of beta thalassemia present with symptoms during the first year after birth. Symptoms are severe and may include:

- **Severe anemia.** Individuals with beta thalassemia major suffer from a hemoglobin level of less than 7 mg/dl.

KEY TERMS

Bilirubin—A yellowish pigment derived from the breakdown of heme during the body's clearance of worn-out red blood cells. Bilirubin is responsible for the discolored appearance of bruises, the yellowish discoloration of the skin in jaundice, and the yellow color of urine.

Chelation therapy (pronounced key-LAY-shun)—A form of therapy in which chelating agents are administered to remove heavy metals from the body. Chelating agents are chemicals that have a special affinity for metal ions.

Cholelithiasis—The formation of gallstones within the gallbladder.

Erythroblast—The immediate precursor of a normal red blood cell.

Ferritin—An intracellular protein that stores iron and releases it in a controlled manner. Ferritin in blood plasma is an indirect marker of the total amount of iron stored in the body.

Globins—A family of heme-containing proteins involved in the binding or transporting of oxygen in the body.

Hematopoiesis—The process of blood cell formation from stem cells in the medulla of the bone (bone marrow).

Heme—The iron-containing molecule in hemoglobin that serves as the site of oxygen binding.

Hemoglobin—The protein-iron compound in the blood that carries oxygen to the cells and carries carbon dioxide away from the cells.

Hemoglobin E—An abnormal hemoglobin with a single-point mutation in the beta chain. People who inherit the hemoglobin E gene from one parent and the beta thalassemia gene from the other develop hemoglobin E beta thalassemia, which is a severe disease.

Hemoglobin S—The most common type of abnormal hemoglobin; it is the basis of sickle cell trait and sickle cell anemia.

Hepatomegaly—Abnormal enlargement of the liver.

Medulla—In general, the central portion of a body organ; with regard to bone, the marrow that lies at the center of the long bones. The English word is derived from the Latin word for marrow.

Red blood cells (RBCs)—Hemoglobin-containing blood cells that transport oxygen from the lungs to tissues. In the tissues, the red blood cells exchange their oxygen for carbon dioxide, which is brought back to the lungs to be exhaled.

Spherocyte—A red blood cell that has an abnormal spherical shape rather than the normal shape of a concave disk.

Splenomegaly—Abnormal enlargement of the spleen.

- **Hyperbilirubinemia.** Individuals will have an increased amount of bilirubin in the blood, resulting from the increased destruction of red blood cells (hemolysis) by the spleen.
- **Jaundice.** Individuals may experience a yellow discoloration of the skin, eyes, and mucous membranes caused by increased amounts of bilirubin in the blood.
- **Extramedullary hematopoiesis.** Abnormal formation of red blood cells outside the bone marrow may occur in the body's attempt to compensate for decreased production of mature red blood cells. This abnormal formation can cause masses or the enlargement of organs, which may be felt during physical examination.
- **Splenomegaly.** Enlargement of the spleen may result due to increased destruction of red blood cells and the occurrence of extramedullary hematopoiesis.
- **Hepatomegaly.** Enlargement of the liver may result due to accumulation of bile or the occurrence of extramedullary hematopoiesis.
- **Cholelithiasis.** Cholelithiasis is the presence of stones in the gallbladder, which may lead to blockage and cause bile to be pushed back into the liver.
- **Bone marrow expansion.** The bone marrow becomes expanded due to the increase of the production of red blood cells (erythropoiesis) in an attempt to produce more mature red blood cells and decrease the anemic state of the body.
- **Facial changes.** Due to expansion of the bone marrow, children will develop prominent cheekbones, depression of the nasal bridge, and protrusion of the upper jaw. These facial changes are a classic sign in children with untreated beta thalassemia.
- **Iron overload.** Iron overload of the tissues can be fatal and is due to erythroid (red blood cell) expansion. The increased destruction of a vast amount of red blood cells causes increased amounts of iron to be released from the hemoglobin.

- Cardiovascular abnormalities. Accumulation of iron deposits in the heart muscle can lead to cardiac abnormalities and possibly cardiac failure.
- Delayed puberty in adolescents.
- Additional abnormalities. Individuals may also suffer from pale skin, fatigue, poor feeding, failure to thrive, and stunted growth.

Symptoms of beta thalassemia minor may be similar to those of sideroblastic anemia and sickle cell disease. Sideroblastic anemia is a disorder characterized by low levels of hemoglobin, fatigue, and weakness. Sickle cell disease is a disease that changes the red blood cell shape, rendering it incapable of functioning.

Symptoms of beta thalassemia major may be similar to those of hereditary spherocytic hemolytic anemia (presence of sphere-shaped red blood cells).

Diagnosis

Completing a family history, performing a complete physical examination, and analyzing results of blood (hematological) tests can lead to a diagnosis of beta thalassemia.

Examination

Bone abnormalities and masses or enlarged organs may be recognized during physical examination. In addition, the doctor may note that the patient has some of the facial features associated with beta thalassemia.

Tests

Blood tests are performed to establish diagnosis. These include complete blood count (CBC), blood smear, iron studies, blood protein analysis, and a hemoglobinopathy test. The goal of the iron studies is to determine whether there is iron deficiency. The goal of the hemoglobinopathy test is to measure the type and relative amounts of hemoglobin present in the red blood cells. Genetic testing can also be used to investigate deletions and mutations in the alpha and beta globin producing genes. Other genetic tests include linkage analysis, sequence analysis of the entire coding region, and sequence analysis of select exons.

Normal hemoglobin results are 13–18 g/dL for males and 12–16 g/dL for women. Normal red blood cell counts are 4.7–6.1 million for males and 4.2–5.4 million for females. In individuals with the beta zero form of beta thalassemia major, there will be no HbA present in the blood.

Prenatal testing to detect beta thalassemia can be done by completing an amniocentesis (obtaining a sample of amniotic fluid, which surrounds the fetus during pregnancy). Lab results will vary depending on the type of beta thalassemia that an individual might have.

Treatment and management

Traditional

Beta thalassemia minima and minor usually require no treatment. Pregnant women who suffer from beta thalassemia minor may require blood transfusions to keep hemoglobin levels normal. Individuals with beta thalassemia intermedia and major can be treated with blood transfusions and iron chelation (binding and isolation of metal) therapy. Although individuals with beta thalassemia intermedia do not usually require transfusions, in certain cases they may be necessary.

Blood transfusions are performed in individuals that present with severe symptoms such as anemia and impaired growth and development. Children may receive transfusions every four to six weeks. A high risk associated with transfusions is iron overload, which is fatal. Iron overload results from inadequate amounts of serum transferrin needed to bind and detoxify iron. Iron accumulation can lead to dysfunction of the heart, liver, and endocrine glands.

Monitoring iron levels in the body is essential. Individuals receiving blood transfusions should keep total body iron levels at 3–7 mg of iron per gram of body weight. Methods to measure iron levels include a serum ferritin test, liver biopsy, and radiological study performed by a Superconducting Quantum Interference Device (SQUID).

The serum ferritin (iron storage protein) test is completed by testing a blood sample for ferritin content. This method is the easiest and most affordable way of testing for body content of iron, but it is not fully reliable. A liver biopsy is an invasive procedure that requires removal of a small piece of the liver. Still, studies have shown that a liver biopsy is very accurate in measuring the level of iron stores in the body. The third method, which requires a SQUID, is also very accurate in measuring iron stores. The SQUID is a highly specialized machine and few centers in the world possess this advanced technology.

Individuals receiving blood transfusions should pay close attention to iron intake in the diet. It is recommended that children under age 10 keep dietary iron intake at 10 mg/day or less. Individuals age 11 or older should keep dietary iron intake at 18 mg/day or less. Foods high in iron include beef, beans, liver, pork, peanut butter, infant cereal, cream of wheat, prunes, spinach, raisins, and leafy green vegetables. Individuals should read food labels and avoid using cast iron cookware, which can provide more iron in food during cooking. Increased amounts of iron in the body can cause a decrease in calcium levels, which impairs organs that aid in building strong bones. Individuals with beta thalassemia major

are at risk of developing osteoporosis (loss of bone mass resulting in weakened bones). Males with thalassemia major are at greater risk than females. Increased dietary intake of calcium and vitamin D can help increase the storage of calcium in the bones, thus making the bones stronger and decreasing the risk of osteoporosis. Treatment with bisphosphonates is an increasingly common therapy for children with beta thalassemia at risk of osteoporosis.

Surgery

In some cases (most often thalassemia major), the doctor may recommend splenectomy (surgical removal of the spleen) to lower the need for transfusions and the associated risk of iron overload. Patients with thalassemia minor may require cholecystectomy (surgical removal of the gallbladder) if large numbers of gallstones are formed in the gallbladder.

Drugs

Iron overload can be prevented with the use of iron chelating therapy. Chelating agents attract the excess iron and assist with the process of binding and detoxifying this iron in the body. The drug deferoxamine (Desferol) is one of the most widely used iron chelating agents. Treatment is completed through nightly infusions of deferoxamine by a pump or with daily intramuscular injections. Infusion by pump is used for the administration of high doses. Low doses are given through injections. Another iron chelating agent, deferiprone (Ferriprox), was approved by the Food and Drug Administration (FDA) in 2011 for the treatment of transfusion-related iron overload in thalassemia patients when deferoxamine treatment is inadequate. Unlike deferoxamine, deferiprone is given by mouth.

Still another orally administered chelating agent is deferasirox (Exjade, Desirox), originally approved by the FDA in 2005 to treat transfusion-related iron overload, and approved by the FDA in 2013 for a new indication, namely the treatment of non-transfusion-related iron overload in patients with thalassemia. Some physicians report that combination chelation therapy, either deferiprone and deferasirox or deferasirox and deferoxamine, yields better results than any of the chelating agents given alone.

Researchers are investigating the use of the drugs hydroxyurea and butyrate compounds to increase the amounts of fetal and total hemoglobin in individuals with beta thalassemia. Other drugs under investigation include demethylating agents (decitabine and 5-azacytidine), histone deacetylase inhibitors (vorinostat and panobinostat), and a derivative of thalidomide known as pomalidomide.

QUESTIONS TO ASK YOUR DOCTOR

- Which subtype of beta thalassemia do I have?
- What are the treatment options?
- Where can I find information about the medications used to treat beta thalassemia?
- What kind of information will the tests provide?
- How does the condition affect quality of life?
- Should genetic testing be performed?

Alternative

Bone marrow transplantation is another form of treatment for beta thalassemia. Outcomes of transplantation are greatly influenced by the health of the individual. This form of treatment is only possible when the individual has a suitable donor.

Studies using gene therapy, such as stem cell replacement, genome editing technologies, and viral vectors are also being conducted.

Clinical trials for the treatment of beta thalassemia are currently sponsored by the National Institutes of Health (NIH) and other agencies. In 2021, the NIH reported 190 ongoing or recently completed studies in the United States. Most are studies of currently approved or investigational chelating agents. Still, some are trials of cord blood, gene therapy, or bone marrow transplantation as therapies for beta thalassemia. Clinical trial information is constantly updated by the NIH. The most recent information on beta thalassemia trials can be found on the Clinical Trials website at <https://clinicaltrials.gov>

Prevention

Beta thalassemia cannot be prevented because it is an inherited disease. Preventive research is currently investigating prenatal and newborn interventions.

Prognosis

Prognosis for beta thalassemia is good for individuals diagnosed early and those who receive proper treatment. Children with beta thalassemia major live 20–30 years longer with treatment by blood transfusions and iron chelation therapy. On the other hand, transfusion therapy is not risk-free. A study sponsored by the Centers for Disease Control and Prevention (CDC) reported in 2014 that 48% of the 407 patients who were followed had allergic or hemolytic reactions to transfusions; 24% were exposed to infectious organisms through transfusions; and other patients had organ dysfunction due to

iron overload in spite of chelation therapy. The most common causes of mortality in persons with beta thalassemia are anemia and iron overload.

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ORGANIZATIONS

AABB [formerly American Association of Blood Banks], 4550 Montgomery Avenue, Suite 700, North Tower, Bethesda, MD 20814, (301) 907-6977, (301) 907-6895, aabb@aabb.org, <http://www.aabb.org/home>

American Society of Hematology (ASH), 2021 L Street NW, Suite 900, Washington, D.C. 20036, (202) 776-0544, (202) 776-0545, <http://www.hematology.org>

Cooley's Anemia Foundation Inc., 330 Seventh Avenue, Unit 900, New York, NY 10001, (212) 279-8090, <http://www.cooleysanemia.org>

Food and Drug Administration (FDA), 10903 New Hampshire Ave., Silver Spring, MD 20993, (888) INFO-FDA (463-6332), <http://www.fda.gov/AboutFDA/Contact-FDA/default.htm>, <http://www.fda.gov/default.htm>

Iron Disorders Institute, P.O. Box 4891, Greenville, SC 29608, info@irondisorders.org, <http://www.irondisorders.org>

Thalassemia Foundation of Canada, 10 Holland Drive, Bolton, ON, Canada L7E 1G6, (416) 242-THAL (8425), (416) 242-THAL, info@thalassemia.ca, <http://www.thalassemia.ca>

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Bicuspid aortic valve

Definition

Bicuspid aortic valve is the most common malformation of the heart valves. In this type of deformity, the aortic valve has only two cusps, which are rigid points such as those seen on leaves, instead of the three cusps normally present. This condition may lead to abnormalities in the flow of blood from the heart to the aorta, leading to changes in the function of the heart and lungs. Treatment consists of surgical repair or replacement of the valve.

Description

A valve is a device that allows a fluid to flow in only one direction in a defined path, thereby preventing backflow of the fluid. The heart has four such valves, which allow the blood to flow in an orderly pattern through each of the four chambers of the heart and out into the largest artery of the body, the aorta. The aorta in turn branches into other blood vessels in the neck, limbs, and organs of the body to supply it with oxygenated blood.

The aortic valve divides the left ventricle of the heart and the aorta. It is the last valve before blood leaves the heart and passes into the aorta. The valve is formed during pregnancy and is normally composed of three separate cusps or leaflets, which, when closed, form a tightly sealed barrier that prevents backflow of blood from the aorta into the heart. Thus, when the heart contracts or pumps, the aortic valve opens and allows blood to pass from the heart into the aorta, and when the heart relaxes, the aortic valve closes and prevents backflow of blood from the aorta into the heart.

The three-cusp structure of the valve is essential for its proper function and was noted as far back as the fifteenth century, when the great master of the High Renaissance, Leonardo da Vinci, reported on his observations of anatomy and blood circulation. In bicuspid aortic valve, the aortic valve fails to form properly during development in the womb; for reasons that are unclear, two of the three cusps fail to separate properly and remain attached along one edge, resulting in an aortic valve with only two cusps.

Bicuspid aortic valve is the most common heart valve defect at birth, and many people live a normal life without even being aware of this condition. Unfortunately, bicuspid aortic valves are also more prone to disease than the normal three-cusped valves. Over the years, conditions such as restricted blood flow to the aorta (aortic stenosis), backflow of blood from the aorta into the heart (aortic regurgitation, or aortic insufficiency), and valve infection (endocarditis) are often detected with associated symptoms during the adult years as progressive damage is done to the bicuspid aortic valve.

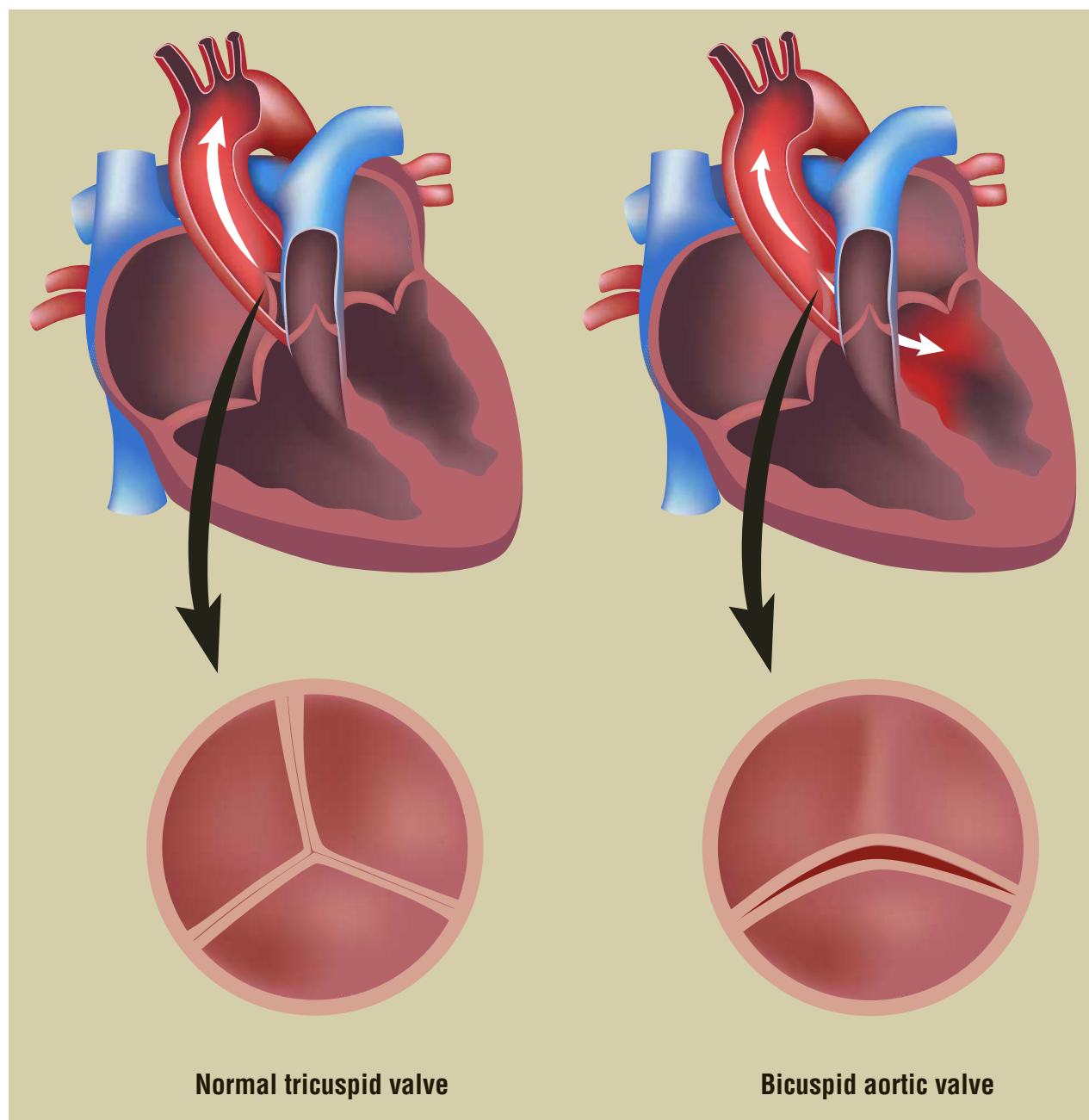


Illustration of a normal heart valve (left) and one with a valve defect. (Alila Medical Media/Shutterstock)

Other conditions that may occur with bicuspid aortic valve include aneurysm of the aorta (ballooning of the aorta wall) and aortic dissection (a life-threatening split in the layers of the aorta).

Genetic profile

Most occurrences of bicuspid aortic valve appear to be sporadic (i.e., random and not associated with an inherited defect) and are not passed on from parent to

child. However, there have been some reports that the valve malformation appears in multiple members of the same family and is associated with a mutation in the *NOTCH1* gene. In at least one report, this familial occurrence appears to be inherited in an autosomal dominant pattern with reduced penetrance (not showing the malformation despite possessing the genetic cause for it). For purposes of genetic counseling, bicuspid aortic valve can be regarded as a sporadic condition with an extremely low risk of being transmitted from parent to child.

Demographics

Bicuspid aortic valve is underdiagnosed but may be present in as many as 1%–2% of the population in the United States. Bicuspid aortic valve is more common among males than females, with lower than expected prevalence in African-Americans.

Risk factors

Risk factors for bicuspid aortic valve include the presence of such other genetic syndromes as Turner syndrome, Down syndrome, velocardiofacial syndrome, and Loeys-Dietz syndrome.

Signs and symptoms

Many people with bicuspid aortic valve experience no symptoms and may live their entire lives unaware of the condition. However, progressive damage or infection of the valve may lead to three serious conditions: aortic stenosis, aortic regurgitation, or endocarditis.

As a person ages, calcium deposits form on a bicuspid aortic valve, making it stiff. Eventually, the valve may become so stiff that it does not open properly, making it more difficult for blood to leave the heart and pass into the aorta, resulting in aortic stenosis. When this blockage becomes serious enough, people may experience shortness of breath, chest pain, or fainting spells. These symptoms usually begin between the ages of 50 and 60 years old. Eventually, the blockage can become so bad that blood backs up in the heart and lungs instead of going out to supply the rest of the body with oxygen (congestive heart failure). Additionally, this condition can lead to thickening of the heart wall, which may cause abnormal heart rhythms leading to sudden death.

Aortic regurgitation results when the valve fails to close properly. People who develop this condition may become short of breath when exerting themselves. The extent of symptoms experienced by the patient depends on the severity of the aortic regurgitation.

Finally, bacteria may deposit on the malformed bicuspid aortic valve, causing endocarditis. People with endocarditis may have symptoms of lingering fevers, fatigue, weight loss, and sometimes damage to the kidneys or spots on their fingers and hands.

Other dangerous conditions associated with bicuspid aortic valve include aortic aneurysm and aortic dissection. People with aortic aneurysms usually do not experience symptoms unless the aneurysm ruptures, but people with aortic dissection experience tearing back pain. Aortic aneurysm rupture and aortic dissection are very dangerous and can rapidly lead to death if not promptly treated.

Diagnosis

Any of the symptoms of aortic stenosis, aortic regurgitation, or endocarditis should prompt a search for an underlying malformation of the aortic valve. Aortic stenosis or regurgitation is diagnosed by a combination of physical exam and cardiovascular tests and imaging.

Examination

The earliest sign of aortic valve problems is a murmur (the sound of abnormal patterns of blood flow) heard with a stethoscope. When the valve has high levels of calcium deposits, a characteristic clicking sound can also be heard with the stethoscope just as the stiff valve attempts to open.

Tests

If these signs are present on examination, it suggests that the aortic valve may be damaged. Tests can then be performed, such as magnetic resonance imaging (MRI) or echocardiography, a method that uses ultrasound waves to look at the aortic valve, similar to the way in which ultrasound is used to look at a fetus during pregnancy. Often, only two cusps are seen on the aortic valve during the echocardiography, confirming a diagnosis of bicuspid aortic valve.

Endocarditis is diagnosed by demonstrating the presence of bacteria in the bloodstream. This is performed by taking blood from the patient and growing the bacteria on plates with specialized nutrients. Skilled technicians can then use different tests to identify which species of bacteria is present so that appropriate treatment can be started. The diagnosis of endocarditis is also confirmed by using echocardiography to look for bacterial growths on the aortic valve. During the echocardiography, a bicuspid valve is often seen and explains the tendency to develop endocarditis.

Treatment and management

Most people with bicuspid aortic valve will not experience any complications or symptoms and will not require treatment. However, in patients with any complication of valve damage, treatment may be necessary.

Traditional

In younger patients who have aortic stenosis, a procedure can be performed in which a small balloon is inserted through one of the major blood vessels and into the aortic valve. The balloon is then inflated, creating a bigger opening for blood to pass. Alternatively, an “open

QUESTIONS TO ASK YOUR DOCTOR

- Should I restrict my level of physical activity?
- What are the possible complications of bicuspid aortic valve?
- Is surgery required?
- What are the treatment options?

heart" procedure can be performed to cut the valve into a more normal configuration. These treatments are usually temporary, and later in life the patient, as well as any adult with advanced aortic stenosis, will most likely require aortic valve replacement.

Valve replacement is an open heart operation in which the original malformed valve is removed and replaced with a new valve. This new valve can come from a human donor who has died, from cows or pigs, or even from another part of the patient's heart. These valves function well but may need to be replaced after 10 to 20 years, as they wear out. Another option is to use an artificial valve made of metal, plastic, or cloth. However, people who receive these artificial valves need to take blood thinners every day in order to prevent blood clots from forming on the new valve.

People who have been identified as having bicuspid aortic valve are followed regularly by a cardiologist, with possible consultation with a cardiothoracic surgeon. The function of the bicuspid aortic valve is monitored with echocardiography, and the state of the heart itself is followed by regular electrocardiograms.

It should be noted that children with aortic stenosis may not be able to engage in vigorous physical activity without the risk of cardiac arrest and should consult with their physician. In addition, all people with bicuspid aortic valve should receive antibiotics prior to any dental procedure or surgery; these procedures may allow bacteria to enter the bloodstream and could result in endocarditis if antibiotics are not given beforehand.

Drugs

Patients with endocarditis need to be hospitalized and treated with high doses of antibiotics given through a vein for several weeks. Damage done to the valve by the bacteria may make it necessary for a valve replacement procedure to be performed after the patient has recovered from the infection.

Prevention

Bicuspid aortic valves run in some families and the condition cannot be prevented.

Prognosis

Most people born with bicuspid aortic valve experience no symptoms or complications, and their lives do not differ from someone born with a normal aortic valve. In patients who do experience complications and require valve replacement, risks of the operation generally depend on age, general health, specific medical conditions, and heart function. It is better to perform the operation before any of the advanced symptoms (shortness of breath, chest pain, fainting spells) develop; in patients without advanced symptoms, the risk of a bad outcome of surgery is only 4%. If a person with advanced symptoms chooses not to undergo surgery, the risk of death within three years is more than 50%. In general, valve replacement greatly reduces the amount and severity of symptoms and allows patients to return to their normal daily activities without discomfort after they recover from the surgery.

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- American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) AHA-USA-1, <http://www.heart.org/HEARTORG>
- Bicuspid Aortic Foundation, 30100 Town Center Drive, Suite O-299, Laguna Niguel, CA 92677, (949) 371-9223, contactus@bicuspidfoundation.com, <http://bicuspidfoundation.com>

Oren Traub, MD, PhD

Biotinidase deficiency

Definition

Biotinidase deficiency is a rare inherited defect in the body's ability to use dietary biotin, one of the B vitamins. The disease is also known as juvenile or late-onset multiple carboxylase deficiency. The milder form of this disorder, partial biotinidase deficiency, if left untreated, may cause muscle weakness (hypotonia), hair loss (alopecia), and skin rashes. The most severe form can cause additional symptoms including fungal infections, breathing problems, vision and hearing loss, impaired movement and balance (ataxia), and developmental delays in children. Symptoms may be improved or prevented by appropriate treatment.

Description

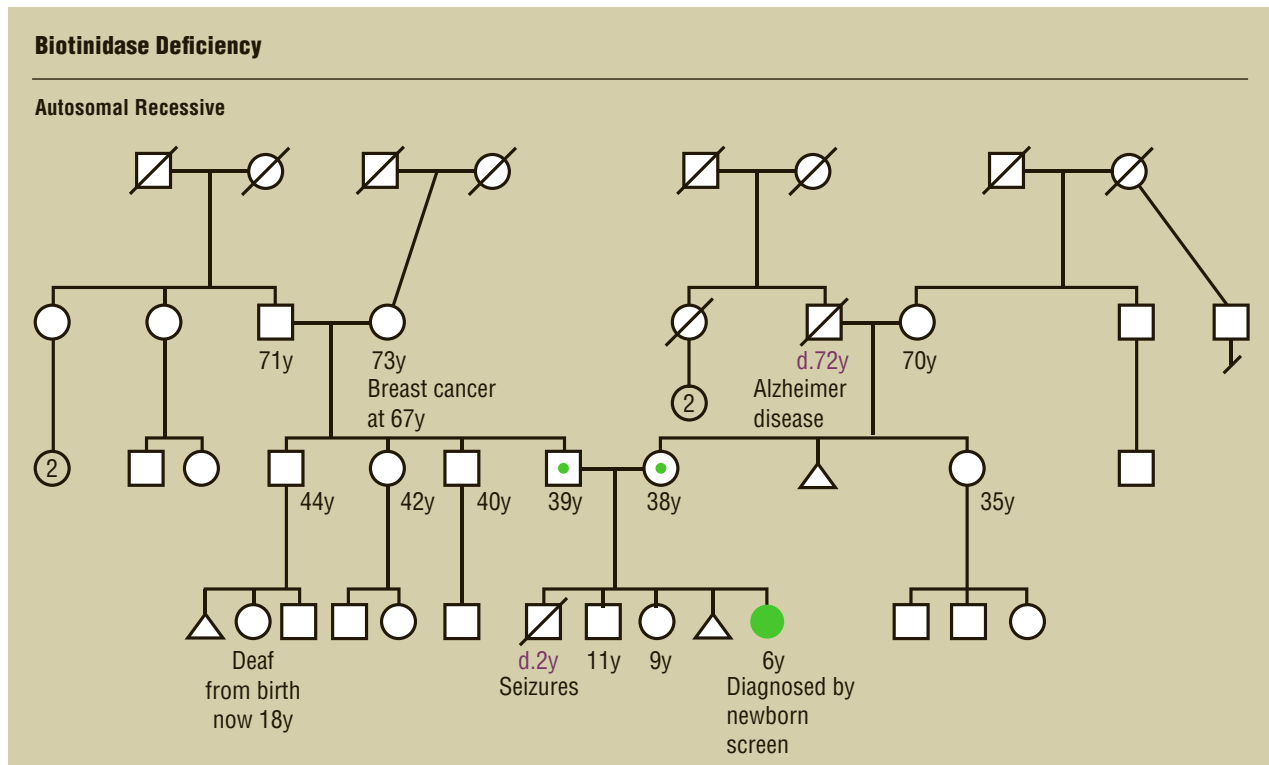
Biotin is essential as a co-factor (co-enzyme) for the reactions of four enzymes called carboxylases. These enzymes, in turn, play important roles in the metabolism of sugars, fats, and proteins within the human body. Another key enzyme, biotinidase, recycles biotin from these reactions so it can be used again. A defect in the biotinidase gene results in decreased amounts of normal enzyme, and prevents the reuse of biotin. The decreased

level of biotin leads to a disruption of the function of the four carboxylases that depend on biotin and results in a variety of abnormalities of the nervous system and skin. Since symptoms usually do not appear immediately at birth, biotinidase deficiency is also referred to as late-onset or juvenile multiple carboxylase deficiency. A related disorder, early-onset or neonatal multiple carboxylase deficiency, is caused by the lack of a different enzyme, holocarboxylase synthetase. As the name suggests, this deficiency results in symptoms in the newborn period.

Genetic profile

Inheritance pattern

Biotinidase deficiency is an autosomal recessive disorder affecting both males and females. It is caused by mutations in the *BTBD* gene, which is responsible for production of the enzyme biotinidase. In individuals with this disorder, both copies of the *BTBD* gene are defective. Both parents of an affected child have one abnormal copy of the gene but usually do not show symptoms because they also have one normal copy. The normal copy provides approximately 50% of the usual enzyme activity, a level adequate for the body's needs. Individuals with one abnormal copy of the gene and 50% enzyme activity are



Biotinidase deficiency: pedigree analysis chart (Gale)

said to be carriers or heterozygotes. As is typical of autosomal recessive inheritance, their risk for having another child with the disorder is 25% in each subsequent pregnancy.

Gene location

The *BDT* gene for biotinidase production is located on the short arm of chromosome 3 (3p25). More than 150 different mutations in this gene have been identified in individuals with biotinidase deficiency. Most *BDT* gene mutations cause profound biotinidase deficiency. This severe form of the disorder results when the activity of biotinidase is reduced to less than 10% of normal. The fact that there are many different types of mutations helps explain why symptoms are variable from one individual to another. However, the presence of variability even within a family suggests there may be other, as yet unknown, factors that affect the severity of the disease.

Demographics

Individuals with biotinidase deficiency have been described in various ethnic groups worldwide. In the general population, the incidence of the disease is estimated at about 1 in 60,000 individuals; 1 in every 123 individuals is a carrier.

Signs and symptoms

The onset of symptoms is typically between three and six months of age but varies widely from one week to several years. The most common clinical features are hair loss (alopecia), skin rash (dermatitis), seizures (convulsions), decreased muscle tone (hypotonia), difficulty walking (ataxia), breathing problems, redness of the eyes (conjunctivitis), hearing and vision loss, and developmental delay. Children with biotinidase deficiency are prone to fungal and bacterial infections, suggesting that the immune system is also affected. Symptoms are highly variable among affected individuals, even within a single family.

Biotinidase deficiency is classified as either partial or profound. If there is at least 10% enzyme activity, the deficiency is considered partial and is usually associated with minimal to mild symptoms. Profound biotinidase deficiency, defined as less than 10% of normal activity, is characterized by many of the symptoms mentioned above, and can result in coma and death if left untreated.

Diagnosis

Children with profound biotinidase deficiency may show general signs such as vomiting, seizures, and low muscle tone, all of which can be associated with a number of different disorders. Diagnosis can be difficult because

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Co-enzyme—A small molecule such as a vitamin that works together with an enzyme to direct a biochemical reaction within the body.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Gene—A building block of inheritance containing the instructions for the production of a particular protein and consisting of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Immune system—A major system of the body that produces specialized cells and substances that interact with and destroy foreign antigens that invade the body.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual and can be transmitted to offspring. The change may manifest as a disease.

of the many different enzyme deficiencies (inborn errors of metabolism) with similar symptoms and test results. For example, abnormally high amounts of certain acidic products in the blood and urine can be typical of a number of different metabolic disorders including biotinidase deficiency. Accurate diagnosis is made by measuring the activity of the enzyme in blood or skin cells. A number of states and countries test for this disorder at birth as part of a comprehensive newborn screening program. Infants whose tests indicate they have biotinidase deficiency can be started on treatment before symptoms appear. With regular treatment these infants usually remain free of any symptoms.

QUESTIONS TO ASK YOUR DOCTOR

- What is biotinidase? How is it involved in my child's biotinidase deficiency condition?
- Our first child was born with biotinidase deficiency disorder. What is the probability that later children may have the same condition?
- Where can we get more detailed information about the genetic basis of this disorder?
- I understand that biotin supplementation may reverse many early symptoms of biotinidase deficiency disorder. Which symptoms are affected by this treatment, and which are not?

Carrier testing

Most carriers can be detected by measuring biotinidase activity in their blood. Fifty percent of normal enzyme activity is characteristic of carriers. Specific DNA tests can usually detect the particular gene mutation in any affected individual or carrier.

Prenatal diagnosis

If a couple has had one child with biotinidase deficiency, they can be offered prenatal testing in future pregnancies. Prenatal testing is accomplished by measuring biotinidase activity in amniotic fluid cells obtained by amniocentesis around the 16th week of pregnancy. Alternately, if specific gene mutations have been identified in the parents, fetal DNA from amniotic fluid cells can be studied to test for these same mutations in the fetus. Carrier couples who are considering prenatal diagnosis should discuss the risks and benefits of this type of testing with a geneticist or genetic counselor.

Treatment and management

Treatment of the profound form of biotinidase deficiency consists of giving large doses of biotin orally. Partial deficiencies are usually treated with lower doses. The biotin must be in a free form; that is, not attached to other molecules, as would be the case with the biotin found in food. Properly treated, biotinidase deficiency is not a life-threatening condition. Still, biotin treatment must continue throughout life. No treatment is needed before birth because the developing fetus is provided with sufficient free biotin from the mother.

Prognosis

Daily treatment with free biotin usually results in rapid improvement of the skin condition, hair regrowth, and a lessening or cessation of seizure activity. Many children whose development has been affected by biotinidase deficiency have shown some improvement after treatment. Hearing and vision losses are less reversible. Children who are diagnosed at birth through newborn screening programs rarely develop symptoms if they are started on biotin replacement therapy immediately.

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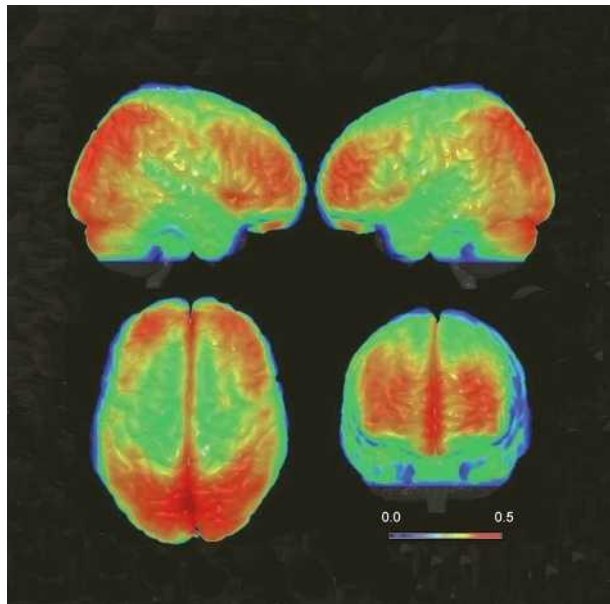
Bipolar disorder

Definition

Bipolar disorder is a psychiatric disorder characterized by severe and unusual changes in energy level, mood, and interactions with others. The mood swings associated with bipolar disorder are unpredictable, ranging from mania to depression. Mania is characterized by elevated or irritable mood; depression is characterized by sadness and loss of interest. Bipolar disorder causes significant impairment in social, occupational, and general functioning.

Description

Bipolar disorder is characterized by extreme fluctuations in mood and energy levels, which alternate over long periods of time. These episodes, appearing in cycles



Composite image of 58 MRI brain scans of individuals diagnosed with bipolar disorder. (*Science Source*)

throughout life, are referred to as mania and depression. Between episodes, approximately two-thirds of bipolar patients are free of symptoms, with the remainder experiencing residual symptoms. A small percentage of patients experience chronic incessant symptoms despite treatment.

Bipolar disorder type I is the classic form of the illness involving recurrent cycles of extreme manic and depressive episodes. Type II bipolar disorder patients never develop severe mania. Rather, they experience milder episodes called hypomania that alternate with depression. A sub type called bipolar disorder mixed features is used to describe people who have symptoms of the disorder that do not clearly meet criteria for type I or type II. People with the mixed-features type often have hypomanic and depressive symptoms at the same time. A mild form of the disorder called cyclothymic disorder also involves symptoms that do not meet the criteria for types I or II, yet last for at least two years. A severe type, called rapid-cycling bipolar disorder, involves four or more episodes of illness within a 12-month period. Multiple episodes may occur within one week or day. Rapid cycling tends to occur later in the course of illness and is more common in women.

Manic episodes are commonly associated with irritability, decreased need for sleep, euphoria (an exaggerated perception of feeling good), social extroversion (excessive friendliness), and grandiosity (feeling more important than one truly is). Depressive episodes are commonly associated with fatigue, impaired concentration and

judgment, and altered sleep and appetite patterns. The depressive cycle can further progress to feelings of excessive shame and guilt, leading to suicidal thoughts. Bipolar disorder is a major affective disorder.

Genetic profile

There is no single gene or environmental factor that causes bipolar disorder. Like other mental illnesses, multiple factors together may contribute. Still, there is a strong tendency for bipolar disorder to run in families. The Child and Adolescent Bipolar Foundation (CABF) reports that the risk for a child of one bipolar parent to develop the disorder is 15% to 30%. If both parents have bipolar disorder, the risk for each child increases to 50% to 75%. The risk in siblings and fraternal twins is 15% to 25%. The risk in identical twins is approximately 70%. Research in identical twins indicates that genes and other factors play roles in developing bipolar disorder.

For the most part, studies show that certain genes can make a person more susceptible to a psychiatric disorder such as bipolar disorder. There appears to be a potential genetic correlation between bipolar disorder and mutations in specific regions of chromosomes 13, 18, and 21. The building blocks of genes, called nucleotides, are normally arranged in a specific order and quantity. If they are repeated in a redundant fashion, a genetic abnormality often results. Some evidence exists for a special type of nucleotide sequence (CAG/CTG repeats) in patients with type II bipolar disorder on chromosome 18. However, not all bipolar patients have this mutation, and the presence of this sequence does not worsen the disorder or change the age of onset.

Although as of 2021, no genes have been found that definitely cause bipolar disorder, many gene mutations have been identified that contribute to bipolar disorder. Among these candidate genes are: *G72/DAOA*, *DISC1*, and *NRG1*, which also have been associated with risk for schizophrenia. There are other candidate genes for bipolar disorder:

- *TPH2* also has been associated with major depressive disorder and major affective disorder 1.
- The *BDNF* gene encodes a protein related to nerve growth factors in the brain.
- The *5-HTT* gene encodes a protein involved in the transport of the neurotransmitter serotonin from synapses to presynaptic neurons.
- *DAT1* mediates reuptake of dopamine from the synapse and has been associated with bipolar disorder and ADHD.

In 2021, researchers at the National Institute of Mental Health (NIMH is one of the National Institutes of Health) explored how major mental disorders such as

bipolar disorder, schizophrenia, and major depressive disorder share common genetic traits but produce different symptoms and presentation in each affected individual. The researchers looked for answers in the brain's transcriptome, the transcripts of instructions for creating proteins to build and maintain cells. When they compared study subjects with mental disorders to those without mental disorders, they found differences in how the transcripts were expressed in subjects with and without different disorders. Parts of a gene's instructions may be included or omitted during the transcription process. The researchers found that a common genetic variant that regulates this inclusion and exclusion process, called splicing quantitative trait loci (sQTLs), may play a key role in the inherited risk for each disorder.

Demographics

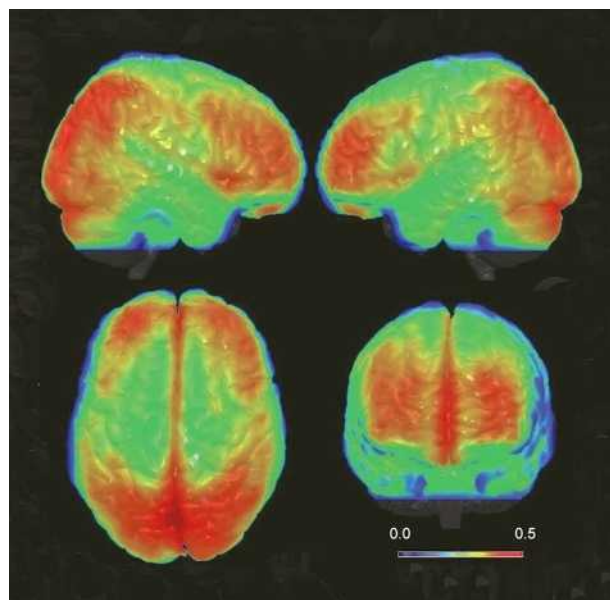
According to the National Institutes of Mental Health (NIMH), approximately 2.8% of the United States adult population has bipolar disorder. It is estimated that more than 5 million adult Americans are affected. Type I is more common than type II. Approximately 25% to 50% of individuals with this type of disorder attempt suicide, with 11% actually committing suicide. Bipolar type I occurs equally in both sexes, but type II and rapid-cycling bipolar disorder are more common in women than in men. Women may also be at increased risk of developing subsequent episodes in the immediate time period after giving birth. In regard to race, bipolar disorder is thought to be under- or misdiagnosed in African Americans as of 2021. Bipolar disorder runs in families, with the rate of disease in identical twins being higher than that in fraternal twins. The age of onset varies greatly. The age range of onset may be in early childhood or up to 50 years of age, with a mean of 25 years. Some patients who have been previously diagnosed with recurrent major depression may have bipolar disorder yet not develop a manic episode until 50 years of age. However, for most patients, mania onset after 50 years of age is due to other medical disorders such as cerebrovascular disease.

Signs and symptoms

Bipolar disorder causes recurrent dramatic mood swings that range from manic highs to depressive lows. There are often periods of normal mood in between episodes of mania and depression. Severe changes in energy and behavior accompany the swings in mood.

Manic episode symptoms include:

- increased energy, activity, and restlessness
- excessively high, euphoric mood
- extreme irritability and reactivity
- racing thoughts and fast speech that jump from one topic to another (known as "flight of ideas")



3D MRI images of the brain of a person with bipolar disorder.
(Science Source)

- distractibility due to unimportant events and the inability to concentrate
- reduced perceived need for sleep
- unrealistic beliefs in one's abilities, powers, or importance
- poor judgment and impulsive behaviors
- increased sexual drive
- provocative, intrusive, or aggressive behavior
- denial that anything is wrong

Depressive episode symptoms include:

- persistent sad, anxious, or empty mood
- feelings of irritability, hopelessness, or negative mood
- feelings of guilt, worthlessness, or helplessness
- inability to take pleasure in activities
- fatigue
- inability to concentrate and poor judgment
- extreme sleep patterns
- extreme appetite changes that result in weight change
- chronic pain or physical discomfort in the absence of physical illness or injury
- thoughts of, and/or attempts at, suicide

Some people with type II bipolar disorder have depressive episodes concurrent with mood reactivity (mood improves with positive event) and can switch from depression to hypomania. Hypomania is characterized as a mild or moderate level of mania. Because hypomania is less severe, it may be associated with increased

KEY TERMS

Neuroprotective—Conveying some form of protection from injury to the nervous system.

Nucleotides—Building blocks of genes arranged in a specific order and quantity.

functioning and enhanced productivity. However, hypomania is not a normal state of mind. Without proper treatment, it may eventually progress into severe mania or switch into depression. Severe episodes of mania or depression may also include symptoms of psychosis. Psychotic symptoms include visual or auditory hallucinations and delusions. Psychotic symptoms in bipolar disorder tend to reflect the current extreme mood episode. During mania, psychotic delusions may include grandiosity, such as believing one has special powers of flight or extreme financial wealth. During depressive episodes, delusions may include paranoid fears of being poisoned or the belief that one has committed a terrible crime. Because of these psychotic symptoms, bipolar disorder is sometimes mistaken for schizophrenia.

Some people who have bipolar disorder have a mixed state of symptoms. A mixed bipolar state is characterized by symptoms of agitation, sleeplessness, appetite changes, psychosis, and suicidal tendencies. A depressed and hopeless mood may occur in conjunction with extreme energy. Signs of bipolar disorder may also be demonstrated outside of mental illness symptoms in behaviors such as alcohol or drug abuse, poor work performance, strained interpersonal relationships, or sexual promiscuity. Symptoms of bipolar disorder with postpartum onset usually occur within four weeks after childbirth. Bipolar disorder with a seasonal pattern displays symptoms related to seasonal change and latitude. The prevalence of the season-specific bipolar symptoms increases with higher latitudes and winter months.

Children and young adolescents who have bipolar disorder tend to have episodes that are less clearly defined than adults with the disorder. Young people often experience very fast swings (rapid cycle) between mania and depression within the same day. Children in a manic episode are more likely to be irritable and destructive than elated. Children and young adolescents are also more prone to mixed symptoms. Bipolar disorder in children and adolescents can be difficult to distinguish from other problems associated with this age group. Symptoms of irritability and aggressiveness may indicate bipolar disorder or may be symptoms of attention-deficit/hyperactivity

disorder, conduct disorder, oppositional defiant disorder, other types of mental disorders, or drug abuse.

Diagnosis

Bipolar disorder is often difficult to diagnose. As with other mental illnesses, it cannot yet be identified through simple laboratory tests. A diagnosis of bipolar disorder is made on the basis of symptoms, course of illness, and family history. The diagnostic criteria for bipolar disorder are described in the *Diagnostic and Statistical Manual for Mental Disorders*, fifth edition (DSM-5). A manic or hypomanic episode is diagnosed when elevated mood or energy, including three or more associated symptoms, lasts for one week or longer. A depressive episode is diagnosed when five or more of the associated symptoms last two weeks or longer. For mixed-features bipolar disorder, the criteria must be met for manic and depressive episodes at the same time. A mental status examination during an episode reveals obvious symptoms associated with bipolar disorder.

Bipolar disorder should be distinguished from major depressive disorder. Close friends, family members, and roommates are often very helpful in assisting the clinician to make the correct diagnosis. Individuals who exhibit bipolar disorder depressive episodes often present with signs of eating more (hyperphagia), sleeping more (hypersomnia), having very low energy levels, being overweight, and experiencing deteriorating mood during evening hours. The person with bipolar disorder also tends to deny or minimize obvious signs of illness. Contrarily, people with major depression usually have anxiety, sleeping difficulty, loss of appetite, and loss of weight. They tend to feel worse during morning hours but improve as the day progresses.

Suicide is the major complication of bipolar disorder, and its occurrence is related to the duration of the depressive episode. The longer the depressive episode lasts, the higher the risk of suicide. Alcoholics and patients with other chronic medical diseases are particularly prone to planning and implementing suicide attempts.

The four main groups who are likely to carry out a suicide attempt include the following:

- Individuals who are overwhelmed by life problems. Suicide attempts in this group tend to be related to aggression and impulsive behaviors, not significant depressive episodes.
- Individuals who are attempting to control others.
- Individuals who are chronically ill with another medical condition or disease.
- Individuals with other severe types of mental illness such as psychosis, delusions, or paranoia.

Treatment and management

Most individuals with bipolar disorder can achieve substantial stabilization of mood swings and related symptoms with proper treatment. Treatment of bipolar disorder is achieved through medication and psychosocial interventions. Medications for bipolar disorder are prescribed by psychiatrists, physicians with advanced training and expertise in the diagnosis and treatment of mental disorders. Primary care physicians may also prescribe medications used to treat bipolar disorder, but it is recommended that bipolar patients see a psychiatrist for treatment.

Medications

Mood-stabilizing medications may be used for long-term maintenance and preventive treatment of bipolar disorder episodes. In the acute phase, the choice of medication for bipolar disorder depends on the stage or type of current episode. The drugs used to treat an acute manic episode are primarily the antipsychotics and benzodiazepines (lorazepam, clonazepam). In the presence of psychotic symptoms, atypical antipsychotics may be used to treat the psychotic symptoms and acute mania. For depressive episodes, antidepressants may be used. These may be added temporarily to treat episodes of mania or depression that break through despite mood stabilizer treatment.

Mood stabilizers have an effect that decreases the extremes of manic and depressive episodes. Lithium was the first mood stabilizer approved by the Food and Drug Administration (FDA) for the treatment of mania and the prevention of both manic and depressive episodes. Lithium carbonate is a first-line medication used in the long-term preventive treatment of extreme mood episodes in bipolar disorder. Lithium carbonate is considered to play a neuroprotective role in brain function. The beneficial effects of lithium carbonate usually appear one or two weeks after administration of oral doses. Lithium treatment has a high response rate, with 70% to 80% of patients with acute manic attacks showing an improvement of symptoms. However, it has many side effects, including gastrointestinal discomfort, diarrhea, baldness, skin eruptions, and fluid retention. Lithium is primarily useful as a prophylactic (preventive) medication for future attacks.

Multiple anticonvulsant medications, such as valproate (Depakote), carbamazepine (Tegretol), and lamotrigine (Lamictal) also act as mood stabilizers. However, not all anticonvulsant medications have been FDA-approved for this use. Valproic acid is a second-line medication intended for patients who respond poorly to lithium or cannot tolerate the side effects. Valproic acid has

QUESTIONS TO ASK YOUR DOCTOR

- What is the basis of your diagnosis of bipolar disorder for my child?
- Are there other conditions with which this disorder may be confused?
- How do you know it is not one of the other similar conditions?
- What medications are available for the treatment of bipolar disorder?
- What side effects should we expect with each medication?
- Do you recommend psychological counseling along with medication in treatment of our child's bipolar disorder?

proven effective in treating and preventing mania, but is especially useful in treating rapid-cycling bipolar disorder. It can be used alone or in combination with lithium. For treatment of depressive bipolar episodes, mood stabilizers are preferred over antidepressants, because antidepressants may cause a switch into a manic episode or aggravate irritability in mixed-symptom mania. Gabapentin (Neurontin) is not a mood stabilizer, but it may have antidepressant and anti-anxiety effects.

Psychosocial interventions

Cognitive-behavioral therapy helps people who have bipolar disorder learn how to change thoughts and patterns that are harmful into more positive thoughts and behaviors. Psychosocial interventions also include patient education and family-focused therapy. It is important for patients to receive social support and illness-management skills. Family and friends must be aware of the high rates of social dysfunction and marital discord. Involvement in national support groups (e.g., the National Depressive and Manic-Depressive Association) may be helpful.

Psychoeducation usually focuses on all of the following:

- assessing which parameters will have an impact on the outcome of the patient's disease
- communicating the boundaries and requirements of treatment
- undergoing a personal cost-benefit analysis concerning specific treatment directions
- implementing a follow-up program

- implementing future directions that may include adjustment or change interventions

Genetic counseling should be included in family education programs, since the predisposition for this disorder has been recognized to increase among first-degree relatives.

Prognosis

Although the episodes of mania and depression appear in cycles, bipolar disorder is a long-term illness that currently has no cure. The long-term prognosis for bipolar disorder is variable. It is critical that bipolar patients maintain consistent and strict adherence with prescribed medications. Patients taking psychotropic medications must understand the importance of regular dosing as prescribed and the necessity of frequent psychiatric follow-up visits. In comparison to major depression (unipolar), bipolar disorder is usually associated with longer depression, more severe depressive symptoms, more relapses, more incapacitation, and more hospitalization. Some studies have shown that early-onset bipolar disorder is associated with more recurrences but not necessarily worse outcomes. Psychotherapy and education can improve prognosis by providing patients and family members with pertinent information about relapses, non-compliance with prescription medications, and specific adjustments necessary for the welfare of the affected individual.

Many individuals with bipolar disorder can lead productive lives when the illness is effectively treated. However, without treatment, the prognosis is very poor. The natural course of bipolar disorder tends to worsen over time, with increased frequency and severity of the manic and the depressive episodes. In most cases, proper treatment can reduce the frequency and severity of episodes to maintain a good quality of life. Remaining on medications, even during well times, is essential for keeping the disease under control and reducing the risk of recurrent worsening episodes.

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ORGANIZATIONS

- American Psychological Association, 750 First Street NE, Washington, DC 20002-4242, (202) 336-5500, (800) 374-2721, <http://www.apa.org/helpcenter/index.aspx>
- Depression and Bipolar Support Alliance, 55 East Jackson Boulevard, Suite 490, Chicago, IL 60604, (800) 826-3632, (312) 642-7243, <http://www.dbsalliance.org>

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Birt-Hogg-Dubé syndrome

Definition

Birt-Hogg-Dubé syndrome is a rare genetic disorder characterized by numerous skin tumors, lung cysts, pneumothorax, and kidney tumors. It is an autosomal recessive disorder.

Description

Birt-Hogg-Dubé syndrome (BHD) was first described in 1977 by three Canadian researchers who found small papular lesions on the face and neck of 15 of 70 individuals involved in an ongoing research study. The researchers

KEY TERMS

Autosomal dominant—A genetic trait that is expressed when only a single copy of a gene is present.

Dermabrasion—Scraping or sanding the epidermal layer of the skin to remove scars and other marks or wrinkles.

Electrodessication and curettage—A procedure by which a papula is cut out of the skin (curettage) and bleeding controlled with an electric current (electrodessication).

Fibrofolliculomas—Small white or yellow dome-shaped benign growths on hair follicles.

Laser ablation—Removal of a skin papula with a laser beam.

Nephrectomy—Surgical removal of a kidney.

Papula—A small raised area of the skin that lacks visible fluid.

Pneumothorax—Abnormal accumulation of air in the chest cavity outside the lung, often responsible for a collapsed lung.

Prevalence—The number of individuals living with a particular illness within a particular population at any given time. Prevalence is often expressed in terms of number of individuals per 100 or per 1,000 members of the population.

Renal—Related to the kidneys.

Sign—An indication of disease, injury, or other physical problem that can be observed by someone other than the person experiencing these conditions.

Symptom—An indication of disease, injury, or other physical problem reported by the person experiencing these conditions, but not by some outside observer.

found what appeared to be three types of lesions: fibrofolliculomas, trichodiscomas, and acrochordons, the most common of which were fibrofolliculomas—small white or yellow dome-shaped benign growths on hair follicles, which is the only skin finding specific for Birt-Hogg-Dubé syndrome. The lesions are generally found on the head, neck, face, and upper chest. They tend to appear first during a person's 20s or 30s. Over time, they become larger and more numerous.

The initial description of BHD was based on skin findings. Therefore, historically, most people with BHD were identified as a result of their skin findings. However,

individuals have been diagnosed with BHD who have pulmonary involvement and/or renal tumors without the associated skin findings. Almost 90% of individuals with BHD have multiple and bilateral lung cysts and about 25% have had at least one pneumothorax. Similar to lung cysts, there are usually multiple, bilateral renal tumors. The average age at which tumors are first detected in affected BHD patients is 48. Severity of the condition differs significantly among members of a family in which the condition occurs.

Demographics

The prevalence of the disorder is estimated at about 1 in 200,000 individuals and is estimated to be underdiagnosed due to its variable presentation. No racial or gender differences in its occurrence have been discovered.

Signs and symptoms

Birt-Hogg-Dubé syndrome is caused by one or more mutations in the *FLCN* (folliculin) gene, found on chromosome 17. The gene directs the synthesis of the protein called folliculin. This protein's precise function has not been determined, but researchers believe it may be a tumor suppressor; tumor suppressors help control the growth and division of cells.

Classic symptoms of BHD are the appearance of multiple bilateral lung cysts and distinctive papulae on the head, face, neck, and upper chest. Up to 34% of individuals with BHD develop kidney tumors. The most common renal tumors are hybrid oncocytic renal cell carcinoma, oncocytoma, chromophobe renal cell carcinoma, and clear cell renal cell carcinoma. Other manifestations include a tendency to have spontaneous pneumothorax, oral papules, parotid oncocytomas, and possibly thyroid and colon cancer.

Diagnosis

CAT scans are used to detect the presence of cysts in the lungs and renal tumors. Genetic testing for mutations in the *FLCN* gene is indicated when there are at least five distinctive papulae characteristic of the syndrome.

The five characteristics include:

- histological confirmation that at least one papula is a fibrofolliculoma
- facial papules histologically confirmed to be angiofibroma when the patient does not have tuberous sclerosis complex or multiple endocrine neoplasia type 1
- multiple and bilateral renal tumors of specific pathology
- a single renal tumor of associated pathology and a family history of renal tumors

QUESTIONS TO ASK YOUR DOCTOR

- How do you assess the severity of a case of Birt-Hogg-Dubé syndrome?
 - What treatments are available for the type of BHD that I have?
 - What tests can you perform to determine the effects of BHD on internal organs?
 - What are the undesirable side effects of cosmetic treatments for the papulae associated with BHD?
 - Has there been any breakthrough in research on possible treatments for BHD?
- a family history of primary spontaneous pneumothorax without a history of smoking or COPD.

Treatment and management

There is no definitive medical treatment for the dermatological manifestations of BHD. A number of standard procedures, such as surgical removal of fibrofolliculomas, laser ablation, dermabrasion, electrodestruction and curettage are temporarily successful. However, lesions tend to recur. Of significantly greater concern is the possibility of lung cysts and tumors. Whenever possible, surgical removal of individual cysts and tumors is preferred. Still, in more serious cases, complete nephrectomy may be necessary. Pneumothorax is treated by standard procedures used for the problem, involving removal of air in the chest cavity in order to allow a lung to reinflate.

Prevention

There is no way to prevent contracting BHD, but some steps can be taken to reduce the severity and most serious consequences of the disorder. For example, patients should not smoke, since smoking is a risk factor for diseases of the lungs and kidneys. Additionally, a person with BHD should avoid situations in which he or she is exposed to unusually high atmospheric pressures, since they can increase the probability of pneumothorax.

Prognosis

Visible manifestations of BHD are cosmetically undesirable, but not life-threatening. The greatest long-term health issues are related to cysts and tumors associated with the lungs and kidney. Prognosis for these problems depends on their severity and the rate at which they develop.

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ORGANIZATIONS

- BHD Foundation, c/o the Myrovlytis Trust, 26 Cadogan Square, London SW1X 0JP, United Kingdom, +44 (0)20 8050 2091, contact@bhdsyndrome.org, <https://bhdsyndrome.org/>
- European Organization for Rare Diseases, 96, rue Didot, Paris, France 75014, +33 (1) 56.53.52.10, +33 (1) 56.53.52.15, eurordis@eurordis.org, <http://www.eurordis.org>.
- Genetic and Rare Diseases Information Center (GARD), PO Box 8126, Gaithersburg, MD 20898-8126, (301) 519-3194, (888) 205-2311, gardinfo@nih.gov, <http://www.genome.gov/10000409>.

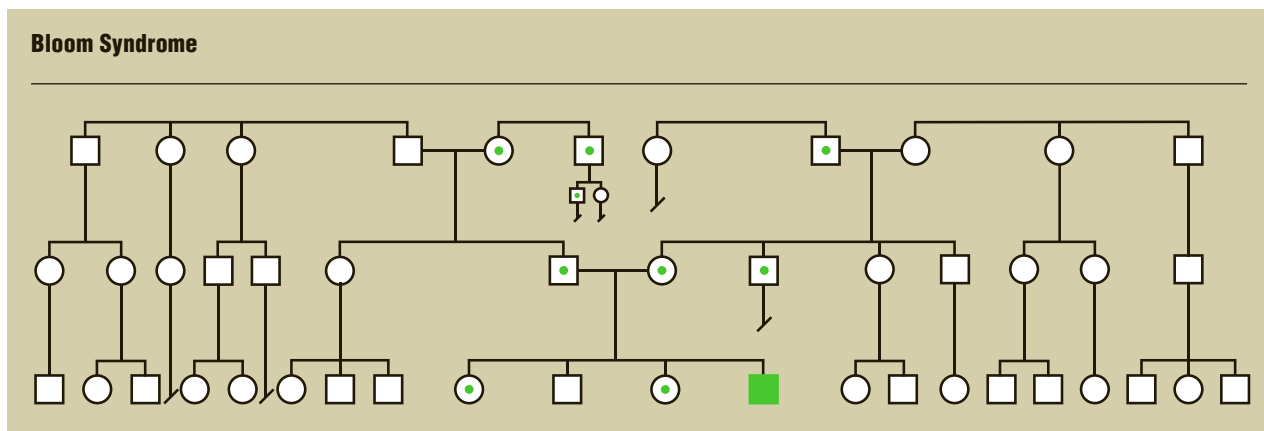
David E. Newton, Ed.D
and Cristi L. Radford, MS, CGC

Bloch-Sulzberger syndrome see **Incontinentia pigmenti**

Bloom syndrome

Definition

Bloom syndrome is a rare inherited genetic disorder characterized by short stature, a predisposition to cancer, a compromised immune system, and other medical problems. It is caused by changes (mutations) in the *BLM* gene that is involved in copying and repairing DNA. These changes cause chromosome instability and breakage. Bloom syndrome is also known as congenital telangiectatic erythema.



Bloom syndrome: pedigree analysis chart (Gale)

Description

Bloom syndrome was first described by Dr. David Bloom in 1954, in patients with short stature (dwarfism) and telangiectatic erythema (red dilated superficial capillaries on the face). These signs, along with sun sensitivity and immune-system deficiency, are the distinguishing characteristics of Bloom syndrome. Genomic instability, which is manifested by the excessive exchange of genetic material between chromosomes, results in a very high incidence of cancer. Immunodeficiency also predisposes Bloom syndrome patients to cancer, as well as to various infections.

DNA is the molecule that encodes the genetic information and determines the structure, function, and behavior of cells. The *BLM* gene, whose official name is “Bloom syndrome, RecQ helicase-like,” produces the BLM protein. This protein is a member of the RecQ helicase family of proteins that bind to DNA and temporarily unwind double-stranded DNA. This creates single-stranded DNA templates for replication (copying) before cell division with the purpose of repairing damaged DNA and transcribing DNA into RNA to produce protein. The BLM protein also may function in a post-replication recombination process that resolves errors generated during replication. In preparation for cell division, the DNA of each chromosome is copied (replicated) to form two identical sister chromatids. Small sections of DNA can be exchanged at this time, in a process called sister-chromatid exchange (SCE). BLM normally helps prevent SCE in order to maintain genome stability during replication. BLM also may help restart the process of replication when it stalls.

Mutations (changes) in the DNA sequence of the *BLM* gene prevent it from making BLM protein. Without normal BLM protein, DNA replication restarts through SCE, which decreases chromosome stability. In Bloom syndrome, the frequency of SCE is increased about 10-fold. As a result,

the chromosomes of people with Bloom syndrome accumulate gaps, breaks, and structural rearrangements. These interfere with normal cell functioning, leading to the medical problems characteristic of Bloom syndrome. These chromosomal problems also greatly increase the risk of cancer. Furthermore, copying mistakes or damage to DNA are less likely to be repaired, leading to additional mutations. The absence of normal BLM protein may also increase the rate of cellular death, accounting for the slow growth observed in people with Bloom syndrome.

Genetic profile

Bloom syndrome is inherited in an autosomal recessive manner. “Autosomal” means that the *BLM* gene is not located in the X or Y sex chromosomes, so it is inherited equally by males and females. “Recessive” means that Bloom syndrome only develops in the presence of two defective *BLM* genes, one inherited from the mother and one from the father. The parents are carriers of the affected gene, but typically do not have symptoms of Bloom syndrome. However, parents with a single defective *BLM* gene have a 50% risk of passing that gene on to each of their offspring. If both parents carry the defective gene, each of their children has a 25% chance of having the disorder. The *BLM* gene is located on the long (q) arm of chromosome 15, within band 26.1 (15q26.1).

More than 70 different mutations that cause Bloom syndrome have been identified in *BLM* genes. Almost all cases of Bloom syndrome among people of Ashkenazi (Central and Eastern European) Jewish ancestry have the mutation *blmAsh*. This mutation replaces six DNA nucleotides (building blocks) with seven different nucleotides at position 2281 in the gene. *blmAsh* is referred to as 2281delta6ins7, where “delta” means deletion and “ins” means insertion. This mutation causes a short, nonfunctional BLM protein. Various other known *BLM* gene

KEY TERMS

Autosomal recessive—A gene, such as the Bloom syndrome gene, that is located on a chromosome other than the X or Y sex chromosomes and encodes a protein that is not expressed unless the second copy of the same gene inherited from the other parent is also mutated or recessive.

BLM—The gene and protein that when mutated cause Bloom syndrome.

blmAsh—The mutation in the BLM gene, known as 2281delta6ins7, that causes Bloom syndrome in people of Ashkenazi Jewish ancestry.

Carcinoma—Any cancer that arises in the epithelium, the tissue that lines the external and internal organs of the body.

Carrier—Having one abnormal gene for a trait, such as Bloom syndrome, and one normal gene for the trait (a heterozygote), without signs or symptoms of the disorder but the possibility of passing the abnormal gene on to offspring.

Chromatid—Each of the two strands formed by replication (copying) of a chromosome; chromatids are held together by the centromere, which subsequently divides and separates the two chromatids to form two new chromosomes.

Fecal blood testing—Examination of the stool for evidence of blood, which may be a sign of a digestive-tract cancer.

Helicase—An enzyme, such as BLM, that unwinds and separates DNA during replication (chromosome copying prior to cell division).

Leukemia—Cancer caused by overproduction of white blood cells.

Lymphoma—A malignant tumor of the lymphatic tissue.

Sigmoidoscopy—Visual examination of the inside of the rectum and sigmoid colon, using a lighted, flexible tube connected to an eyepiece or video screen for viewing.

Sister-chromatid exchange (SCE)—Exchange of DNA between sister chromatids during DNA replication; excessive SCE can cause the gaps, breaks, and structural rearrangements of chromosomes that are diagnostic of Bloom syndrome.

Telangiectatic erythema—A localized collection of dilated blood capillaries near the surface of the skin; congenital telangiectatic erythema is another name for Bloom syndrome.

mutations change a single amino acid in the protein or produce no BLM protein.

Demographics

Bloom syndrome is very rare, affecting fewer than one in six million people in the general population. However, in the Ashkenazi Jewish population, approximately 1 in 50,000 are affected with Bloom syndrome, with approximately 1 in 100 people carrying a *BLM* gene mutation. These carriers do not appear to have an increased risk for cancer or other symptoms associated with Bloom syndrome. Furthermore, carriers have normal or near-normal genome stability. About one-third of all people with Bloom syndrome are of Ashkenazi Jewish ancestry. However, worldwide, Bloom syndrome may be underdiagnosed or mistaken for another rare disorder.

Signs and symptoms

Almost all people with Bloom syndrome are very sensitive to sunlight and are of small stature. Newborns are generally of low birth weight. The average height for adult males is 58.1 in. (147.5 cm) and for females is 54.6 in. (138.6 cm). The head and brain are often small. The head may be dolichocephalic—relatively long and narrow. Infants and children have very little body fat and remain thin as adults.

Both benign (noncancerous) and malignant (cancerous) tumors arise at an early age and with great frequency in a variety of cell types and locations. Malignant tumors affect 37% of patients between ages 2 and 46, with a mean age of cancer diagnosis of 24 years. Lymphomas and leukemias are common, usually before age 25. Carcinomas are common as well, usually developing after age 20, most often in the colon, skin, breast, or cervix. Many people develop more than one type of cancer. Radiation treatments and chemotherapy for cancer may lead to further complications because these treatments can further damage fragile chromosomes.

Other common signs and symptoms that vary in severity may include:

- unique facial features like a prominent nose, small lower jaw, and protuberant ears, in addition to a long, narrow face
- a high-pitched, squeaky voice
- repeated respiratory tract and ear infections in infants
- vomiting and diarrhea in infants, possibly leading to a life-threatening loss of body water (dehydration)
- telangiectatic erythema—a reddish “butterfly” rash on the cheeks and nose upon exposure to sunlight; it can vary from a faint blush in the summer to severely

disfiguring, flaming-red lesions and dilated blood vessels

- similar rashes on other parts of the body exposed to sunlight, especially the arms and hands
- patchy skin pigmentation developing during childhood, with some spots of less pigment (hypopigmentation) and some with excessive pigment (hyperpigmentation)
- infertility in most males due to abnormally small testes and the inability to produce sperm
- reduced fertility and early menopause in women
- early-onset type 2 diabetes (at an average age of 25 years)
- increased susceptibility to bacterial infections due to immune-system deficiency
- chronic obstructive pulmonary disease (COPD)
- occasionally, minimal-to-severe intellectual disabilities
- learning disabilities and/or short attention span in individuals with normal intelligence
- a persistent optimistic attitude

Diagnosis

Bloom syndrome may be suspected at birth but is generally confirmed by cytogenetic SCE analysis of the chromosomes from a blood sample. Bloom syndrome is the only known disorder that causes congenital (present at birth) SCE. Analysis for SCE may be performed for any patient with unexplained growth deficiency regardless of whether or not other signs of Bloom syndrome are present. In addition to an approximately 10-fold increase in SCE, unique chromosome structures called quadriradials are usually visible. Although SCE and quadriradials are present in cells from individuals without Bloom syndrome, they occur much less frequently.

Genetic testing can determine the specific BLM mutation. Genetic testing is also used to identify Ashkenazi Jewish carriers of a BLM mutation with an accuracy of up to 99%. In February 2015, the Food and Drug Administration (FDA) ruled that the personal genomics testing company, 23andMe, could market a genetic test for BLM mutations. This was the first disease-predicting genetic test allowed by the FDA after it halted all of 23andMe's health-prediction services in 2013. Genetic counseling and testing is recommended before conception, and prenatal diagnosis is available for couples with previously identified BLM mutations.

Treatment and management

There is no treatment or cure for Bloom syndrome. However, early diagnosis and management can relieve some symptoms and increase life expectancy. For example, babies and young children with Bloom syndrome are often poor eaters, avoiding nutritious food and

QUESTIONS TO ASK YOUR DOCTOR

- Should my partner and I have genetic testing for Bloom syndrome before conceiving a child?
- What information will genetic testing provide?
- Is prenatal testing available for Bloom syndrome?
- What characteristic signs and symptoms are associated with Bloom syndrome?
- What treatments are available for controlling the progression of Bloom syndrome?
- What is the normal life expectancy of a child with Bloom syndrome?

multivitamins that may improve growth. Treatment with growth hormone has generally been ineffective and may further increase cancer risk. Skin lesions can be controlled by avoiding sunlight, wearing a hat, and using sunscreen. Avoidance of sun exposure is especially critical in the first few years of life, since the severity of skin lesions appears to depend on early exposure. Immune-system deficiencies require that infections be treated promptly.

Cancer surveillance is of utmost importance. After the age of 20, annual sigmoidoscopy and fecal blood testing are recommended for colon cancer, as well as Pap smears and mammography for cervical and breast cancers, respectively. Patients should be followed closely by a physician or clinic specializing in Bloom syndrome to detect subtle symptoms of carcinomas. Early surgical removal of tumors provides the best chance for a cure. Removal and storage of bone marrow early in life is sometimes recommended so that the patient's own bone marrow is available for later cancer treatment. Patients should avoid x-rays, chemotherapy drugs, and environmental exposures that may damage their fragile chromosomes.

Prognosis

The mean life expectancy of people with Bloom syndrome is 23 years and the average life expectancy is 27 years. There are no reports of patients surviving past 48 years. About 80% of deaths are caused by cancer. Chronic respiratory infection is the second most common cause of death.

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ORGANIZATIONS

Genetic Disease Foundation, Mount Sinai School of Medicine, One Gustavo L. Levy Place, Box 1497, New York, NY 10029, (212) 659-6704, <http://www.geneticdiseasefoundation.org>

Jewish Genetics Disease Center, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029-6574, (212) 241-6500, <http://icahn.mssm.edu/research/programs/jewish-genetics-disease-center>

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Blue rubber bleb nevus syndrome

Definition

Blue rubber bleb nevus syndrome (BRBNS) is a rare disorder characterized by hemangiomas of the skin and gastrointestinal (GI) tract. Hemangiomas are benign or noncancerous tumors of newly formed blood vessels and skin. This syndrome derives its name from these distinctive rubber-like skin lesions, or blebs. Blebs are nevi (skin anomalies, such as moles) that measure more than 5 millimeters around.

Description

In 1860, G. G. Gascoven first reported the association of cutaneous or skin nevi and intestinal lesions with GI bleeding. William Bean in 1958 first used the term *BRBNS* to describe the rubber-like tumors. Because of his description, BRBNS is sometimes called Bean syndrome. Besides the skin and GI tract, nevi are found on

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Cutaneous—Of, pertaining to, or affecting the skin.

Endoscopy—A slender, tubular optical instrument used as a viewing system for examining an inner part of the body and, with an attached instrument, for biopsy or surgery.

Nevus (plural, nevi)—Any anomaly of the skin present at birth, including moles and various types of birthmarks.

all internal organs and even the brain. Nevi are birthmarks of the skin that are probably hereditary because they are not caused by external factors.

Genetic profile

Mutations in the *TEK* gene on the short arm of chromosome 9 were identified as the cause of BRBNS in 2016. Some cases of BRBNS are familial and support an autosomal dominant form of inheritance, meaning that only one copy of the nonworking gene is required to manifest the condition. An affected parent has a 50% chance of passing the disorder to his or her offspring. However, most cases are sporadic without a familial tendency.

Demographics

Fewer than 180 cases have been reported worldwide. BRBNS affects all races and both sexes and may be present at birth. The effects on life expectancy are unknown because so few cases exist.

Signs and symptoms

The distinctive blue skin blebs are the hallmark of BRBNS and are not cancerous. Composed of skin and large dilated blood vessels, the nevi do not disappear and are found on internal organs such as the stomach, liver, spleen, heart, bone, muscle, bladder, and vulva. They are easily compressible and refill after compression. Occasionally, the nevi are painful. Ranging in size from millimeters to several centimeters, the nevi can number from a few to hundreds. As the patient ages, they can increase in size and number. In rare cases, large lesions can cause skeletal deformities that may lead to amputation.

Nevi are usually present at birth. Sometimes, however, they may not appear until age two or three.

Patients with BRBNS develop an extreme paleness or pallor of the skin. This paleness results because anemia, a low blood count, decreases the amount of oxygen available to the surface skin. Often patients complain of fatigue that results from low iron stores and the anemia.

Chronic or acute bleeding in the GI tract may be detected when blood is present in the stool. Chronic bleeding causes anemia, pallor, fatigue, and low iron stores. Iron supplements will help to increase the blood count. Acute bleeding in the GI tract happens quickly and can rapidly decrease a normal blood count. Immediate blood transfusion or surgery to remove the bleeding nevus can correct this condition.

Diagnosis

The first key to diagnosis of this condition is the appearance of the skin nevi. If they do not have the distinct rubbery texture and blue color and do not refill after they have been compressed, another diagnosis should be considered. Endoscopy is required to examine the GI tract for nevi. If they are present, then the diagnosis is confirmed. However, lack of nevi in the GI tract does not completely rule out BRBNS, since nevi may not develop until adolescence.

During an endoscopy, a viewing instrument attached to a flexible tube is passed through the mouth to the small intestine. The tube can also be inserted through the rectum to the colon. The doctor can then examine the GI tract for nevi.

A patient will require blood tests to assess anemia and iron deficiency as well as a stool test for the presence of blood. Although nevi may be found on the brain, few patients have neurological signs such as seizures or partial paralysis.

Treatment and management

Treatment of BRBNS will depend upon the severity, number, size, and location of the nevi. Skin lesions that are life-threatening can be safely removed by surgery or laser therapy. The severity of bleeding from GI lesions will determine how they are treated. Surgery can remove single lesions; however, the number may be too great to excise them all. Treatment methods that are less invasive than surgery use endoscopy to tie off bleeding nevi.

Patients who have neurological signs should have magnetic resonance imaging (MRI) of the brain to discover the extent of nevi. Seizures can usually be controlled by medications. Physical therapy may improve paralysis.

QUESTIONS TO ASK YOUR DOCTOR

- How did this disorder get its name and what does the name mean?
- Are there signs and symptoms of blue rubber bleb nevus syndrome that clearly distinguish the disorder from other medical conditions?
- What treatments would my child require if he or she were to be born with blue rubber bleb nevus syndrome?
- Can you predict the life expectancy of a child born with this disorder?

Prognosis

Although BRBNS is a chronic progressive disease, it does not appear to be fatal; most patients can expect to have a normal lifespan. If the GI bleeding and anemia are treated, the patient will usually cope well. If a patient expresses concerns about his or her physical appearance, psychological counseling should be considered.

Resources

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ORGANIZATIONS

Nevus Network, The Congenital Nevus Support Group, PO Box 305, West Salem, OH 44287, (419) 853-4525, (405) 377-3403, info@nevusnetwork.org, <http://www.nevusnetwork.org>
Nevus Outreach, 361 Southwest Drive, #353, Jonesboro, AR 72404, (918) 331-0595, <http://www.nevus.org>

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Brachydactyly

Definition

Brachydactyly (BD) refers to shortening of the fingers or toes due to underdevelopment of the bones in the hands or feet.

Description

The word brachydactyly comes from the Greek terms “brachy,” meaning “short,” and “daktylos,” meaning “digit.” This term is used to describe the hands and feet of people who have shortened digits (fingers or toes). The digits themselves may be shorter than normal, or they may appear small because of shortening of the other bones in the hands or feet. This shortening occurs when one or more of the hand or foot bones fail to develop or grow normally.

BD is usually isolated, meaning that it is not associated with any other medical problems. BD may occur along with other physical differences or health problems, often as part of a syndrome.

BD occurs in a variety of patterns, depending upon which hand or foot bones are affected and how severely they are shortened. It is important to know some basic information about the bone structure of the hands and feet in order to understand the various patterns of BD. Beyond the wrist and ankle, each hand and foot contains 19 tube-shaped (tubular) bones in a specific arrangement. For purposes of orientation, the fingers and toes are numbered from one (thumb or great toe) to five (little finger or little toe). When a fist is made, the bones in the hand that extend from the wrist to the knuckles are called metacarpals. There are five metacarpals, one for the thumb (first metacarpal) and each finger. Each thumb and finger contains several bones called phalanges. A single one of these bones is called a phalanx. The phalanges are arranged end to end and are separated by joints. The thumb has two phalanges, and each finger has three phalanges. The phalanges within a particular finger are named according to their location. The phalanges closest to the metacarpals are called the “proximal” phalanges, those in the middle of the fingers are called the “middle” phalanges, and those at the ends of the fingers are called the “distal” or “terminal” phalanges. The thumbs have only proximal and distal phalanges.

The foot bones are very similar to the hand bones. Like the metacarpals, there are five metatarsal bones that extend from the ankle to each of the toes. The bones in the toes are also called phalanges. There are two phalanges in the great toe and three phalanges in each of the other toes.

KEY TERMS

Clinodactyly—An abnormal inward curving of the fingers or toes.

Digit—A finger or toe.

Metacarpal—A hand bone extending from the wrist to a finger or thumb.

Metatarsal—A foot bone extending from the ankle to a toe.

Phalanges (singular, phalanx)—Long bones of the fingers and toes, divided by cartilage around the knuckles.

Symphalangism—Fusion of phalanges at their ends.

Syndactyly—Webbing or fusion between the fingers or toes.

BD can involve any of the phalanges, metacarpals, and metatarsals in many different combinations. The shortening of these bones may range from mild to severe. Sometimes certain bones are completely absent. Shortening of the bones may occur in one, several, or all of the digits. For a particular finger or toe, the entire digit may be short or only a particular phalanx may be underdeveloped. When BD involves the distal phalanges, the fingernails or toenails may be small or absent. A digit may also be of normal length but appear short due to shortening of its corresponding metacarpal or metatarsal bone. Reduced length of a metacarpal bone is often easiest to appreciate when the hand is held in a fist.

BD can also occur with other abnormalities of the hands and feet. When a phalanx is abnormally shaped, the finger or toe may be bent to one side (clinodactyly). Sometimes the digits have webbing between them (syndactyly). The phalanges may also be fused together at their ends (sympchalangism). This makes it difficult to bend a digit at the joint where the phalanges are fused.

BD frequently occurs in characteristic patterns that can be inherited through families. These patterns are classified as particular types of BD, depending upon which bones and which digits of the hands and/or feet are shortened. There are several classification systems used to describe these different types of BD. The system that is used most frequently was developed by Dr. Julia Bell in 1951 and is called the Bell Classification.

There are five main types of BD in the Bell Classification, which are designated A through E. Their major features are as follows:

- In type A, the middle phalanges of one, several, or all of the fingers and/or toes are shortened. This form of BD is

further divided into types A1, A2, and A3. In type A1, the middle phalanges of all digits and the proximal phalanges of the thumbs and great toes are shortened. People with this form of BD generally have hands and feet that appear small with relatively equal shortening of all digits. In type A2, the middle phalanges of the index finger and second toe are shortened and often abnormally shaped. In type A3, the middle phalanx of the fifth finger is shortened and this finger often bends toward the fourth finger. Several other forms of BD type A have also been described.

- In type B, the distal phalanges and nails of the fingers and/or toes are small or absent. The middle phalanges may also be shortened, and the tips of the thumbs and/or great toes may be broad or have a “duplicated” (double) appearance. In this type of BD, the digits typically look as though their tips have been amputated.
- In type C, the middle phalanges of all of the fingers may be shortened, but the fourth finger is least affected and is often the longest finger. The index and middle fingers may be bent toward the fourth finger. The first metacarpal bone can also be short, making the thumb appear small.
- In type D, the distal phalanges of the thumbs and/or great toes are shortened and broad.
- In type E, the metacarpals and/or metatarsals are shortened. The fourth and fifth metacarpals and metatarsals are most commonly shortened, but any of them may be affected.

Genetic profile

Many different genetic signals are required for normal formation of the hand and foot bones. BD is usually caused by abnormalities in these genetic blueprints. Sometimes BD can be caused by exposure to drugs or medications taken during pregnancy. Problems with blood flow to the hands or feet during fetal life may also cause BD.

The types of BD in the Bell Classification are inherited in families from one generation to the next. Their pattern of inheritance is autosomal dominant. This means that they are caused by abnormalities in only one copy of a gene from a particular gene pair. In fact, one form of BD (type A1) was the first human condition that was recognized to have this type of inheritance pattern. Autosomal dominant forms of BD can be inherited by a child of either sex from a parent of either sex. The gene change causing BD may also occur in a particular person for the very first time within a family. Each child born to a person having autosomal dominant BD has a 50% chance of also having BD. However, the degree of hand or foot abnormalities can be very different between people with

QUESTIONS TO ASK YOUR DOCTOR

- How likely is it that my child’s brachydactyly is a symptom of some other disease?
- Will it be necessary to have surgery or some other kind of treatment for my child’s condition?
- How will my child’s brachydactyly affect his or her probable lifespan?
- Should my child have counseling in order to deal more successfully with this medical condition?

the same type of BD, and even among members of the same family.

Until recently, nothing was known about the genes that cause BD. This has changed with the identification of the genes that cause two forms of autosomal dominant BD (types B and C) in the past several years. The gene causing BD type C was the first to be identified in 1997. The name of this gene is the “Cartilage Derived Morphogenetic Protein 1” gene, abbreviated as *CDMP1*. This gene is located on the long arm of chromosome 20 (at location 20q11.2) and provides an important genetic signal to the developing bones of the limbs. Most people with BD type C have abnormalities in one of their two copies of this gene.

The gene causing BD type B was identified in 2000. This gene is called *ROR2* and is located on the long arm of chromosome 9. Like *CDMP1*, *ROR2* also provides an important genetic blueprint for the normal development of bones. BD type B is caused by alterations in one copy of this gene.

One interesting feature of the *CDMP1* and *ROR2* genes is that they can also cause other medical conditions with bone problems that are much more severe than BD. This happens when both copies of either gene are altered in the same person. Another gene associated with autosomal dominant BD is the *HOXD13* gene on chromosome 2, linked to BD types D and E.

Demographics

BD occurs in people of many different racial and ethnic backgrounds. It is difficult to determine the overall frequency of BD in the general population because many people who have BD never seek medical attention for their shortened digits. Types A3 and D are the most common forms of BD, but their frequencies vary widely between groups of people from different backgrounds. For example, type A3 has been found in less than 1% of

Americans, compared to 21% of Japanese people. Because isolated forms of BD are generally inherited as autosomal dominant traits, they should affect males and females in equal numbers. However, several types of BD may be more common in females.

Signs and symptoms

BD is often evident at birth, but it may also develop or become more obvious during childhood. It usually does not cause pain or other physical symptoms. In fact, many people who have BD consider it to be a normal family trait rather than a medical condition. When BD does cause problems, they are usually related to the size, appearance, or function of the hands or feet. The altered appearance of the hands or feet may make persons with BD feel self-conscious. Shortening of the digits may also make it difficult to find comfortable shoes or gloves. In its severe forms, BD may affect a person's ability to grip objects or participate in certain jobs or leisure activities. Hand function may be especially affected when BD is associated with clinodactyly, syndactyly, or symphalangism. When BD is associated with significant deformities of the feet, walking may be difficult or painful.

In some cases, BD occurs in combination with other physical changes or medical problems. For instance, people with autosomal dominant forms of BD are often shorter than expected and may have other alterations of the skeleton besides short digits. Some people with BD type E also have hypertension (high blood pressure). BD may also be present as one finding in a number of different genetic conditions (syndromes).

Diagnosis

The diagnosis of BD is made when a person has shortening of the digits due to lack of normal growth and development of one or more bones in the hands or feet. When the bones are significantly shortened, this is easily noticed in the appearance of the hands and feet. When the shortening is mild, it may only be apparent on x-rays. Some people may not realize that they have BD until told by a physician who has carefully examined their hands and feet.

X-rays of the hands and feet are used to look at the bones in detail. A special analysis of the hand x-rays called a metacarpophalangeal profile is often performed for people with BD. This involves measuring the length of each hand and finger bone. These measurements are then compared to the normal range of sizes for each bone. The metacarpophalangeal profile is used to identify particular patterns of BD. X-rays may also reveal other bone changes that help to pinpoint a specific type of BD or another genetic condition. If a person has short stature or other

bone changes, a series of x-rays of the entire skeleton (skeletal survey) may be recommended.

Since BD is often inherited, detailed information about a person's relatives can be very important in evaluating someone with BD. A geneticist may wish to examine other family members or obtain x-rays of their hands and feet. Because BD can occur in a variety of genetic conditions, a geneticist evaluating someone with BD will usually review his or her medical history and perform a detailed physical examination. The presence of other physical differences or medical problems may indicate that the brachydactyly is part of another condition rather than an isolated finding.

Laboratory tests are usually not helpful in diagnosing BD when it is an isolated finding. Although the genes for BD types B, C, D, and E are known, testing of these genes is not routinely available or usually necessary. If a person with BD has signs or symptoms of another underlying condition, certain laboratory tests may be recommended. These tests may identify other associated medical problems or help to pinpoint a specific diagnosis.

Treatment and management

Many people who have BD are perfectly healthy and do not require any specific treatment for their hands and feet. When use of the hands is impaired, physical therapy or hand exercises may improve grip strength or flexibility. Evaluation by an orthopedist or physical therapist may also be helpful for people who have trouble walking comfortably due to bone changes in the feet. Surgery can be used to lengthen the hand or foot bones in some severe forms of BD. Surgery may also be helpful for people who have significant clinodactyly, syndactyly, or symphalangism. For most people with BD, however, surgery is not needed. If BD is associated with other medical problems, such as hypertension, specific treatments for these problems may be indicated.

Prognosis

Isolated BD generally has an excellent prognosis. When BD is associated with other health problems or is part of another condition, the overall prognosis depends upon the nature of the associated condition.

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ORGANIZATIONS

Genetic Disease Foundation, Mount Sinai School of Medicine, One Gustavo L. Levy Place, Box 1497, New York, NY 10029, <http://www.geneticdiseasefoundation.org>

David B. Everman, MD, CGC

Branchiootorenal (BOR) syndrome

Definition

Branchiootorenal (BOR) syndrome is an autosomal dominant condition characterized by ear abnormalities, hearing loss, cysts in the neck, and kidney problems.

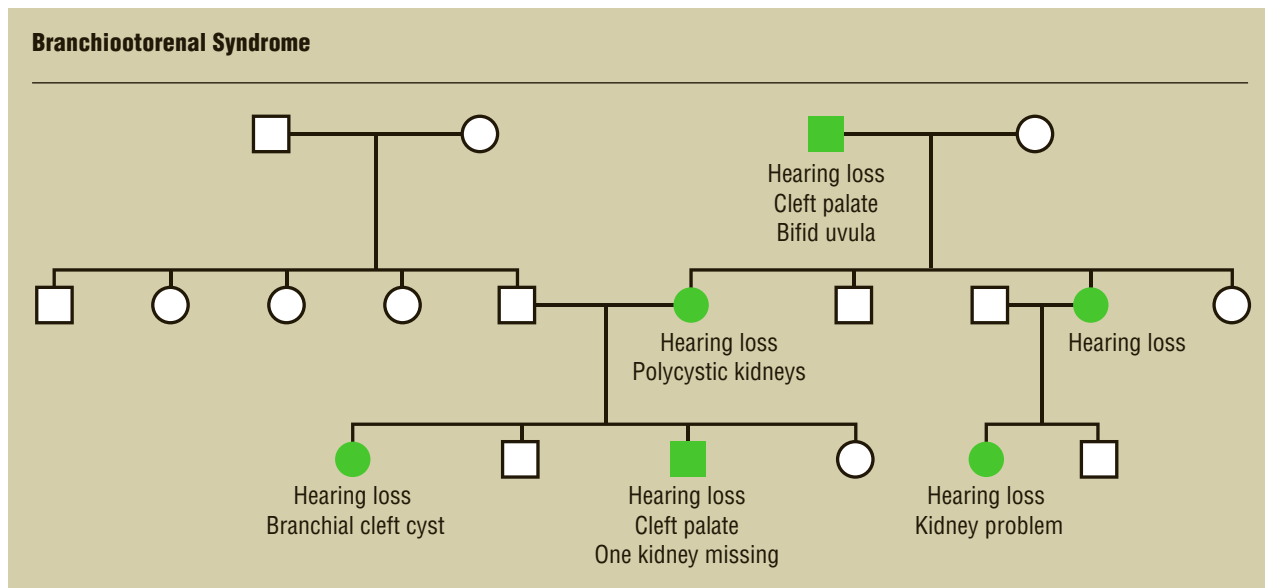
Description

The name branchiootorenal syndrome describes the body systems most commonly affected by this genetic disorder. The term "branchio" refers to the abnormalities of the neck found in individuals with this syndrome. Cysts (lumps or swellings that can be filled with fluid) and fistulas (abnormal passages from the throat to the skin) in the neck occur frequently. The term "oto" refers to the ear disorders associated with the syndrome. For example, the outer ear can be unusual in appearance. Hearing loss is also common. Finally, the term "renal" stands for the kidney problems commonly seen in patients with this condition. These can be very mild or very severe, as can any of the symptoms associated with this disorder.

Dr. M. Melnick first described BOR syndrome in 1975. Another name for BOR syndrome is Melnick-Fraser syndrome. Individuals with BOR syndrome typically have physical differences that are present at birth (congenital). These birth defects are caused by a change (mutation) in a gene.

Genetic profile

Mutations in the *EYA1* gene are found in 40% of those with a clinical diagnosis of BOR syndrome. The *EYA1* gene is located on chromosome 8. Mutations in the *SIX5* gene on chromosome 19 account for about 5% of those with the diagnosis. Mutations in the *SIX1* gene on chromosome 1 have been found in a few families. It is likely that there are other causative genes for BOR syndrome that have not been identified yet account for the



Branchiootorenal syndrome: pedigree analysis chart (Gale)

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Bilateral—Related to or affecting both sides of the body or both of a pair of organs.

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Congenital—Refers to a disorder that is present at birth.

Cyst—An abnormal sac or closed cavity filled with liquid or semi-solid matter.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Ear tags—Excess pieces of skin on the outside of the ear.

Fistula—An abnormal passage or communication between two different organs or surfaces.

Gene—A building block of inheritance, which contains the instructions for the production of a

particular protein. It is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Gustatory lacrimation—Abnormal development of the tear ducts causing tears when chewing.

Lacrimal ducts—Tear ducts.

Microtia—Small or underdeveloped external ears.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Preauricular pits—Small pits in the skin on the outside of the ear.

Renal agenesis—Absence or failure of one or both kidneys to develop normally.

Renal hypoplasia—Abnormally small kidneys.

Unilateral—Refers to one side of the body or only one organ in a pair.

Variable expressivity—Differences in the symptoms of a disorder between family members with the same genetic disease.

remaining families. The exact function of these genes is unknown, but mutations in them disrupt normal development, producing the physical differences common to BOR syndrome. Mutations in these genes can affect the normal development of the ear, kidney, and the branchial arches. The branchial arches are tissues that develop very early in pregnancy and are involved in the formation of the face and neck.

BOR syndrome is inherited in an autosomal dominant manner. This means that only one gene in the pair must be mutated in order for the individual to be affected. The characteristics of the syndrome can be extremely variable in severity from person to person with the condition. If a child inherits an abnormal gene from a parent, the signs of the disorder can be very different between the parent and the child. This is called *variable expressivity*. For example, a parent who has a very mild form of BOR syndrome can have a severely affected child. The reverse situation can also occur. A mutation in one of the causative genes may be inherited from a parent with BOR syndrome. Still, it can also occur by chance in an individual without a family history of BOR syndrome.

Genetic testing for the three genes known to cause BOR syndrome is available. The recommended testing

strategy is to study the DNA sequence of the *EYAI* gene first, and then if no mutations are found, to perform a chromosome study, looking for structural rearrangements in the areas of the three known genes. A chromosome study may also detect deletions or duplications of genetic material involving the three genes. If no changes are found, then mutation analysis of the other two genes is recommended. The clinical features of the syndrome in a person may help guide testing. Those with mutations in the *EYAI* gene are likely to have a milder set of clinical features. Those with *SIX1* are less likely to have renal disease and those with *SIX5* may have normal hearing.

Demographics

BOR syndrome occurs 1 in every 40,000 live births, although the condition is likely underdiagnosed. BOR syndrome is seen in all ethnic groups and cultures. It also affects males and females equally. One study suggested that 2% of individuals with severe hearing loss have BOR syndrome.

Signs and symptoms

The characteristics associated with BOR syndrome are highly variable. Some individuals with BOR syndrome

have many physical deformations. Other individuals with BOR syndrome have a few minor physical differences. The birth defects can occur on only one side of the face (unilateral) or be present on both sides (bilateral).

Abnormal development of the external ear is the most common characteristic of BOR syndrome. The ears may be smaller than normal (microtia) and may have an unusual shape. Ear tags (excess pieces of skin) are present on the cheek next to the ear in 13% of those with the condition. Preauricular pits (small pits in the skin on the outside of the ear) are found in 80% of patients with BOR syndrome. Hearing loss is present in 90% of individuals with BOR syndrome and this loss may be mild or severe. The type of hearing loss most common is mixed hearing loss followed by conductive and sensorineural. There may also be malformations in the inner or middle ear or the external auditory canal.

The most distinctive finding in individuals with BOR syndrome is the presence of cysts or fistulas in the neck region due to abnormal development of the branchial arches. These cysts and fistulas can be filled with or discharge fluid.

Approximately two-thirds of individuals with BOR syndrome also have kidney abnormalities. These abnormalities can be very mild and cause no health problems or they can be very severe and life-threatening. The kidneys can be smaller than normal (renal hypoplasia), abnormally shaped, malfunctioning, or totally absent (renal agenesis).

Other less common characteristics associated with BOR syndrome include cleft palate, facial nerve paralysis, and small lower jaw. Some exhibit abnormalities of the tear ducts. The tear ducts (lacrimal ducts) may be absent or abnormal. Some patients with BOR syndrome express uncontrollable tears while chewing (gustatory lacrimation).

Of the features associated with BOR syndrome, some are considered major while others are considered minor when making a diagnosis. The major criteria are:

- second branchial arch anomalies
- deafness
- preauricular pits
- changes in the shape of the outer ear
- renal anomalies

The minor criteria are:

- changes in the external auditory canal
- middle ear anomalies
- inner ear anomalies
- preauricular tags
- facial asymmetry or palate abnormalities

QUESTIONS TO ASK YOUR DOCTOR

- Is it possible to detect my child's having branchiootorenal syndrome with a prenatal test?
- Are there any risks associated with such a test?
- What abnormal characteristics are associated with branchiootorenal syndrome?
- Would my child be able to live a normal life if born with branchiootorenal syndrome?

Diagnosis

The diagnosis of BOR syndrome is made when an individual has the common clinical characteristics associated with the condition. An individual does not need to have all three components of the disorder in order to be diagnosed with the condition. The usual method of diagnosis is that a person is considered affected if they have three or more major criteria or two major and one minor criteria. If a person has an affected first-degree relative, then one major feature is enough to make the diagnosis.

Differential diagnosis

There are a number of other syndromes with overlapping clinical features that should be considered when diagnosing a person with BOR syndrome. When branchial and facial features are present but not renal, then brachiofacial syndrome is a possibility. If branchial and renal features are present but no hearing loss or ear abnormalities, branchiooculorenal syndrome is a possibility, especially if certain eye abnormalities are present. Goldenhar, Treacher Collins, Townes-Brocks, and CHARGE syndromes all have features similar to BOR syndrome. A careful examination by a medical geneticist can ensure the best clinical diagnosis is made and appropriate genetic tests are offered.

Treatment and management

Once a child is diagnosed with BOR syndrome, additional tests should be performed. A hearing evaluation is necessary to determine if there is hearing loss. If hearing loss is evident, the child should be referred to a hearing specialist. Hearing tests may need to be performed on a regular basis. Hearing aids or cochlear implants may be considered. Those with hearing loss should also be offered an appropriate educational setting. Speech therapy may also be helpful. An ultrasound of the kidney may be necessary, due to the increased risk for birth defects in these areas. If renal problems are present, there

may be a need for renal dialysis or surgery. If end-stage renal disease is reached, then a renal transplant may be considered. A nephrologist or kidney specialist should be involved in the care of a person with BOR syndrome. Finally, minor surgery may be required to correct the branchial cysts and fistulas commonly found in BOR syndrome.

Prognosis

The prognosis for individuals with BOR syndrome is very good. Individuals with BOR syndrome typically have a normal lifespan and normal intelligence. There are several organizations listed at the end of this entry where individuals and families with BOR syndrome may connect with other families, learn more about the condition, find recent research and useful resources, and become involved in advocacy.

Resources

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- Carey, John C., et al., eds. *Management of Genetic Syndromes*. 4th ed. Hoboken, NJ: Wiley-Blackwell, 2021.
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- "Branchiootorenal/Branchiootic Syndrome." MedlinePlus. August 18, 2020. <https://medlineplus.gov/genetics/condition/branchiootorenal-branchiootic-syndrome/> (accessed May 25, 2021).

ORGANIZATIONS

- American Society for Deaf Children, PO Box 23, Woodbine, MD 21797, (800) 942-2732, info@deafchildren.org, <http://www.deafchildren.org>
- Cain Foundation for Branchio-oto-renal (BOR) Syndrome, PO Box 306, Jannali, 2226, <http://www.thecainfoundation.com>
- National Association of the Deaf, 8630 Fenton Street, Suite 820, Silver Spring, MD 20910, (301) 587-1788 or (301) 328-1443, nad.info@nad.org, <http://www.nad.org>
- National Kidney Foundation, 30 E. 33rd St., New York, NY 10016, (800) 622-9010, <http://www.kidney.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06812, (800) 999-6673, <http://www.rarediseases.org>

Sonja E. Higgins, MS

Breast cancer

Definition

Breast cancer is a disease in which abnormal breast cells begin to grow uncontrollably, forming tumors. It often shows up as a breast lump, breast thickening, or skin change.

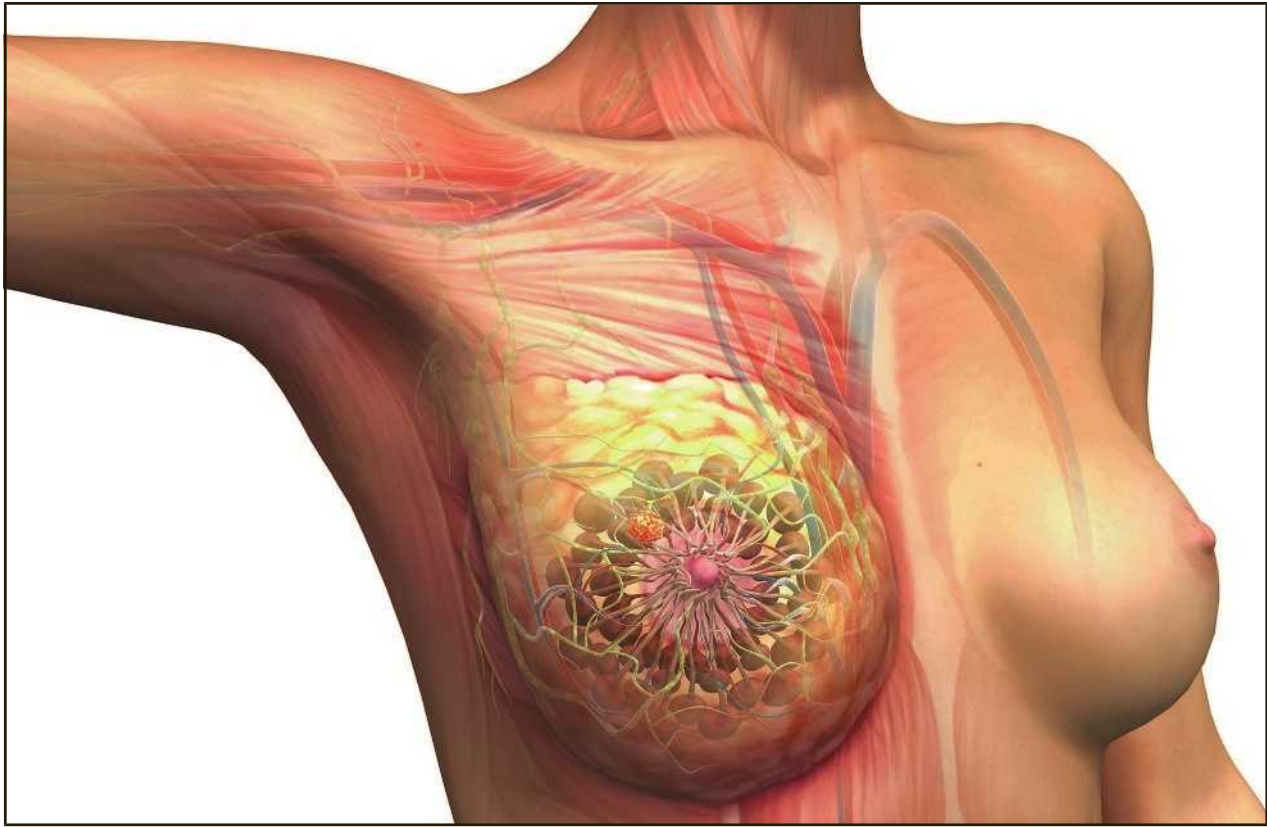
Description

The breasts are areas of tissue located on the front chest wall, and they are essentially part of the skin. In their structure and function, they are like specialized sweat glands in that they can produce and secrete fluids (milk). They are made of ductal tissue, supporting connective tissue, and fat. The breasts naturally drain fluid through the lymph channels to the axillary lymph nodes, located in the armpit areas. Within the breasts are intricate structures of ducts and lobules, which are channels and areas that create and transport milk during lactation.

Excluding skin cancers, breast cancer is the most common cancer among women and one of the leading causes of death in women in their middle years of life. Male breast cancer is rare and accounts for less than 1% of all breast cancers. Both genetic and environmental factors are thought to cause breast cancer. Of all breast cancer diagnoses, only approximately 5% to 10% are caused by hereditary factors such as specific alterations in breast cancer susceptibility genes or by a genetic cancer syndrome. In these instances, individuals may have a strong family history of cancer and the cancers may be diagnosed at an earlier age than usual.

Breast cancers vary in their type and size. This can be determined by a breast biopsy. Breast cancer may commonly be detected by a mammogram, a physician's clinical breast examination (CBE), or a patient's own breast self-examination (BSE). Breast cancer, if it is the first cancer developed, may sometimes metastasize (spread) to other organs, such as the liver, bone, lungs, skin, or brain. The breasts may also be the site of metastasis from other primary cancers.

Breast cancer may present as a lump or other change within the breast. As with other types of cancer, the initial diagnosis may be unexpected. Each cancer has a unique prognosis, which will affect the patient's concern. If an individual has a very strong family history of breast cancer, the diagnosis may be somewhat expected but no less emotionally taxing. Treatment and management of the cancer may be extremely exhausting, painful, and stressful for the patient and his or her family.



An anterolateral illustration of the right breast depicting cancer in the glandular tissue and lymph nodes. (MedicalRf/Science Source)

Genetic profile

Cells in breast tissue normally divide and grow according to controls and instructions of various genes. If these genes have changes within them, the instructions for cellular growth and division may go awry. Abnormal uncontrolled cell growth may occur, causing breast cancer. Therefore, all breast cancers are genetic, because they all result from changes within genes. However, most breast cancers occur later in life after years of exposure to various environmental factors that can cause alterations (such as the body's own hormones, asbestos, or smoking).

A small proportion of breast cancer is caused by inherited genetic alterations (pathogenic variants). In 1994, a breast cancer susceptibility gene known as *BRCA1* (location 17q21), was identified. The next year, the discovery of *BRCA2* (location 13q12) followed. Women with alterations in these genes have an increased risk for breast and ovarian cancer, and men have an increased risk for prostate cancer. Men with a *BRCA2* alteration have an increased risk for breast cancer. Slightly increased risks for colon and pancreatic cancers (in men and women) are associated with *BRCA2* alterations.

BRCA1 and *BRCA2* alterations are inherited in an autosomal dominant manner; an individual has one copy of a *BRCA* alteration and has a 50% chance of passing it on to each of his or her children, regardless of that child's gender. Nearly all individuals with a *BRCA* alteration (or other gene alterations associated with breast cancer susceptibility) have a family history of the alteration, usually a parent. In turn, they also may have a very strong family history of breast, ovarian, prostate, colon, and/or pancreatic cancers. Aside from *BRCA1* and *BRCA2*, there are other genes that when altered increase an individual's susceptibility to breast cancer, such as *CDH1*, *PTEN*, *STK11*, and *TP53*. Other genes exist that convey a smaller risk for breast cancer while conveying a larger risk for other cancers.

BRCA1 and *BRCA2* are thought to function as "tumor-suppressor genes," meaning that their normal role is to prevent tumors from forming. Specifically, they control cellular growth and division, all the while preventing the overgrowth that may lead to cancer. Alterations in tumor-suppressor genes, such as *BRCA1* and *BRCA2*, would naturally lead to an increased risk of developing cancer. However, this risk is not 100%.



A doctor assisting a patient undergoing a mammogram to test for breast cancer (Tyler Olson/Shutterstock)

Not only variations of the *BRCA1* and *BRCA2* genes increase the risk of developing breast cancer. Variations in *CDH1*, *PTEN*, *STK11*, and *TP53* have also recently been shown to increase risk. Mutations in these genes cause syndromes that greatly increase the chance of developing several types of cancer over a person's lifetime. Some of these syndromes also include other signs and symptoms, such as the growth of noncancerous (benign) tumors. Some research suggests that inherited variants of the *ATM*, *BARD1*, *BRIPI*, *CHEK2*, *NBN*, *PALB2*, *RAD50*, and *RAD51* genes, as well as certain versions of the *AR* gene, may also be associated with breast cancer risk.

A 2021 study sought to better define the genes most associated with breast cancer risk. Researchers designed a panel with 34 known or suspected genes that increase susceptibility and compared with data to estimate breast cancer risk. Nine of the genes had a strong association. These include:

- *ATM*
- *BRCA1*
- *BRCA2*
- *CHEK2*
- *PALB2*
- *BARD1*
- *RAD51C*
- *RAD51D*
- *TP53*. As a result, the authors suggested that these genes be included in testing panels for predicting breast cancer risk, and further defined how protein-truncating variants in some genes affect risk for improved genetic counseling.

There are rare genetic cancer syndromes that may include breast cancer. As a group, these comprise less

than 1% of all breast cancer diagnoses. In these instances, an individual may have other health problems (unrelated to cancer) and a family history of a wide variety of cancers and symptoms. These health problems can initially appear unrelated, but they may be caused by alterations (pathogenic variants) in a specific gene.

Demographics

In 2021, the Centers for Disease Control and Prevention (CDC) reported that in 2017, more than 250,520 women and 2,276 men had been diagnosed with breast cancer in the United States. That year, 42,000 women and 510 men died from breast cancer. According to the American Cancer Society (ACS), breast cancer is the most common cancer among American women except for skin cancers. The chance of developing invasive breast cancer at some time in a woman's life is about 13 percent. In 2021, the ACS estimated that 281,550 new cases of invasive breast cancer would be diagnosed among women in the United States. After increasing during the 1980s and 1990s, female breast cancer incidence rates decreased by 3.5% per year from 2001 to 2004 and then began to rise slightly again. Breast cancer is the second leading cause of cancer death in women, exceeded only by lung cancer. The chance that breast cancer will be responsible for a woman's death is about 1 in 36 (about 3%). Death rates from breast cancer have been declining since about 1990, with larger decreases in women younger than age 50. These decreases are believed to be the result of earlier detection through screening and increased awareness, as well as improved treatment. In 2020, there were about 3.8 million breast cancer survivors in the United States.

According to ACS, white women are slightly more likely to develop breast cancer than are African American women, but African American women are more likely to die of this cancer. This disparity seems to be because African American women tend to have more aggressive tumors, although the cause is unknown. Asian, Hispanic, and Native American women have a lower risk of developing and dying from breast cancer.

Signs and symptoms

Various symptoms may bring someone to medical attention in order to investigate the possibility of breast cancer. These may include a breast lump that persists, as compared to one that only appears at certain times of a woman's menstrual cycle (which is more common). Other signs include changes from the normal breast shape, pain, itchiness, a turned-in nipple, fatigue, or unexplained weight loss. Fluid leaking from the nipple is a particular concern if the woman is not pregnant.

Sometimes individuals may feel a breast lump or change while examining their own breasts, or a physician may note it on a CBE. Additionally, it may be seen on a screening mammogram. It is important to note that not all breast lumps or breast changes signify cancer—they may be benign growths or cysts that need to be removed or drained.

Signs of a possible *BRCA1* or *BRCA2* alteration in a family, signifying hereditary breast or ovarian cancer, include:

- several relatives with cancer
- close genetic relationships between people with cancer, such as parent–child, sibling–sibling
- early ages of cancer onset, such as before ages 45 and 50
- an individual with both breast and ovarian cancer
- an individual with bilateral or multifocal breast cancer
- the presence of ovarian, prostate, colon, or pancreatic cancers in the same family
- case(s) of breast cancer in men

Suspicion of a *BRCA* alteration may be raised if someone has the above features in their family and is of a particular ethnic group, such as an Ashkenazi Jew. This is because specific *BRCA1* and *BRCA2* alterations are known to be more common in that group of individuals.

Diagnosis

Once a suspicious breast abnormality has been found, the next step is to determine whether it is breast cancer. A mammogram can identify an area of increased breast density, which is a common sign of a malignant tumor. Women in their 20s and 30s naturally have denser breasts, so mammograms may not be as effective in that age group, because the increased breast density associated with a tumor is difficult to see. Breast ultrasound, a way of visualizing the breast tissue using sound waves, can be helpful in younger women, because breast density is not a large factor in its effectiveness. A breast biopsy can determine specifically whether the breast tissue has undergone a benign or malignant change, because the breast tissue is studied directly under a microscope. Sometimes, biopsies are performed with a very thin needle (known as fine needle aspiration) or with x-ray guidance using a thicker needle (known as a core needle biopsy).

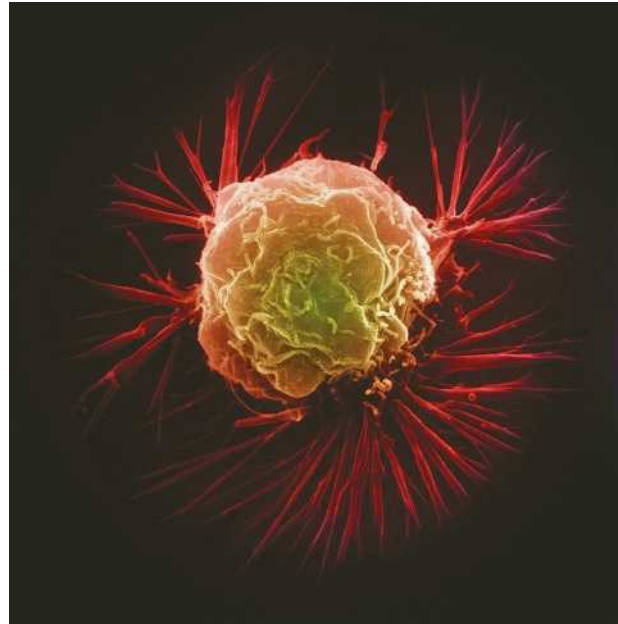
Newer techniques have improved breast cancer screening and diagnosis. Digital mammograms have ended the need for film. The digital images provide finer detail and allow the images to be rotated in order to get several different views of the breasts. Magnetic resonance imaging (MRI) uses magnetic energy to create an image. Its effectiveness is currently the subject of research

studies. MRI is not widely used, because it is expensive. Still, MRI often provides very detailed imaging of tumors.

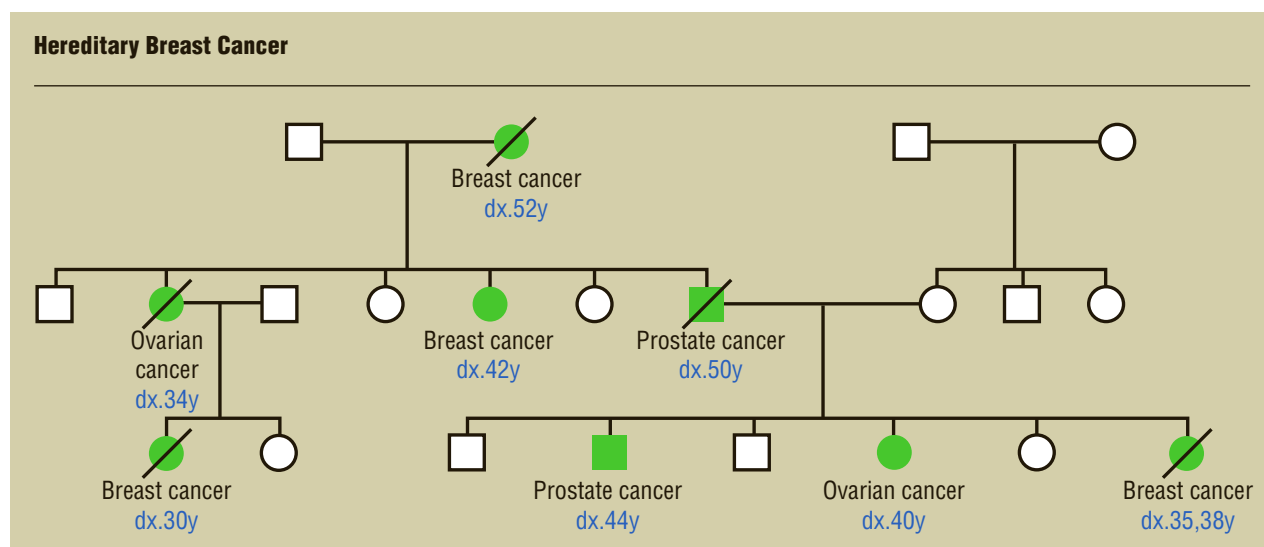
A U.S. Supreme Court decision in 2013 that banned the patenting of human genes (including *BRCA*) led to a rapid increase in the number of laboratories that offer molecular DNA testing for breast cancer susceptibility genes, including *BRCA1* and *BRCA2*. The development of new DNA sequencing techniques called next-generation sequencing (NGS) has enabled the development of multigene panel testing for breast cancer susceptibility genes.

Next-generation DNA sequencing allows parallel sequencing or reading of millions of short pieces of DNA simultaneously. Before this new technology, genetic testing usually started with the most commonly involved genes (*BRCA1* and *BRCA2*) and then proceeded to less likely genes only if clinical suspicion was still high enough to warrant further testing. However, multigene panels allow testing of multiple breast cancer genes at the same time without substantially increasing the cost. In addition, they allow testing for other inherited cancer syndromes that might have clinical overlap with inherited breast cancer.

Genetic testing using next-generation sequencing allows for the analysis of multiple genes at one time (multigene panel testing). As gene sequencing became more affordable, larger panels became possible. A 2019 study reported that analyses can vary from six to more than



A scanning electron micrograph of a breast cancer cell.
(Cultura RM/Alamy)



Breast cancer: pedigree analysis chart (Gale)

100 genes. Multigene panels for breast cancer susceptibility genes may contain genes that confer different risks for breast cancer (high, moderate, low) or genes associated with different genetic syndromes linked to breast cancer (e.g., Li-Fraumeni syndrome).

In general, multigene panel testing decreases cost and improves efficiency of testing. However, it can increase patient anxiety. Results of multigene panel testing can be more difficult to interpret, with more variants of unknown significance (VUS) being detected. In addition, not all of the alterations (pathogenic variants) have well-established cancer-prevention guidelines. However, as more testing and research is performed, these disadvantages will lessen.

With any method of DNA testing, it is best to begin the testing process with an individual who has survived breast and/or ovarian cancer, because tests are more likely to find an alteration in a cancer survivor than in someone who has not had cancer. A result is abnormal (or “positive”) if a known cancer-causing *BRCA* alteration (pathogenic variant) is found. If an alteration is found, it is assumed to have caused the cancer(s) in the tested, affected individual. That individual may also identify new cancer risks from the positive result. For example, if a woman survived breast cancer and was found to have a *BRCA* alteration through testing, she would now be at an increased risk to develop ovarian cancer as well as a second breast cancer.

For people who go through testing and are not found to have a *BRCA* alteration (a “negative” result), this result is not informative. There are several possibilities for a negative result. First, there could be a *BRCA* alteration

in the family, although the person did not inherit it. In that case, the cancer would be due to reasons unrelated to *BRCA1* and *BRCA2*. Additionally, they could have an alteration in an unknown gene for which there is no testing available. Lastly, they could have a *BRCA1* or *BRCA2* alteration that is undetectable by available testing methods.

There is a possibility that individuals may have an unknown alteration in one of their *BRCA* or other inherited breast cancer susceptibility genes. This is termed a variant of unknown significance or VUS. In such a scenario, a change in the DNA is identified, but its significance is unclear. Therefore, it is unknown whether the gene change causes cancer. In these situations, the results are most often considered uninformative, until more information about the alteration becomes available in the future.

Once an alteration (pathogenic variant) is identified, other at-risk relatives, both affected and unaffected, can pursue targeted analysis for the confirmed familial alteration. This is much quicker and far less expensive than the initial analysis.

Unaffected individuals who test positive for a known alteration in the family are at a significantly increased risk to develop the associated cancers. A woman’s risks associated with a *BRCA1* alteration are 57% to 87% for breast cancer by age 70 and 24% to 54% for ovarian cancer by age 70. A man’s risk with a *BRCA1* alteration is about 7% for prostate cancer by age 70. A woman’s risks with a *BRCA2* alteration are 41% to 84% for breast cancer by age 70, and 11% to 27% for ovarian cancer by age 70. Up to 7% of men with *BRCA2* alteration develop breast

cancer. Furthermore, they are at a slight or moderate risk for prostate cancer. For *BRCA2* in men and women, there is an increased risk for colon and pancreatic cancers. Information about lifetime risks associated with alterations in other breast cancer susceptibility genes varies depending upon the gene involved.

When a person who has not had cancer has test results that are negative for a known familial *BRCA* alteration, they are lowered to the general risk of developing associated cancers. For example, the lifetime risk for a woman to develop breast cancer has a 12% estimate. This lowered expected risk is because he or she did not inherit the genetic alteration causing cancer in his or her family.

Everyone should receive proper genetic counseling before pursuing any DNA testing. This counseling should include questions about what the patient hopes to learn from the testing. Many people are not aware of the testing limitations and may be expecting a clear “yes/no” answer from the results. Asking people what they hope to learn from testing allows the counselor an opportunity to provide them with accurate facts, such as the possibility of a result that is not informative. Common motivations for getting tested include the need to make informed medical decisions, financially planning for the future, or just “wanting to know” about cancer risk.

Genetic testing for cancer susceptibility often triggers strong emotional responses. It is important to find out about an individual’s support system before beginning testing. Having a close friend, family member, or religious leader to talk with is often helpful for people who are pursuing testing. Someone who tests positive may be concerned because his or her risks for cancer are now higher than they were before the testing. Additionally, someone may feel empowered by the knowledge, because they can better plan for medical procedures. Someone with a family history of a *BRCA* alteration may feel relief if they test negative, because they initially assumed that they would develop cancer. Alternately, someone who tests negative in this situation may feel “survivor guilt” for not having inherited the altered gene in the family. All of these feelings may change the way an individual interacts with his or her family and friends. People may not be aware of the emotional changes that can occur from learning about cancer risk through genetic testing.

It is important to discuss the possibility of insurance coverage for the testing, particularly because testing is so expensive. Insurance companies might not routinely cover the testing unless a physician or genetic counselor describes the need for testing in a letter. Some companies are willing to cover the testing without wanting to know the results.

KEY TERMS

Alteration—Change or mutation in a gene, specifically in the DNA that codes for the gene.

Benign—Referring to a noncancerous tumor that does not spread and is not life-threatening.

Bilateral breast cancer—Cancer of both breasts, caused by two separate cancer processes.

Bile—A substance produced by the liver and concentrated and stored in the gallbladder. Bile contains a number of different substances, including bile salts, cholesterol, and bilirubin.

Breast biopsy—A small sample of tissue taken from the breast and studied to diagnose and determine the exact type of breast cancer.

Breast self-exam (BSE)—Examination by an individual of their own breasts.

CA-125 (Carbohydrate antigen 125)—A protein that is sometimes high when ovarian cancer is present. A blood sample can determine the level of CA-125.

Clinical breast exam (CBE)—Examination of the breasts, performed by a physician or nurse.

Malignant—Referring to a tumor growth that spreads to another part of the body, usually cancerous.

Mammogram—A procedure in which both breasts are compressed/flattened and exposed to low doses of x-rays, in an attempt to visualize the inner breast tissue.

Metastasis—The spreading of cancer from the original site to other locations in the body.

Multifocal breast cancer—Multiple primary cancers in the same breast.

Primary cancer—The first or original cancer site before any metastasis.

Tumor—An abnormal growth of cells. Tumors may be benign (noncancerous) or malignant (cancerous).

Treatment and management

Breast cancer treatment is determined by the exact size and type of cancer, so it is often unique to an individual. Increasingly, staging of breast cancer and treatment decisions also consider certain genetic results that indicate more aggressive or less aggressive cancer. Treatment may include surgeries, such as a lumpectomy (removal of the breast lump) or mastectomy (removal of the entire breast). Breast reconstruction (re-creation of the breast)

by plastic surgery is an option that some individuals may pursue.

Chemotherapy, or using strong chemicals to kill fast-growing cells, is a common treatment. Side effects from chemotherapy may include nausea, vomiting, hair loss, exhaustion, and sores in the mouth. Symptoms associated with menopause (such as hot flashes and the absence of menstrual periods) may occur. Additionally, menopause may actually begin because of chemotherapy. Radiation therapy is another common form of treatment, in which directed radioactive waves are used to kill fast-growing cells. Some side effects of radiation therapy are dry and itchy skin, rashes, exhaustion, nausea, and vomiting.

Sometimes, medications such as tamoxifen are used to prevent a breast cancer from coming back. Tamoxifen is often used for five years following a breast cancer diagnosis to actively prevent a recurrence. It is only effective in specific types of breast cancer, which again are unique to each individual. Some side effects of tamoxifen include beginning menopause as well as an increased risk for uterine cancer. Other drugs, such as raloxifene, are currently being studied for breast cancer prevention, because they may be able to do the same things as tamoxifen but without the side effects. Research studies are under way to determine whether tamoxifen or raloxifene can reduce the risk of breast cancer in women with *BRCA* or other breast cancer susceptibility gene alterations.

An example of a screening program for women at high risk to develop breast cancer includes:

- BSEs monthly starting in early adulthood (about 20 to 25 years of age)
- CBEs every six months or yearly starting at age 25 to 35
- mammograms yearly starting at age 25 to 35

Exact screening guidelines may vary among physicians. For men with a *BRCA2* alteration, breast cancer screening is recommended, though no formal program is specifically recommended.

In addition to screening, women with *BRCA1* or *BRCA2* alterations or other high-risk gene mutations should know about their preventive surgery options. They may consider having their healthy breasts and/or ovaries removed, in order to reduce their risks of developing breast and/or ovarian cancer. Women may be more agreeable to an oophorectomy, because ovarian cancer is difficult to detect. Surgeries may greatly reduce a woman's cancer risk, but they can never eliminate the risk entirely.

There are support and discussion groups available if someone has cancer or is at risk for cancer. These may be invaluable to those who feel alone in their situation.

QUESTIONS TO ASK YOUR DOCTOR

- What type of breast cancer do I have?
- What stage of breast cancer do I have?
- What treatment options are available for my breast cancer?
- What are the risks and benefits of each possible type of treatment?

Clinical trials

Clinical trials for the treatment of breast cancer and the evaluation of new drugs are sponsored by the National Institutes of Health (NIH) and other agencies. Some of these trials address treatment options, and many studies look specifically at hereditary breast cancer or the genetics of breast cancer.

Prognosis

The type and size of breast cancer developed largely determine the overall prognosis. Those with larger tumors and those with a type of breast tumor that does not usually respond to treatment may have a less hopeful outcome. Once cancer has spread to other areas of the body, the prognosis worsens, because the cancer is more difficult to treat. It may also be more likely to continue spreading to other areas of the body.

For cancer-free individuals identified to have *BRCA* (or other gene alterations associated with breast cancer susceptibility), it is important to remember that they are at an increased risk to develop the associated cancers, but that the risk is *not* 100%. Though people with *BRCA* or other breast cancer susceptibility gene alterations may feel “destined” to develop cancer, it is by no means a certainty. It is also important to emphasize that breast cancer screening techniques and treatments are constantly being evaluated and improved.

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ORGANIZATIONS

American Cancer Society, 250 Williams Street SW, Atlanta, GA 30329, (800) 227-2345, <http://www.cancer.org>

Breastcancer.org, 7 East Lancaster Avenue, 3rd Floor, Ardmore, PA 19003, (610) 642-6550, <http://www.breastcancer.org>

National Cancer Institute (NCI), 9609 Medical Center Drive, Bethesda, MD 20892-9760, (800) 422-6237, <http://www.cancer.gov>

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Revised by Teresa G. Odle, BS, ELS

Broad-thumb-hallux syndrome see
Rubinstein-Taybi syndrome

Bruton agammaglobulinemia

Definition

Bruton agammaglobulinemia is an X-linked genetic condition caused by a mutation in the key enzyme Bruton’s tyrosine kinase (BTK) that is needed for proper function of the immune system. People who have this disorder have low levels of protective antibodies and do not produce mature B cells, making them vulnerable to repeated and potentially fatal infections.

Description

The body’s ability to resist and fight off infections by microorganisms like bacteria, viruses, parasites, and fungi depends on the function of the immune system. The immune system is composed of specialized cells whose function is to recognize organisms that are foreign to the body and destroy them. B cells are one set of specialized cells that fight infection. B cells circulate in the bloodstream and produce proteins called antibodies that are made of different classes of immunoglobulin. Immunoglobulin antibodies are then released into the bloodstream where they attach to invading microorganisms. Antibodies are specially designed to bind specific microorganisms, very similar to a lock and key. Once the antibodies attach to the microorganism, they trigger other specialized cells of the immune system to attack and destroy the invader, thus preventing or fighting an existing infection.

In order for antibodies to be produced by the body, the B cells must develop and mature so they are capable of producing the infection-fighting antibodies. When this process does not occur normally, the immune system cannot work properly to fight off infection, a state known as immunodeficiency. Bruton agammaglobulinemia (also called X-linked agammaglobulinemia, congenital agammaglobulinemia, or LXA) is an inherited immunodeficiency characterized by the failure to produce mature B cells or antibodies. The abnormality in this disorder resides in Bruton tyrosine kinase (BTK, also known as

BPK or ATK), an enzyme needed for the maturation of B cells. As a result, people with this condition have low levels of mature B cells and the antibodies that they produce, making them vulnerable to frequent and sometimes dangerous infections.

Bruton agammaglobulinemia was discovered by physician Colonel Ogden C. Bruton in 1952 and was the first immunodeficiency disease to be identified. Bruton's patient was a four-year-old boy who was admitted to Walter Reed Army Hospital because of an infected knee. The child recovered well when Bruton gave him antibiotics, but over the next four years had multiple infections. At that time a new instrument was installed in the hospital's laboratory that was able to measure levels of antibodies in the bloodstream. At first the technician believed the machine was defective because it did not detect gammaglobulins (the building blocks of antibodies) in the boy, but Bruton recognized the significance of this finding and remarked, "Things began to click then. No gammaglobulins; can't build antibodies."

Genetic profile

Bruton agammaglobulinemia is inherited in an X-linked recessive manner and so affects males more often than females. Females have two X chromosomes, which means they have two copies of the *BTK* gene, whereas males only have one X chromosome and one copy of the *BTK* gene. If a male has a mutated *BTK* gene, he will have Bruton agammaglobulinemia. If a female has one mutant *BTK* gene, she will be a carrier and will be able to pass the mutated gene on to her children. If her son inherits the altered gene, he will have the disease; if her daughter inherits the altered gene, she will be a carrier like her mother. Alternatively, if her son does not inherit the mutated *BTK* gene, he will not be affected and will not pass the altered gene on to his children because fathers only pass a Y chromosome to their sons and an X chromosome to their daughters.

Mutations in the gene that codes for *BTK* (located at Xq21.3-22) are responsible for the disease. Over 250 different mutations in *BTK* have been identified; they are spread almost evenly throughout the *BTK* gene. While this abnormal gene can be passed from parent to child, in half of the cases a child will show the disease without having a carrier. This is because new mutations in the *BTK* gene can occur and then be passed on to the affected individual's children.

Demographics

Bruton agammaglobulinemia occurs in all racial groups, with an incidence between 1 in 50,000 and 1 in 100,000 individuals.

KEY TERMS

Antibiotics—A group of medications that kill or slow the growth of bacteria.

Antibody—A protein produced by the mature B cells of the immune system that attaches to invading microorganisms and targets them for destruction by other immune system cells.

B cell—A specialized type of white blood cell that is capable of secreting infection-fighting antibodies.

Bruton tyrosine kinase (BTK)—An enzyme vital for the maturation of B cells.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Immune system—A major system of the body that produces specialized cells and substances that interact with and destroy foreign antigens that invade the body.

Immunodeficiency—A defect in the immune system, leaving an individual vulnerable to infection.

Immunoglobulin—A protein molecule formed by mature B cells in response to foreign proteins in the body; the building blocks for antibodies.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual or manifest as disease and can be transmitted to offspring.

Vaccine—An injection, usually derived from a microorganism, that can be injected into an individual to provoke an immune response and prevent future occurrence of an infection by that microorganism.

X chromosome—One of the two sex chromosomes (the other is Y) containing genetic material that, among other things, determines a person's sex.

Signs and symptoms

Children with Bruton agammaglobulinemia are born healthy and usually begin to show signs of infection in the first three to nine months of life, when antibodies that come from the mother during pregnancy and early breastfeeding disappear. In 20%–30% of the cases, patients may have slightly higher levels of antibodies present and symptoms will not appear until later in childhood.

Patients with Bruton agammaglobulinemia can have infections that involve the skin, bone, brain, gastrointestinal tract, sinuses, eyes, ears, nose, airways to the lung, or the lung itself. In addition, the bacteria may migrate from the original site of infection and enter the bloodstream, leading to an overwhelming infection of the body that is potentially fatal.

Besides immunological signs of Bruton agammaglobulinemia, other physical symptoms include slow growth, wheezing, small tonsils, and abnormal levels of tooth decay. Children may also develop unusual symptoms such as joint disease, destruction of red blood cells, kidney damage, and skin and muscle inflammation. Increased incidences of cancers, such as leukemia, lymphoma, and colon cancer, have been associated with Bruton agammaglobulinemia in a small percentage of people.

Bacteria that are easily destroyed by a normal-functioning immune system can cause infections in individuals with Bruton agammaglobulinemia. The most common bacterial species responsible for these infections include *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Neisseria meningitidis*, *Klebsiella pneumoniae*, *Hemophilus influenzae*, and *Mycoplasma* species. Chronic stomach and intestine infections are often linked to the parasite *Giardia lamblia*.

Patients with Bruton agammaglobulinemia can successfully defend themselves against infection from viruses and fungi because other aspects of the immune system are still functional. However, there are some notable exceptions—people with this disorder are still vulnerable to the hepatitis virus, poliomyelitis virus, and echovirus. Echovirus is particularly troubling because it can lead to progressive and fatal infections of the brain, joints, and skin.

Diagnosis

Recurrent infections or infections that fail to respond completely or quickly to antibiotics should prompt a diagnostic search for immunodeficiency and Bruton agammaglobulinemia. Another helpful sign of Bruton agammaglobulinemia is the presence of unusually small lymph nodes and tonsils. Additionally, many patients with this disorder have a history of continuous illness where they do not recover between bouts.

When a patient is suspected of having Bruton agammaglobulinemia, the diagnosis is established through the use of several tests. The amount of immunoglobulin is measured in a blood sample from the affected individual by a technique called immunoelectrophoresis. In Bruton agammaglobulinemia, all of the immunoglobulins will

QUESTIONS TO ASK YOUR DOCTOR

- What are the most serious health problems associated with Bruton agammaglobulinemia?
- What treatments are available for Bruton agammaglobulinemia?
- Under what conditions, if any, should my child be expected to have a reasonably normal life as a person with Bruton agammaglobulinemia?
- What support groups are available for individuals with Bruton agammaglobulinemia and their families?

be markedly reduced or absent. There is some difficulty in diagnosing the disease in unweaned infants because immunoglobulins from the mother are still present in the child during the first few months of life.

When the diagnosis is still unclear, further tests can be performed to determine if there has been any response to normal childhood immunizations because patients with Bruton agammaglobulinemia are unable to respond to immunization with antibody production. Confirmation of the diagnosis can be made by demonstrating abnormally low numbers of mature B cells in the blood or by genetic studies that look for mutations in the *BTK* gene. When a diagnosis of Bruton agammaglobulinemia is made in a child, genetic testing of the *BTK* gene can be offered to determine whether the specific gene mutation can be identified. If the mutation is identified, carrier testing can be offered to the mother and other female relatives. In families in which the mother has been identified to be a carrier of a *BTK* gene mutation, diagnosis of Bruton agammaglobulinemia before birth is possible with prenatal genetic diagnosis techniques. In some families, a *BTK* gene mutation cannot be identified and other laboratory techniques may be available to these families, such as linkage studies or X chromosome inactivation studies.

Other diagnostic tests have been advocated to track the ongoing health of the patient with Bruton agammaglobulinemia. X-rays of the sinuses and chest should be obtained at regular intervals to monitor for the early development of infections and to determine whether proper treatment has been established. Lung function tests should also be performed on a regular basis, when the patient is old enough to cooperate. Patients who have ongoing gastrointestinal tract symptoms should be tested for the parasite *Giardia lamblia*.

Treatment and management

There is currently no cure for Bruton agammaglobulinemia and so the goals of treatment are threefold: to treat infection effectively, to prevent repeated infections, and to prevent the lung damage that may result from repeated infections.

The main complication in patients with Bruton agammaglobulinemia is a lack of immunoglobulins, which are the building blocks of antibodies. Treatment focuses on replacing immunoglobulin and thereby providing patients with the antibodies they need to fight infection. Immunoglobulin can be injected into Bruton agammaglobulinemia patients either intravenously or subcutaneously. Treatment with immunoglobulin is given every three to four weeks and is usually effective in preventing infection by various microorganisms. Individuals with Bruton agammaglobulinemia can live relatively normal lives and are at no greater risk for developing other autoimmune disorders.

Side effects from or allergic reactions to immunoglobulin are infrequent, only affecting about 3%–12% of people treated with injections. Symptoms will usually subside if the immunoglobulin is given slowly and the reactions may disappear after receiving the immunoglobulin several times. Patients should not receive live viral vaccines; in some cases Bruton agammaglobulinemia patients can transmit the diseases that they are being vaccinated against.

If infection does occur in a patient with Bruton agammaglobulinemia, antibiotics (medications that kill bacteria) are also given to help fight off the infection. Recurrent or chronic infections will develop in some patients despite the use of immunoglobulin. In these cases antibiotics may be given every day even when there is no infection present, in order to prevent an infection from forming. If chronic diarrhea is experienced by the patient, tests should be performed to look for the parasite *Giardia lamblia* and proper antibiotics should be given to kill the organism.

Preventative techniques are also very important. Children with Bruton agammaglobulinemia should be treated promptly for even minor cuts and scrapes and taught to avoid crowds and people with infections. People with this disorder and their family members should not be given vaccinations that contain live organisms, as the organisms may result in the immunocompromised person contracting the disease that the vaccination is intended to prevent. Referral for genetic counseling is appropriate for female relatives seeking information about their carrier status and for family members making reproductive decisions.

Prognosis

Without immunoglobulin treatment, 90% of patients with Bruton agammaglobulinemia will die by the age of eight years. In most patients who have been diagnosed early and are receiving immunoglobulin on a regular basis, the prognosis is reasonably good. They should be able to lead a relatively normal childhood and need not be isolated to prevent dangerous infections.

While current therapy allows most individuals with Bruton agammaglobulinemia to reach adulthood, the prognosis must be guarded. Paralysis of the legs may result from the poliomyelitis virus. Despite what may appear to be adequate immunoglobulin therapy, many patients develop severe irreversible lung disease. Fatal brain infections have been reported even in patients receiving immunoglobulin therapy, and patients who recover from these infections may be left with severe brain damage. Finally, some patients may develop leukemia or lymphoma.

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ORGANIZATIONS

- Immune Deficiency Foundation, 110 West Road, Suite 300, Towson, MD 21204, (800) 296-4433, (410) 321-9165, <http://www.primaryimmune.org>

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Bulldog syndrome see **Simpson-Golabi-
Behmel syndrome**



Campomelic dwarfism see **Campomelic dysplasia**

Campomelic dysplasia

Definition

Campomelic dysplasia is a rare, often lethal genetic disorder characterized by multiple abnormalities, including short limbs, bowed legs, distinctive facial features, and a narrow chest. It is also often associated with abnormal development of the reproductive organs in males. The disorder is also known as campotomelic dysplasia, campomelic dwarfism, and campomelic syndrome.

Description

Campomelic dysplasia is a disorder that affects the bones and cartilage of the body, causing significantly short arms and legs, bowing of the legs, small chest size, and other skeletal (bony) and nonskeletal problems. Some genetic males with campomelic dysplasia have female sex organs. Death often results in the newborn period due to breathing problems related to the small chest size. Campomelic dysplasia is caused by an alteration (mutation) in a gene called *SOX9*. This mutation is usually sporadic (occurs randomly).

Genetic profile

Campomelic dysplasia is caused by an alteration in the *SOX9* gene, which plays a role in bone formation and testicular development. Genes are units of hereditary material found on chromosomes, which are passed from a parent to a child through the egg and sperm. The information contained in genes is responsible for the development of all the cells and tissues of the body.

The *SOX9* gene is located on the long (q) arm of chromosome 17 (one of the 22 non-sex chromosomes) at position 17q24. This gene codes for a protein transcription

factor that plays a role in both bone formation and testis development. Any mutation within the coding region of this gene can cause campomelic dysplasia. The testes are responsible for producing male hormones. Every developing baby in the womb (fetus), whether genetically male (XY) or female (XX), starts life with the capacity to develop either male or female sex organs. After a few weeks, in an XY fetus, the genitals develop into male genitals when male hormones are present. In the absence of male hormones, a female body type with female genitals results.

In individuals with campomelic dysplasia, the *SOX9* gene is altered such that it does not interact normally with the *SRY* gene on the Y chromosome. In normal fetal development, when the *SRY* gene is expressed in the fetus, a series of gene interactions controlled by the *SOX9* gene is initiated and eventually leads to male sex development in the fetus. A mutation in the *SOX9* gene thus results in improper formation of the testes and loss of male hormone production. Thus, individuals who are genetically male (XY) can develop as normal females. This phenomenon is known as sex reversal and occurs in about 75% of genetic males with campomelic dysplasia. Since the *SOX9* gene is also important for proper bone formation, the bones of the body are also affected by the mutation, resulting in short stature, bowed legs, and other problems.

There are usually two normal copies of the *SOX9* gene: one copy of the gene is inherited from the mother and one from the father. Campomelic dysplasia is inherited as an autosomal dominant condition. In this pattern of inheritance, a person needs only one altered gene copy to develop the condition. The alteration in the *SOX9* gene that causes campomelic dysplasia is usually random, which means that some unknown event has caused the *SOX9* gene to become altered in either the sperm of the father or the egg of the mother. When this altered sperm or egg is fertilized, the child that results has campomelic dysplasia. The chance for parents of a child with campomelic dysplasia to have a second child with the same condition is slightly higher than it would be for another

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman’s abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal dominant—A pattern of inheritance in which one copy of the altered gene in each cell is sufficient to cause the disorder.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother’s vagina or abdominal wall and a sample of cells is collected from around the early embryo. These cells are then tested for chromosome abnormalities or other genetic diseases.

Dysplasia—The abnormal growth or development of a tissue or organ.

Fetus—The term used to describe a developing human infant from approximately the third month of pregnancy until delivery. The term “embryo” is used prior to the third month.

Genitals—The internal and external reproductive organs in males and females.

Gonads—The organs that will become either testes (male reproductive organs) or ovaries (female reproductive organs) during fetal development.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Ovaries—The female reproductive organs that produce the reproductive cells (ova) and female hormones.

Pierre Robin sequence—A malformation of the jaw, mouth, and tongue that includes a cleft palate, a small lower jaw (micrognathia), and a tongue set too far back in the mouth. It is named for Pierre Robin, the French physician who first described the sequence in 1923.

Testes (singular, testis)—The male reproductive organs that produce male reproductive cells (sperm) and male hormones.

Transcription factor—A protein that binds to specific DNA sequences and controls the rate of transcription of genetic information from DNA to messenger RNA.

couple who has not had a child with this condition. A person who has campomelic dysplasia can pass on their altered *SOX9* gene to his or her future children. However, there have not been any reports of individuals with campomelic dysplasia having children.

Demographics

Campomelic dysplasia is a rare condition that affects males and females of all racial and ethnic groups. It is estimated that between 5 and 9 per 10,000 live newborns are affected with this condition. Other estimates fall between 1 in 40,000 and 1 in 300,000 newborns.

Signs and symptoms

Campomelic dysplasia can affect the body in several ways. The English word *campomelic* is derived from two Greek words that mean “bent” and “limb,” and refers to the fact that individuals with campomelic dysplasia typically have curved or bowed legs. Usually there is a dimple in the leg just below the knee. The condition is also characterized by significantly short stature, which is evident from birth.

Other features include very small shoulder blades, a very small chest, a curved and twisted spine (kyphoscoliosis), feet that are often turned inward (clubfoot), dislocated hips, and short fingers and toes. Often there are 11 pairs of ribs instead of the usual 12. In some individuals, the pelvic bones and the bones of the spine can also be affected.

Common features can also include a large head size and distinctive facial features, such as a high forehead; a flat, small face; small chin; low-set ears; and widely spaced eyes. Some individuals have an incomplete closure of the roof of the mouth (cleft palate) combined with an underdeveloped lower jaw (micrognathia) and a tongue that is placed farther back in the mouth than is normal. This combination of features is known as Pierre Robin (pronounced roh-BAN) sequence.

Breathing problems are common in campomelic dysplasia and are often the cause of death in newborns. The breathing problems usually result from the small chest size, small lungs, and narrow airway passages. Those who survive into early infancy frequently have feeding problems and difficulty breathing.

Individuals with campomelic dysplasia may also have heart defects and hearing loss. Some females with the condition have a Y chromosome. Females with campomelic dysplasia who have a Y chromosome are genetically male. However, their sex organs are female and thus they are treated as normal females. The intellect of individuals with campomelic dysplasia is usually normal, although there have been reports of some individuals with developmental disabilities. One survivor, aged 17 at the time of her case report in 1993, was said to have an IQ of 45.

Diagnosis

The diagnosis of campomelic dysplasia is based on the presence of certain clinical features. Prenatal diagnosis can be performed by ultrasound and is based on such visible features as bowing of the femur and tibia (the long bones of the upper and lower legs), an undersized jaw, clubbed feet, a pronounced curvature of the neck, and a bell-shaped chest. Some of the bony abnormalities are more obvious on x-ray. However, radiographic examination is most often performed after birth. The features that suggest a diagnosis of campomelic dysplasia include significantly short stature present from birth, small shoulder blades, 11 pairs of ribs instead of 12, small chest size, bowed legs, and a dimple on the leg below the knee. About 10% of individuals who survive past infancy, however, lack the characteristic bowed legs associated with the disorder. This subtype of the disorder is called acampomelic campomelic dysplasia, or ACD.

The diagnosis of campomelic dysplasia can be confirmed through genetic testing, which requires a blood sample from the affected individual. The genetic test involves identifying the specific alteration in the *SOX9* gene. Parents of an affected child may seek testing for campomelic dysplasia in future pregnancies. This can be performed on the developing baby before birth through amniocentesis or chorionic villus sampling if an alteration in the *SOX9* gene is identified in the previously affected individual. Prenatal testing should be considered only after the gene alteration has been confirmed in the affected individual and the couple has been counseled regarding the risks of recurrence.

Treatment and management

Campomelic dysplasia is associated with a significant risk of death in the newborn period due to the small chest and small lungs. There is no effective treatment to expand the size of the chest. Those who survive into early infancy have feeding problems and often have difficulty breathing. An occupational therapist may be able to assist

QUESTIONS TO ASK YOUR DOCTOR

- Is there a particular pattern of inheritance for campomelic dysplasia?
- What is the prognosis for a child born with campomelic dysplasia, and what factors, if any, affect that prognosis?
- Are there medications or surgical treatments that can be used to deal with the symptoms of campomelic dysplasia?
- Are there support organizations for individuals who are living with campomelic dysplasia and their families?

with the feeding issues. Breathing problems may necessitate that the child be placed on oxygen.

Some individuals with campomelic dysplasia have significant twisting and bending of their spine (kyphoscoliosis), which can interfere with breathing. A bone specialist (orthopedist) should be consulted for advice on potential treatments such as bracing or surgery. An orthopedist should also be consulted regarding the other bony problems such as clubfoot and bowed legs. Individuals with campomelic dysplasia should also have their hearing assessed and their heart examined because of the increased risk of hearing loss and heart defects, respectively.

In females with campomelic dysplasia who have a Y chromosome, the gonads (the organs that later become either ovaries or testes during fetal development) do not develop into normal ovaries. It is generally recommended that they be surgically removed because there is an increased chance for tumors to occur in the gonads when they do not develop properly.

Very few individuals with campomelic dysplasia live beyond the newborn period but most who do are of normal intelligence. During the school years, it may be necessary to make some changes (such as providing the individual with a stepstool in the bathroom) to foster independence. For some, meeting other individuals of short stature may be beneficial. Such groups as the Little People of America (LPA) serve as a source of information and offer opportunities to meet other people facing similar challenges. Individuals with campomelic dysplasia and their families may benefit from genetic counseling, which can provide them with further information on the condition itself and recurrence risks for future pregnancies.

Prognosis

Campomelic dysplasia is associated with a significant risk of death in the newborn period. Most newborns die during the first few hours after birth from breathing problems due to the small chest size and underdeveloped lungs; only 5%–10% survive. A few individuals with campomelic dysplasia live into late adolescence.

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Kathryn and Alan C. Greenberg Center for Skeletal Dysplasias, McKusick-Nathans Institute of Genetic Medicine. Johns Hopkins University, 600 N. Wolfe St., Baltimore, MD 21287, (410) 614-0977, (410) 502-2475, <https://igm.jhmi.edu/content/greenberg-center-skeletal-dysplasias-welcome>

Little People of America (LPA), 617 Broadway #518, Sonoma, CA 95476, (888) LPA-2001, info@lpaonline.org, <http://www.lpaonline.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Nemours Children's Health System, 10140 Centurion Pkwy. N., Jacksonville, FL 32256, (904) 697-4100, <http://www.nemours.org/welcome.html>

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Campomelic syndrome see **Campomelic dysplasia**

Camurati-Engelmann disease

Definition

Camurati-Engelmann disease—also known as diaphyseal dysplasia, diaphyseal hyperostosis, and Engelmann's disease—is a rare genetic condition that affects the bones of the body. The long bones in the arms and legs become abnormally long and other bones in the body may become thickened. The increased bone density throughout the body may cause bone pain (especially in the legs), vision and hearing loss, neurological impairments, skeletal disorders, decreased body mass, weakness, and fatigue.

Description

Despite their strength and durability, human bones are living organisms. Throughout the lifespan, bones are constantly being broken down and rebuilt again without losing their proper size and shape. Diseases that interfere with this delicately orchestrated process (called bone remodeling) can produce pain and restrict freedom of movement. In Camurati-Engelmann disease, which was first described in 1920, the shafts of the long bones in the legs become thicker than normal. The femur (thigh bone) and tibia (shin bone) are primarily affected. These changes often cause severe bone pain and weak muscles in the legs. The weak, aching muscles associated with Camurati-Engelmann disease may result in an unusual walk that resembles a waddle. People with Engelmann may be bow-legged and have thin, elongated legs that look as if they are "wasting away."

Aside from bones in the leg, Camurati-Engelmann disease can cause abnormal changes in other bones. People with Camurati-Engelmann disease may develop scoliosis (in which the spine curves to the left or right side) or lumbar lordosis (a forward curvature of the spine). Camurati-Engelmann disease can also cause bones to become abnormally hardened (a process referred to as sclerosis). This hardening can affect the bones at the base of the skull as well as those in the hands and feet. In rare cases, sclerosis may affect the jaw. Individuals with this disease often experience bone pain, weak muscles, and extreme fatigue.

Thickening of the skull causes increased pressure on the brain and can lead to a variety of neurological problems, including vision and hearing loss, headaches, dizziness (vertigo), ringing in the ears (tinnitus), and facial paralysis. Other features of Camurati-Engelmann disease include decreased body fat and delayed puberty.

Camurati-Engelmann disease can also affect internal organs and sight. The liver and spleen may become

enlarged. Loss of vision may occur if bones near the eye sockets are affected. Some people with Camurati-Engelmann disease report headaches, fatigue, and lack of appetite.

Camurati-Engelmann disease is often referred to as Camurati diaphyseal dysplasia, or progressive diaphyseal dysplasia (PDD). Less common names for the condition include osteopathia hyperostotica scleroticans and multiplex infantilis. Camurati-Engelmann disease was sometimes referred to as ribbing disease in the past but this name is no longer used.

Genetic profile

Camurati-Engelmann disease is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is enough to cause the disorder. An affected individual may inherit the mutation from one affected parent or a new mutation in the gene may occur.

Ten different mutations in the *TGFB-1* gene have been found to cause Camurati-Engelmann disease. Located on the long (q) arm of chromosome 19, the *TGFB-1* gene provides instructions for producing a protein called transforming growth factor beta-1 (TGFB-1). Found throughout the body, this protein helps control several functions: the growth and division of cells in the body, the process by which cells mature, cell movement, and the self-destruction of cells (apoptosis). The TGFB-1 protein is found throughout the body and facilitates development before birth, the formation of blood vessels, the regulation of muscle tissue and body fat development, wound healing, and immune system function. TGFB-1 is found in skeletal tissues where it helps regulate bone growth.

Within cells, the TGFB-1 protein is normally inactive until a chemical signal in the cells tells it to become active. In Camurati-Engelmann disease, the TGFB-1 protein is always active. This leads to increased bone density and decreased body fat and muscle tissue, and causes the symptoms of Camurati-Engelmann disease.

Occasionally, individuals with Camurati-Engelmann disease do not have identified mutations in the *TGFB-1* gene, and the cause of the disease is unknown.

Demographics

Camurati-Engelmann disease, which affects men and women equally, is a very rare disease that develops during childhood or young adulthood. It usually develops between ages four and ten, but may affect children as young as three months old. Some individuals may

KEY TERMS

Endosteal—Relating to the endosteum, which is the lining of the medullary cavity.

Intracranial pressure—The pressure of the fluid between the brain and skull.

Medullary cavity—The marrow-filled cavity inside a long bone (such as the femur).

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual and can be transmitted to offspring. The change may manifest itself as a disease.

Periosteal—Relating to the periosteum, which is the connective tissue that covers all human bones.

develop Camurati-Engelmann disease any time before age 30.

Signs and symptoms

The main symptoms of Camurati-Engelmann disease are severe pain in the legs, weak and underdeveloped leg muscles, and a “waddling” walk. Other symptoms include bowed legs, unusually long limbs, spine problems such as scoliosis or lumbar lordosis, and flat feet. People with the disease may complain of headaches, lack of energy or appetite, vision problems, and an aching feeling in their hands and feet and, less often, in the jaw. Infants with Camurati-Engelmann disease may experience feeding problems or a failure to thrive, and have a malnourished appearance.

Camurati-Engelmann disease causes telltale changes in the structure of the femur and tibia around the mid-shaft areas. Certain bone regions (specifically, the endosteal and periosteal surfaces) become abnormally thickened and hardened, which in turn narrows the medullary canal. Camurati-Engelmann disease also causes the long bones to become fusiform, a technical term indicating a tapered, spindle-like shape. In addition to these changes, Camurati-Engelmann disease may cause abnormal hardening of other bones: in the hands and feet, at the base of the skull, and in the jaw. Camurati-Engelmann disease may also involve liver and spleen enlargement, compression of the optic nerves, and increased intracranial pressure.

Diagnosis

Classic symptoms such as severe leg pain, underdeveloped leg muscles, and a waddling gait are often the first indication of the disease. An infant may initially

QUESTIONS TO ASK YOUR DOCTOR

- At what age can Camurati-Engelmann disease be diagnosed, and on what characteristics is that diagnosis made?
- What kinds of medication and/or surgical procedures are used to treat Camurati-Engelmann disease?
- Does this genetic disorder become worse or better over time?
- Could this genetic disorder remain about the same as a child grows older?
- If my spouse and I are planning to have other children, should we consult a genetic counselor for more information about this disease?

experience feeding problems or failure to thrive (though these are more often the result of other problems). Imaging procedures such as a CT scan are used to detect the bone abnormalities associated with the condition, which mainly involve the thickening and sclerosis of the long bones of the legs. In some cases, x-ray studies of the skull are necessary. Blood tests and a biopsy of muscle tissue may be recommended.

In diagnosing Camurati-Engelmann disease, a doctor must distinguish it from other conditions that produce similar symptoms, such as Paget disease and certain types of muscular dystrophy.

Treatment and management

The treatment of Camurati-Engelmann disease focuses on alleviating symptoms. While the changes in bone associated with the condition cannot be reversed, the use of steroid drugs such as cortisone or prednisone can ease bone pain and strengthen muscle. Surgery to repair muscles or bones is rarely necessary. Procedures to repair nerves in the eye are generally considered ineffective.

Prognosis

While Camurati-Engelmann disease does not affect life expectancy, the prognosis for the condition varies. Some people affected by the disease are virtually free of symptoms; others are severely disabled. In some cases, the muscle weakness associated with Camurati-Engelmann disease diminishes or goes away completely with the passage of time. In other people, the effects of

the disease seem to remain the same or slowly worsen during adulthood.

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- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Canavan disease

Definition

Canavan disease, which occurs when the body produces less-than-normal amounts of a protein called aspartoacylase, is a fatal inherited disorder characterized by progressive damage to the brain and nervous system.

Description

Canavan disease is named after Dr. Myrtille Canavan, who described a patient with the symptoms of Canavan disease but mistakenly diagnosed this patient with Schilder's disease. It was not until 1949 that Canavan disease was recognized as a unique genetic disease by Van Bogaert and Bertrand. The credit went to Dr. Canavan,

KEY TERMS

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid or cells from it can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Amniotic fluid—The fluid that surrounds a developing baby during pregnancy.

Amniotic sac—A sac that contains the fetus, which is surrounded by amniotic fluid.

Biochemical testing—Measuring the amount or activity of a particular enzyme or protein in a sample of blood or urine or other tissue from the body.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10 to 12 weeks of gestation. Under ultrasound guidance, a needle is inserted either through the mother's vagina or abdominal wall, and a sample of cells is collected from around the early embryo. These cells are then tested for chromosomal abnormalities or other genetic diseases.

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their

shape and size (structure) may lead to physical or mental abnormalities.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

DNA testing—Analysis of DNA (the genetic component of cells) to determine changes in genes that may indicate a specific disorder.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein. It is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Poor muscle tone (hypotonia)—A condition in which infants appear limp at birth and cannot keep their knees and elbows bent.

Prenatal testing—Testing for a disease such as a genetic condition in an unborn baby.

Protein—Important building blocks of the body, composed of amino acids with functions contributing to the formation of body structures and controlling the basic functions of the human body.

White matter—A substance found in the brain and nervous system that protects nerves and allows messages to be sent to and from the brain to the various parts of the body.

however, whose initial description of the disease dominated the medical literature.

Canavan disease, which is also called aspartoacylase deficiency, spongy degeneration of the brain, and infantile spongy degeneration, results from a deficiency of the enzyme aspartoacylase. This deficiency ultimately causes progressive damage to the brain and nervous system, along with intellectual disability, seizures, tremors, muscle weakness, blindness, and an increase in head size. Although most people with Canavan disease die in their teens, some die in childhood, and some live into their 20s and 30s.

Canavan disease is sometimes called spongy degeneration of the brain, because it is characterized by a sponginess or swelling of the brain cells and by a destruction of the white matter of the brain. It is an autosomal

recessive genetic condition that is found in all ethnic groups, but is most common in people of Ashkenazi (Eastern European) Jewish descent.

Genetic profile

Canavan disease is a rare autosomal recessive genetic disease. A person with Canavan disease has changes (mutations) in both of the genes responsible for producing the enzyme aspartoacylase and has inherited one changed gene from his or her mother and one changed gene from his or her father. The aspartoacylase gene is called *ASPA* and is located on chromosome number 17. There are a number of different types of changes in the *ASPA* gene that can cause Canavan disease, although there are three common gene changes. When the *ASPA* gene is altered, it produces reduced levels of

aspartoacylase or none at all. The amount of aspartoacylase produced depends on the type of gene alteration. Reduced production of aspartoacylase leads to lower-than-normal amounts of this enzyme in the brain and nervous system. Aspartoacylase is responsible for breaking down a substance called N-acetylaspartic acid (NAA). When the body produces decreased levels of aspartoacylase, higher levels of NAA build up. This substance destroys the white matter of the brain and nervous system and causes the symptoms of Canavan disease.

Parents who have a child with Canavan disease are called carriers, since they each possess one changed *ASPA* gene and one unchanged *ASPA* gene. Carriers usually do not have any symptoms, since they have one unchanged gene that can produce enough aspartoacylase to prevent the buildup of NAA. Each child born to parents who are both carriers for Canavan disease has a 25% chance of having Canavan disease, a 50% chance of being a carrier, and a 25% chance of being neither a carrier nor affected with Canavan disease.

Demographics

Although Canavan disease is found in people of all ethnicities, it is most common in Ashkenazi Jewish individuals. Approximately one in 40 Ashkenazi Jewish individuals is a carrier for Canavan disease, and approximately one in 6,400 Ashkenazi Jewish people is born with Canavan disease.

Signs and symptoms

Most infants with Canavan disease appear normal for the first month of life. The onset of symptoms, such as a lack of head control and poor muscle tone, usually begins by two to three months of age. Still, some may have an onset of the disease in later childhood. Children with Canavan disease usually experience sleep disturbances, irritability, and swallowing and feeding difficulties after the first or second year of life. In many cases, irritability resolves by the third year. As the child with Canavan disease grows older, there is a deterioration of mental and physical functioning. The speed at which this deterioration occurs will vary for each affected person. Children with Canavan disease have an intellectual disability. Most will never be able to sit, stand, walk, or talk, although they may learn to laugh, smile, and reach for objects. People with Canavan disease have increasing difficulties in controlling their muscles. Initially, those affected have poor muscle tone; eventually their muscles become stiff and difficult to move and may exhibit spasms. Canavan disease can cause vision problems to the point that some people with it may eventually become blind. People with

Canavan disease typically have disproportionately large heads and may experience seizures.

Diagnosis

Diagnostic testing

Canavan disease should be suspected in a person with a large head who has poor muscle control, a lack of head control, and destroyed white matter of the brain. Abnormalities of the brain can be detected through a computed tomography (CT) scan or magnetic resonance imaging (MRI). A diagnosis of Canavan disease can usually be confirmed by measuring the amount of NAA in a urine sample, since a person with Canavan disease typically has five to ten times the normal amount of NAA in their urine. Canavan disease can be less accurately diagnosed by measuring the amount of aspartoacylase enzyme present in a sample of skin cells or by measuring the enzyme from a blood sample.

Once a biochemical diagnosis of Canavan disease is made, DNA testing may be recommended. Detection of an *ASPA* gene alteration in a person with Canavan disease can confirm an uncertain diagnosis and help facilitate prenatal diagnosis and carrier testing of relatives. Testing for the *ASPA* gene is available from certain laboratories. These tests are specifically designed to detect variants of the *ASPA* gene. Two mutations have been identified that make up 98% of the alterations that cause the disease in people of Ashkenazi Jewish descent. Tests search for several genes that can occur among people of Ashkenazi Jewish descent. The tests include the *ASPA* gene.

Carrier testing

DNA testing is the only means of identifying carriers of Canavan disease. If possible, it should be performed on the affected family member first. If a change in the *ASPA* gene is detected, then carrier testing can be performed on relatives such as siblings, with an accuracy of greater than 99%. If the affected relative does not possess a detectable *ASPA* gene change, then carrier testing will be inaccurate and should not be performed. If DNA testing of the affected relative cannot be performed, carrier testing of family members can still be performed but will be less accurate. Carrier testing for the three common *ASPA* gene mutations identifies approximately 97%–99% of Ashkenazi Jewish carriers and 40% to 55% of carriers from other ethnic backgrounds.

Carrier testing of individuals without a family history of Canavan disease is only recommended for people of Ashkenazi Jewish background, since they have a higher risk of being carriers. Both the American College of Obstetricians and Gynecologists and the American College of Medical Genetics have recommended that

DNA testing for Canavan disease be offered to all couples of Eastern European Jewish (Ashkenazi) descent who are planning to have children or who are currently expecting. If only one member of the couple is of Ashkenazi Jewish background, then testing of them should be performed first. If the Jewish partner is a carrier, then testing of the non-Jewish partner is recommended.

Prenatal testing

Prenatal testing through chorionic villus sampling (CVS) and amniocentesis is available to parents who are both carriers for Canavan disease. If both parents possess an *ASPA* gene change, which is identified through DNA testing, then DNA testing of their baby can be performed. Some parents are known to be carriers for Canavan disease, yet they do not possess *ASPA* gene changes that are detectable through DNA testing. Prenatal diagnosis can be performed in those cases by measuring the amount of NAA in the amniotic fluid obtained from an amniocentesis. This type of prenatal testing is less accurate than DNA testing and can lead to misdiagnoses.

Treatment and management

As of 2021, there was no cure for Canavan disease. Therefore, treatment largely involves the management of symptoms. Seizures and irritability can often be controlled through medication. Children with loss of head control will often benefit from the use of modified seats that can provide full head support. When feeding and swallowing become difficult, treatment may involve liquid diets, feeding tubes, or both. Feeding tubes are inserted either through the nose (nasogastric tube) or through a permanent incision in the stomach (gastrostomy). Patients with a later onset and slower progression of the disease may benefit from special-needs education and physical therapy.

A new type of treatment called gene replacement therapy shows promise in helping people with Canavan disease. The goal of gene replacement therapy is to restore normal amounts of aspartoacylase in the brain and nervous system and to prevent the build-up of NAA and the symptoms of Canavan disease. The clinical trials that have delivered the *ASPA* gene encoding the NAA enzyme to the brain have offered promising results.

Clinical trials for Canavan disease including new gene therapies, experimental drug treatments, and procedures are underway. Participation in a U.S. clinical trial is voluntary and cost-free to the participant. All clinical trials receiving U.S. government funding and some supported by private industry are posted at [## **QUESTIONS TO ASK YOUR DOCTOR**](https://www</p>
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- Please explain the cause or causes of Canavan disease.
- Are there treatments or other forms of care that can be provided to a child born with Canavan disease to extend his or her life?
- Is it possible to predict the lifespan of a child born with Canavan disease, and, if so, on what is that prediction based?
- What types of medical specialists will a child born with Canavan disease need to see?

.clinicaltrials.gov. Foreign trials are posted at <https://www.orpha.net>.

Prognosis

The lifespan and progression of Canavan disease are variable and may be partially dependent on the type of medical care provided and other genetic risk factors. Most people with Canavan disease die before age 10, although some live into their teens or survive their 20s. There can be a high degree of variability, even within families. Some families report having one child die in infancy and another die in adulthood.

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ORGANIZATIONS

Canavan Foundation, 600 West 111th Street, 8A, New York, NY 10025-1813, (866) 907-1847, info@canavanfoundation.org, <https://www.canavanfoundation.org>

Jewish Genetic Diseases Center at Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029-6574, (212) 241-6500, <http://icahn.mssm.edu/research/programs/jewish-genetics-disease-center>

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Cancer

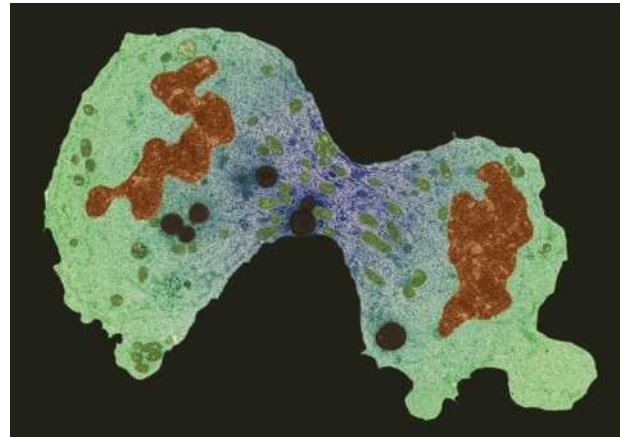
Definition

Cancer is not just one disease, but a large group of diseases characterized by uncontrolled and malignant growth of some cells in the human body and the ability of these cells to spread to distant sites (metastasis). If the spread is not controlled through surgery, chemotherapy, radiation, or other treatments, cancer can result in death. According to predictions from the American Cancer Society, the most common cause of cancer in males in the United States in 2021 was prostate cancer (26 percent of all male cancers), followed by lung cancer (12 percent). Among females, the most common cause of cancer in 2021 was breast cancer (30 percent), followed by lung cancer (13 percent). In considering deaths from lung cancer for both men and women together, lung cancer was responsible for 22 percent of all cancer deaths in 2021.

Description

Cancer by definition is a disease of the genes, which are formed from deoxyribonucleic acid (DNA) and located on chromosomes. They carry the hereditary instructions for the cell to make the proteins required for many body functions. Proteins are special chemical compounds that mostly contain carbon, hydrogen, oxygen, and nitrogen. Our bodies need them to carry out all of the processes that allow us to breathe, think, move, or do most anything else.

Throughout people's lives, the cells in their bodies are growing, dividing, and replacing themselves. Many genes produce proteins that are involved in controlling the processes of cell growth and division. A change (mutation) occurring in the DNA molecules can disrupt the genes and produce faulty proteins and cells. Abnormal cells can start dividing uncontrollably, eventually forming a new growth known as a "tumor" or "neoplasm"



Colored transmission electron micrograph (TEM) of a cancer cell dividing by mitosis into two new daughter cells. This image was made during the telophase (fourth stage) of mitotic division, when the cell's genetic material (dark blue) has been separated via the spindle (center) into two identical populations. (Steve Gschmeissner/Science Source)

(medical term for cancer meaning "new growth"). In a healthy individual, the immune system can recognize the neoplastic cells and destroy them before they get a chance to divide. However, some abnormal cells may escape immune detection and survive to become cancerous.

Tumors are of two type: benign or malignant. A benign tumor is usually slowly growing and does not spread or invade the surrounding tissue. Once the tumor is removed, it will not usually start growing again. A malignant tumor, on the other hand, invades surrounding tissue and may spread to other parts of the body, often very distant from the location of the first tumor. Malignant tumors often can be surgically removed, but if the cancer cells have spread too much or too far, the cancer becomes very difficult, if not impossible, to treat.

Most cancers are caused by changes in the cell's DNA that result from exposure to a harmful environment. Environmental factors that are responsible for causing the initial mutation in the DNA are called carcinogens. Other factors can cause cancer as well. For example, certain hormones have been shown to have an effect on the growth or control of a particular cell line. Hormones are substances made by one organ and passed through the bloodstream to affect the function of other cells in another organ.

While there is scientific evidence that both environmental and genetic factors play roles in most cancers, only 5%–10% of all cancers are classified as hereditary, which means that a faulty gene that may cause cancer is passed from parent to child. That results in a greater risk for that type of cancer in the offspring of the family.

However, if someone has a cancer-causing gene, they will not necessarily develop cancer. Rather, they are thought to be predisposed to a type of cancer or more likely to get that cancer, compared to the general population. Various cancers are known to have a hereditary component. A few examples are breast cancer, prostate cancer, colon cancer, ovarian cancer, and skin cancer.

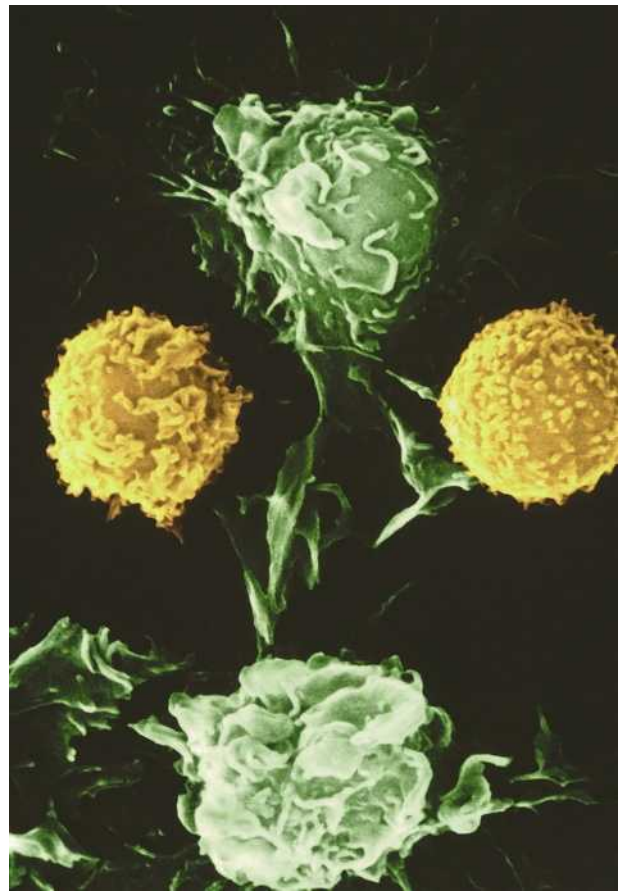
Aside from genes, certain physiological traits that are inherited can contribute to cancers as well. For example, fair skin makes a person more likely to develop skin cancer but only if they also have prolonged exposure to intensive sunlight.

According to experts such as Rebecca L. Siegel et al. of the American Cancer Society, the coronavirus disease 2019 (COVID-19) pandemic likely had some effects on cancer, but it will take several years for researchers to assess its effects. For example, because of this pandemic in 2020 and 2021, many routine screenings for cancer were delayed, such as screening for breast cancer (mammograms) or for colorectal cancer (colonoscopies). Some treatments for cancer patients may also have been delayed, affecting patients' prognoses. Future research will provide this information.

There are several different types of cancers. Some of the most common types include:

- **Carcinomas.** These cancers arise in the epithelium (the layers of cells covering the body's surface and lining the internal organs and various glands). About 80% of human cancers fall into this category. Carcinomas can be subdivided into two subtypes: adenocarcinomas and squamous cell carcinomas. Adenocarcinomas are cancers that develop in an organ or a gland, while squamous cell carcinomas refer to cancers that originate in the skin.
- **Melanomas.** These cancers also originate in the skin, usually in the pigment cells (melanocytes).
- **Sarcomas.** These are cancers of the supporting tissues of the body, such as bone, muscle, cartilage, and fat.
- **Leukemias.** Cancers of the blood or blood-forming organs.
- **Lymphomas.** This type affects the lymphatic system, a network of vessels and nodes that acts as a filter in the body. It distributes nutrients to blood and tissue and prevents bacteria and other foreign substances from entering the bloodstream.
- **Gliomas.** Cancers of the nerve tissue.

The most common cancers are skin cancer, lung cancer, colon and rectal (colorectal) cancer, breast cancer (in women), uterine cancer in women, bladder cancer in men, and prostate cancer (in men). In addition, cancers of the kidneys, ovaries, pancreas, thyroid gland, and blood and lymph node cancer (leukemias and lymphomas) are included among the major cancers that affect most Americans.



Colored scanning electron micrograph of cancer cells (green). Two lymphocyte blood cells (yellow) are also pictured. (Stem Jems/Science Source)

Genetic profile

Three classes of genes are believed to play roles in the development of cancer:

- **Proto-oncogenes.** These genes encourage and promote the normal growth and division of cells. When they are defective, they become oncogenes, which are overactive proto-oncogenes that cause excessive cell multiplication that can lead to tumors.
- **Tumor suppressor genes.** These genes act as brakes on cell growth. They prevent cells from multiplying uncontrollably. If these genes are defective, there is no control over cell growth and tumors can result. According to the American Cancer Society, most family cancer syndromes are caused by inherited defects in the tumor suppressor genes.
- **DNA repair genes.** These genes ensure that each strand of DNA is correctly copied during cell division. When these genes do not function properly, the replicated DNA is likely to have mistakes. These errors lead to defects in other genes and can also lead to tumor formation.

Childhood cancers associated with congenital syndromes or malformations

Syndrome or Anomaly	Tumor
Aniridia	Wilms tumor
Hemihypertrophy	Wilms tumor, hepatoblastoma, adrenocortical carcinoma
Genito-urinary abnormalities (including testicle maldescent) Beckwith-Wiedemann syndrome	Wilms tumor, Ewing sarcoma, nephroblastoma, testicular carcinoma Wilms tumor, neuroblastoma, adrenocortical carcinoma
Dysplastic naevus syndrome	Melanoma
Nevoid basal cell carcinoma syndrome	Basal cell carcinoma, medulloblastoma, rhabdomyosarcoma Leukemia
Poland syndrome	Leukemia, retinoblastoma
Trisomy-21 (Down syndrome)	Leukemia, gastrointestinal carcinoma
Bloom syndrome	EBV-associated B-lymphocyte lymphoma/leukemia EBV-associated B-lymphocyte lymphoma
Severe combined immune deficiency disease Wiscott-Aldridge syndrome	EBV-associated B-lymphocyte lymphoma, gastric carcinoma Wilms tumor, osteosarcoma, Ewing sarcoma
Ataxia telangiectasia Retinoblastoma Fanconi anemia	Leukemia, squamous cell carcinoma
Multiple endocrine neoplasia syndromes (MEN I, II, III)	Adenomas of islet cells, pituitary, parathyroids, and adrenal glands Submucosal neuromas of the tongue, lips, eyelids Pheochromocytomas, medullary carcinoma of the thyroid, malignant schwannoma, non-appendiceal carcinoid
Neurofibromatosis (von Recklinghausen syndrome)	Rhabdomyosarcoma, fibrosarcoma, pheochromocytomas, opticglioma, meningioma

Childhood cancers associated with congenital syndromes or malformations (Gale)

As stated, approximately 5% to 10% of cancers have a hereditary component. In those cancers, children do not inherit cancer from their parents. Rather, they inherit a predisposition to cancer. For example, a child may inherit a faulty tumor suppressor gene from one parent. This gene is not able to control cell growth, but the corresponding gene inherited from the other parent may still be functional. Cell growth is then under control. However, as this child grows up, radiation, pollution, or any other harmful environmental factor could change (mutate) the previously healthy gene, making it abnormal as well. However, if a child inherits mutated tumor suppressor genes from both parents, a tumor is most likely to develop. Defects in proto-oncogenes and DNA repair genes can be inherited as well, leaving a person more vulnerable to cancer than other individuals.

Additionally, some cancers seem to be familial. In those cancers, there is not a specific gene that is responsible for the clustering of cancer in a family. However, a particular type of cancer may be seen more often than expected, which may be due to a combination of genetic and environmental factors.

Demographics

Cancer is the second leading cause of death in the United States, surpassed only by heart disease. Nearly 1.9 million new cases of cancer will be diagnosed in 2021, as predicted by the American Cancer Society. In addition,

there will be an estimated 608,570 cancer deaths in 2021, or more than 1,600 deaths per day. Some people diagnosed with cancer in 2021 will be cured of their cancer, while others will remain affected with the disease and undergoing treatment. Many patients will die of their cancer.

Anyone is potentially at risk for developing cancer. Since the occurrence of cancer increases as a person ages, most of the cases are seen in adults who are middle-aged or older. Nearly 80% of cancers are diagnosed in people who are 55 years of age and older.

Lifetime risk is the term that cancer researchers use to refer to the probability that an individual will develop cancer over the course of their lifetime. In the United States, men have a one-in-two lifetime risk of developing cancer, and for women the risk is one in three. Overall, African Americans are more likely to develop cancer than Caucasians, and they are also 33% more likely to die of cancer than Caucasians. Racial disparity is even greater for American Indian/Alaska Natives with cancer, who have a 51% higher risk for death from cancer than do Caucasian individuals with cancer.

The major risk factors for cancer are: tobacco, alcohol, diet, sexual and reproductive behavior, infectious agents, family history, occupation, environment, and pollution.

Tobacco

Smoking continues to be the leading preventable cause of cancer, while lung cancer itself is the leading cause of

cancer deaths in both men and women. About 82 percent of the lung cancer cases occur in smokers, yet researchers have discovered that individuals who end their smoking habit by age 40 reduce their risk of smoking-related disease by an estimated 90 percent. There are many medications and treatments to help people stop smoking. Smoking has also been shown to be a contributory factor in cancers of the mouth, pharynx, larynx, esophagus, pancreas, uterine cervix, kidney, and bladder. Scientists have also shown that secondhand smoke (or passive smoking) increases one's risk of developing cancer.

Alcohol

Excessive consumption of alcohol is a risk factor in some cancers, such as liver cancer and breast cancer. Alcohol in combination with tobacco significantly increases the chances that an individual will develop mouth, pharynx, larynx, and esophageal cancers. The combined effect of tobacco and alcohol is greater than the sum of their individual effects.

Diet and physical activity

One-third of all cancer deaths are due to a poor adult diet. High-fat diets have been associated with cancers of the colon and rectum, prostate, endometrium, and possibly breast. Consumption of meat, especially red meat, has been associated with increased cancer at various sites, such as the colon and prostate. Additionally, a high-calorie diet and low level of physical activity can lead to obesity, which increases the risk for cancer at various sites, including the breast, colon and rectum, prostate, kidney, and endometrium.

Sexual and reproductive behavior

The human papilloma virus (HPV), which is a sexually transmitted pathogen, has been shown to cause cancer of the female cervix and oropharyngeal cancer in men who have oral sex with infected partners. Having many sexual partners and becoming sexually active early in life has been shown to increase a woman's chances of contracting this disease and, therefore, developing cervical cancer. In addition, it has also been shown that women who do not bear any children or those who become pregnant late in life have an increased risk for both ovarian and breast cancer. A vaccine against HPV is available to adolescents and young adults up to age 26 years. This vaccine protects individuals as well as their future sex partners from HPV.

Hormone replacement therapy

As women go through menopause, some doctors may recommend hormone replacement therapy (HRT). HRT involves taking female hormones (estrogen and

progesterone) to control certain symptoms that occur during that time of a woman's life, such as hot flashes and vaginal dryness. According to the nonprofit advocacy group breastcancer.org, located in Ardmore, Pennsylvania, taking combination therapy (both progesterone and estrogen) increases the risk for breast cancer by about 75%, especially in the first few years of taking this form of hormone replacement therapy. In contrast, taking estrogen therapy alone also elevates the risk for breast cancer, but the risk occurs after about a decade of taking estrogen replacement therapy (ERT). However, ERT may also increase a woman's risk for ovarian cancer. Taking estrogen alone also may increase the risk for uterine cancer. As a result, menopausal women should only consider any form of HRT after a very careful consultation with a physician as well as considering the personal possible risk factors for breast cancer, such as a family history of the disease.

Family history

Some types of cancers tend to occur more frequently among members of a family. In most cases, this happens either by chance or due to common family habits such as cigarette smoking, excessive eating causing obesity, or excessive sun exposure. However, familial cancer can also be due to a genetic predisposition that is passed from generation to generation. For example, if a certain gene called *BRCA1* or *BRCA2* is defective in a given family, members of that family may have an increased risk to develop breast, colon, ovarian, and prostate cancer. Other defective genes have been identified that can make a person susceptible to various types of cancer. Therefore, inheriting particular genes can increase a person's chance to develop cancer.

Occupational hazards

There is strong evidence proving that occupational hazards account for 4% of all cancer deaths. For example, asbestos workers have an increased incidence of lung cancer. Similarly, bladder cancer is associated with dye, rubber, and gas workers; skin and lung cancer with smelters, gold miners, and arsenic workers; leukemia with glue and varnish workers; liver cancer with PVC manufacturers; and lung, bone, and bone marrow cancer with radiologists and uranium miners.

Environment

High-frequency radiation has been shown to cause cancer. Ultraviolet radiation from the sun accounts for a majority of melanomas. Other sources of radiation are x-rays, radioactive substances, and rays that enter the Earth's atmosphere from outer space. Virtually any part of the body can be affected by these types of radiation, especially the bone marrow and the thyroid gland.

Being exposed to substances such as certain chemicals, metals, or pesticides can increase the risk of cancer. Asbestos is an example of a well-known carcinogen. It increases the risk for lung cancer. This risk is increased even further for a smoker who is exposed to asbestos over a period of time.

Signs and symptoms

Almost every tissue of the body can give rise to abnormal cells that cause cancer, and each of these cancers is very different in symptoms and prognosis.

Cancer is also a progressive disease and goes through several stages. Each stage can produce a number of symptoms. Unfortunately, many types of cancer do not display any obvious symptoms or cause pain until the disease has progressed to an advanced stage. Early signs of cancer are often subtle and are easily mistaken for signs of other less dangerous diseases. However, if cancer is diagnosed in its early stages, the prognosis is much improved compared to when diagnosis occurs at an advanced stage.

Despite the fact that there are several hundred different types of cancers producing very different symptoms, the American Cancer Society (ACS) has established the following seven symptoms as possible warning signs of cancer:

- changes in the size, color, or shape of a wart or a mole
- a sore that does not heal
- persistent cough, hoarseness, or sore throat
- a lump or thickening in the breast or elsewhere
- unusual bleeding or discharge
- chronic indigestion or difficulty in swallowing
- any change in bowel or bladder habits

Many other diseases can produce similar symptoms. However, it is important to have these symptoms checked as soon as possible, especially if they do not stop. The earlier a cancer is diagnosed and treated, the better the chance of a successful treatment. Many cancers, such as breast cancer, might not have any early symptoms. Therefore, it is important to undergo routine screening tests, such as mammograms.

Diagnosis

If a person has symptoms of cancer, the doctor will begin with a complete medical history and a thorough physical examination. Different parts of the body will be examined to identify any variations from the normal size, feel, and texture of the organ or tissue. The doctor may order various other tests as well.

Laboratory tests of blood and urine are often used to obtain information about a person's health. If cancer is suspected, a special test can be done that measures the amount of certain substances called tumor markers in the blood, urine, or particular tissues. These proteins are released from some types of cancer cells. Thus, the levels of these substances may be abnormal when certain cancers are present. However, laboratory tests alone cannot be used to make a definitive diagnosis of cancer. Blood tests are generally more useful in monitoring the effectiveness of the treatment or in following the course of the disease and detecting any signs of recurrence.

A doctor may also look for tumors by examining pictures of areas inside the body. The most common way to obtain these images is by using x-rays or imaging scans to obtain pictures of the inside of the body, such as computed tomography scanning (CT scan), magnetic resonance imaging (MRI), positron emission tomography (PET), or ultrasonography.

The most definitive diagnostic test is the biopsy. In this technique, a piece of tissue from the suspected cancerous tumor is surgically removed for examination under a microscope. A biopsy provides information about the cellular nature of the abnormality, the stage it has reached, the aggressiveness of the cancer, and the extent of its spread. Further analysis of the tissue defines the cause of the abnormality. Since a biopsy provides the most accurate analysis, it is considered the gold standard of diagnostic tests for cancer.

Regular screening examinations conducted by healthcare professionals can result in the early detection of various types of cancer. If detected at an early stage, treatment is more likely to be successful. For example, the American Cancer Society recommends an annual mammogram (x-ray of the breast) for women aged 45 to 54 years to screen for breast cancer. If a woman wishes to start breast cancer screening between the ages of 40 and 44, this option should be extended to her. Women who are age 55 and older may have annual screening or screening every two years, for as long as the woman is anticipated to live at least ten more years. The American Cancer Society also recommends either stool tests or a colonoscopy or sigmoidoscopy to detect cancer or a risk for cancer in the colon, starting at age 45. A colonoscopy is a procedure in which a thin lighted tube is rectally inserted so that the doctor may view the inside of the entire colon. If the doctor detects any precancerous polyps, they will be removed during the procedure. A sigmoidoscopy is another procedure, but it does not examine the entire colon. Stool-based tests include the fecal immunochemical test (FIT), which checks for blood in the stool. Patients can perform this test in their own home. A guaiac-based fecal occult blood test (gFOBT) is another

KEY TERMS

Adenocarcinoma—A type of cancer that originates in glandular tissue, has a glandular form, or both.

Adenomatous—Derived from glandular structures.

Aflatoxin—A substance produced by molds that grow on rice and peanuts. Exposure to aflatoxin is thought to explain the high rates of primary liver cancer in Africa and parts of Asia.

Alpha-fetoprotein (AFP)—A chemical substance produced by the fetus and found in the fetal circulation. AFP is also found in abnormally high concentrations in most patients with primary liver cancer.

Alteration—Change or mutation in a gene, specifically in the DNA that codes for the gene.

Anti-androgen drugs—Drugs that block the activity of the male hormone.

Astrocytoma—Tumor of the central nervous system derived from astrocytes.

Barium—A chemical swallowed to help with outlining the gastrointestinal system during an x-ray study.

Benign—Referring to a noncancerous tumor that does not spread and is not life-threatening.

Benign prostatic hyperplasia (BPH)—A noncancerous condition of the prostate that causes growth of the prostate tissue, thus enlarging the prostate and blocking urination.

Bilateral breast cancer—Cancer of both breasts, caused by two separate cancer processes.

Bile—A substance produced by the liver and concentrated and stored in the gallbladder. Bile contains a number of different substances, including bile salts, cholesterol, and bilirubin.

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Bone marrow—A spongy tissue located in the hollow centers of certain bones, particularly the bones of the central skeleton. Bone marrow is the site of blood cell generation.

BRCA2—A gene, when altered, that is known to cause increased risks of breast, ovarian, and possibly pancreatic cancer.

Breast biopsy—A small sample of tissue taken from the breast and studied, to diagnose and determine the exact type of breast cancer.

Breast self-exam (BSE)—Examination by an individual of their own breasts.

CA-125 (Carbohydrate antigen 125)—A protein that is sometimes high when ovarian cancer is present. A blood sample can determine the level of CA-125 present.

Cancer—A disease caused by uncontrolled growth of the body's cells.

Carcinogen—Any substance capable of causing cancer by damaging a cell's genome.

Cationic trypsinogen gene—A gene known to cause hereditary pancreatitis when significantly altered.

CDH1—A gene involved in cell-to-cell connection. Alterations in this gene have been found in several families with increased rates of gastric cancer.

CDKN2A—Gene, when altered, known to cause Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome and possibly increased pancreatic cancer risk.

Central nervous system—In humans, the brain, the cranial nerves, and the spinal cord. It is responsible for the coordination and control of all bodily activities.

Chemotherapy—Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of the cancerous cells or by killing them.

type of stool test that patients may perform at home. The stool DNA test is a third type of stool test; it checks for abnormal DNA cells as well as for hidden blood. In the United States, only the Cologuard test is approved to test for both blood in the stool and DNA changes. If a stool-based test is positive, a doctor may choose to perform a colonoscopy. Patients should check with their physicians to determine the needed frequency of these tests. Self-examinations for cancers of the breast, testes, mouth, and skin can also help in detecting tumors.

Recent progress in molecular biology and cancer genetics have led to the development of several tests designed to assess one's risk of developing certain types of cancer. This genetic testing involves looking closely at genes that have been linked to particular cancers. If these genes are abnormal, a person's risk for certain types of cancer increases. At present, there are many limitations to genetic testing. The tests may be uninformative, and they are useful to a very small number of people. There are also concerns about insurance

KEY TERMS (continued)

Chronic atrophic gastritis—Irritation and breakdown of the stomach wall over a period of time.

Cirrhosis—A chronic degenerative disease of the liver in which normal cells are replaced by fibrous tissue. Cirrhosis is a major risk factor for the later development of liver cancer.

Clinical breast exam (CBE)—Examination of the breasts, performed by a physician or nurse.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Desmoid tumor—A benign, firm mass of scar-like connective tissue.

Distal—Away from the point of origin.

Dominant inheritance—A type of genetic inheritance pattern that results in one form of a gene being dominant over other forms. Therefore, the dominant allele can express itself and cause disease, even if only one copy is present.

Duct—A tube-like structure that carries secretions from glands.

Duodenum—The portion of the small intestine nearest the stomach; the first of three parts of the small intestine.

Endoscope—A slender, tubular optical instrument used as a viewing system for examining an inner part of the body and, with an attached instrument, for biopsy or surgery.

Endoscopic retrograde cholangiopancreatography (ERCP)—A method of viewing the pancreas by inserting a thin tube down the throat into the pancreatic and bile ducts, injecting dye, and performing x-rays.

Ependymoma—A tumor of the central nervous system derived from cells that line the central canal of the spinal cord and the ventricles of the brain.

Epidermoid cyst—A benign cystic tumor derived from epithelial cells.

Epithelium—The layer of cells that cover the open surfaces of the body, such as the skin and mucous membranes.

Esophagus—The part of the digestive tract that connects the mouth and stomach; the food pipe.

Estrogen—A female sex hormone.

Exocrine pancreas—The part of the pancreas that secretes digestive enzymes.

Familial adenomatous polyposis (FAP)—An inherited syndrome causing large numbers of polyps and increased risk of colon cancer and other cancers.

Familial gastric cancer—Gastric cancer that occurs at a higher rate in some families.

Fecal occult blood test—A laboratory test of a stool (feces) sample done to identify loss of blood in the gastrointestinal system.

Fine needle aspiration (FNA)—Insertion of a thin needle through the skin to an area of sample tissue.

Gastric—Associated with the stomach.

Gastrointestinal (GI) system—The body system involved in digestion, the breaking down and use of food.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Genetic counselor—A health professional with advanced training in genetics and psychology who educates people about genetic conditions and testing.

Glioblastoma multiforme—A tumor of the central nervous system consisting of undifferentiated glial cells.

coverage and employment discrimination for someone who has an increased risk for cancer. A hereditary cancer clinic can help to assess who may benefit from this type of testing.

Treatment and management

The aim of cancer treatment is to remove all or as much of the tumor as possible and to prevent the metastasis of the primary tumor. While devising a treatment plan

for cancer, the likelihood of curing the cancer must be weighed against the side effects of the treatment. For example, if the cancer is very aggressive and a cure is not possible, then the treatment should be aimed at relieving the symptoms and controlling the cancer for as long as possible.

Cancer treatment can take many different forms, and it is always tailored to the individual patient. The decision on which type of treatment to use depends on the type and

KEY TERMS (continued)

***Helicobacter pylori* (H. pylori)**—A bacterium that infects humans and may be associated with an increased risk of gastric cancer.

Hepatitis—A viral disease characterized by inflammation of the liver cells (hepatocytes). People who are infected with hepatitis B or hepatitis C virus are at an increased risk for developing liver cancer.

Hereditary non-polyposis colon cancer (HNPCC)—A genetic syndrome causing increased cancer risks, most notably colon cancer. Also called Lynch syndrome.

Hormone therapy—Treatment of cancer by changing the hormonal environment, such as by administering testosterone and estrogen.

Immunotherapy—Treatment of cancer by stimulating the body's immune defense system.

Insulin—A hormone produced by the pancreas that is secreted into the bloodstream and regulates blood sugar levels.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Laparoscopy—A diagnostic procedure in which a small incision is made in the abdomen, and a slender, hollow, lighted instrument is passed through it.

Laparotomy—An operation in which the abdominal cavity is opened up through incisions in the abdominal wall.

Li-Fraumeni syndrome—Inherited syndrome known to cause increased risk of different cancers, most notably sarcomas.

Lymph node—A bean-sized mass of tissue that is part of the immune system and is found in different areas of the body.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to

create detailed images of internal body structures and organs, including the brain.

Malignant—Referring to a tumor growth that spreads to another part of the body, usually cancerous.

Mammogram—A procedure in which both breasts are compressed (or flattened) and exposed to low doses of x-rays, in an attempt to visualize the inner breast tissue.

Medulloblastoma—Tumor of the central nervous system derived from undifferentiated cells of the primitive medullary tube.

Melanoma—A type of skin cancer that develops from melanocytes, the pigment-producing cells in the skin.

Metachronous—Referring to tumors of a similar type that are discovered at different times within the body.

Metastasis—The spreading of cancer from the original site to other locations in the body.

Metastatic cancer—A cancer that has spread to an organ or tissue from a primary cancer located elsewhere in the body.

Multifocal breast cancer—Multiple primary cancers in the same breast.

Mutation—A permanent change in the genetic material; it may alter a trait or characteristic of an individual or manifest as disease, and it can be transmitted to offspring.

Nitrates/nitrites—Chemical compounds found in certain foods and water that, when consumed, may increase the risk of gastric cancer.

Osteoma—A benign bone tumor.

Palliative—Referring to treatment given for relief of symptoms rather than a cure.

location of cancer and the extent to which it has already spread. The doctor will also consider the patient's age, sex, general health status, and personal treatment preferences. Treatment can be local, meaning that it seeks to destroy cancer cells in the tumor and the surrounding area. It can also be systemic, meaning that the treatment drugs will travel through the bloodstream and reach cancer cells all over the body. Surgery and radiation are local treatments. Chemotherapy, immunotherapy, and hormone therapy are examples of systemic treatments.

Surgery

Surgery can be used for many purposes in cancer therapy.

- **Treatment surgery:** This involves removal of the tumor to cure the disease. It is typically performed when the cancer is localized to a discrete area. Along with the cancer, some of the surrounding tissue may also be removed to ensure that no cancer cells remain in the area. Since cancer usually spreads via the lymphatic system,

KEY TERMS (continued)

Pancreas—An organ located in the abdomen that secretes pancreatic juices for digestion and hormones for maintaining blood sugar levels.

Pancreatitis—Inflammation of the pancreas.

Pelvic examination—A physical examination performed by a physician, often associated with a Pap smear. The physician inserts his or her finger into a woman's vagina, attempting to feel the ovaries directly.

Pernicious anemia—A blood condition with decreased numbers of red blood cells related to poor vitamin B12 absorption.

Peutz-Jeghers syndrome (PJS)—An inherited syndrome causing polyps in the digestive tract and spots on the mouth as well as increased risk of cancer.

Polyp—A mass of tissue bulging out from the normal surface of a mucous membrane.

Primary cancer—The first or original cancer site before any metastasis.

Prophylactic—Referring to a procedure or medication given to prevent disease.

Prostatectomy—The surgical removal of the prostate gland.

Proximal—Near the point of origin.

Radiation—High-energy rays used in cancer treatment to kill or shrink cancer cells.

Radiation therapy—Treatment using high-energy radiation from x-ray machines, cobalt, radium, or other sources.

Rectum—The lowermost portion of the intestine that leads to the anus.

Semen—A whitish, opaque fluid that is released at ejaculation and contains sperm.

Seminal vesicles—The pouches above the prostate that store semen.

Sore—An open wound or a bruise or lesion on the skin.

Staging—A method of describing the degree and location of cancer.

Stomach—The muscular hollow organ that secretes enzymes and gastric acid to aid in the digestion of food.

Synchronous—Occurring or existing at the same time.

Testicles—Two egg-shaped glands that produce sperm and male sex hormones.

Testosterone—Hormone produced in the testicles that is involved in male secondary sex characteristics.

Transrectal ultrasound—A procedure where a probe is placed in the rectum. High-frequency sound waves are sent out from the probe and reflected by the prostate. These sound waves produce a pattern of echoes that are then used by the computer to create sonograms or pictures of structures inside the body.

Transvaginal ultrasound—A way to view the ovaries by using sound waves. A probe is inserted into the vagina, and the ovaries can be seen. Color doppler imaging measures the amount of blood flow, as tumors sometimes have high levels of blood flow.

Tumor—An abnormal growth of cells. A tumor may be benign (noncancerous) or malignant (cancerous).

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.

Whipple procedure—Surgical removal of the pancreas and surrounding areas, including a portion of the small intestine, the duodenum.

X-ray—A high-energy form of electromagnetic radiation. X-rays are used to treat as well as diagnose cancer.

lymph nodes that are near the tumor site may be examined and removed as well.

- **Preventive surgery:** Preventive or prophylactic surgery involves removal of an abnormal area that is likely to become malignant over time. For example, people with a colon disease called ulcerative colitis have an elevated risk of dying from colon cancer. Rather than live with the fear of developing colon cancer, some people may choose to have their colons removed in order to reduce their risk of cancer.

- **Diagnostic purposes:** The most definitive tool for diagnosing cancer is a biopsy. Sometimes a biopsy can be performed by inserting a needle through the skin. In other cases, the only way to obtain a tissue sample for a biopsy is by performing a surgical operation.
- **Cytoreductive surgery:** This is a procedure in which the doctor removes as much of the cancer as possible. He or she then treats the remaining cancer cells with radiation therapy, chemotherapy, or both.

- **Palliative surgery:** This type of surgery is aimed at relieving cancer symptoms or slowing the progression of disease. It is not designed to cure the cancer. For example, if the tumor is very large or has spread to many places in the body, removing the entire tumor may not be an option. However, by decreasing the size of the tumor, pain may be alleviated. This is known as debulking surgery.

Radiation therapy

Radiation therapy uses high-energy rays to kill cancer cells. This treatment may be used instead of surgery. It also may be used before surgery to shrink a tumor, or after surgery to destroy any remaining cancer cells.

Radiation can be either external or internal. In the external form, the radiation comes from a machine that aims the rays at the tumor. In internal radiation (also known as brachytherapy), radioactive material is sealed in needles, seeds, or wires and placed directly in or near the tumor. Radiation may lead to various side effects, such as fatigue, hair loss, and a susceptibility to infections. However, these side effects can usually be controlled.

Chemotherapy

Chemotherapy is the use of drugs to kill cancer cells. The anticancer drugs are usually released into the entire body (systemic therapy) so as to destroy the hard-to-detect cancer cells that have spread and are circulating in the body. Chemotherapy is based on the principle that cancer cells are affected more severely than the normal cells because they are rapidly dividing. Chemotherapeutic drugs can be injected into a vein, the muscle, or the skin, or they may be taken by mouth.

When chemotherapy is used before surgery, it is known as primary chemotherapy or neoadjuvant chemotherapy. Its purpose is usually to reduce the size of the tumor. The more common use of chemotherapy is in adjuvant therapy. In this form of treatment, chemotherapy is given after surgery to destroy any remaining cancer cells and to help prevent cancer from recurring. Chemotherapy can also be used in conjunction with radiation therapy.

The side effects of chemotherapy vary but can include susceptibility to infections, fatigue, poor appetite, weight loss, nausea, diarrhea, and hair loss. Decreased fertility can be a long-term side effect in some patients who undergo chemotherapy.

Bone marrow failure is a complication of chemotherapy. When high-dose chemotherapy is used, this failure is anticipated. Bone marrow transplantation (BMT) or peripheral stem cell transplantation (PSCT) are techniques used to treat this complication. Both techniques provide healthy stem cells for the patient. Stem cells are

QUESTIONS TO ASK YOUR DOCTOR

- What type of cancer do I have?
- What is the stage of my cancer?
- What types of treatments are available for the kind of cancer I have?
- What side effects are associated with each treatment that might be used for my cancer?

immature cells that mature into blood cells. They can replace the patient's own stem cells that have been damaged or destroyed by chemotherapy or radiation. The process allows a patient to undergo very aggressive treatment for their cancer. Patients who receive BMT or PSCT have an increased risk of infection, bleeding, and other side effects due to the chemotherapy and radiation. Graft-versus-host disease may occur as well. This complication occurs when the donated marrow reacts against a patient's tissues. It can occur any time after the transplant. Drugs may be given to reduce the risk of graft-versus-host disease and to treat the problem if it occurs.

Immunotherapy

Immunotherapy, also called biological therapy, is the use of treatments that promote or support the body's immune system response to cancer. The side effects of this immunotherapy are variable but include flu-like symptoms, weakness, loss of appetite, and skin rash. These symptoms will subside after the treatment is completed.

Hormone therapy

Hormone therapy is used to fight certain cancers that depend on hormones for their growth. Drugs can be used to block the production of hormones or change the way they work. Organs that produce hormones may be removed as well. As a result of this therapy, the growth of the tumor slows, and survival may be extended for several months or years.

Alternative and complementary therapies

There are certain cancer therapies that have not been scientifically tested and approved. If these unproven treatments are used instead of the standard therapy, they are known as alternative therapy. If used along with standard therapy, they are known as complementary therapy. The use of alternative therapies must be carefully considered, because some of these unproven treatments

may have life-threatening side effects. If someone uses alternative therapy, they may lose the opportunity to benefit from the standard, proven therapy. However, some complementary therapies may help to relieve symptoms of cancer, decrease the magnitude of side effects from treatment, or improve a patient's sense of well-being. The American Cancer Society recommends that anyone who is considering alternative or complementary therapy consult a healthcare team.

Prevention

According to experts from leading universities in the United States, a person can reduce the chances of getting cancer by following these guidelines:

- eating plenty of fruits and vegetables
- exercising vigorously for at least 20 minutes every day
- avoiding excessive weight gain
- avoiding tobacco (including second hand smoke)
- decreasing or avoiding consumption of animal fats and red meats
- avoiding excessive amounts of alcohol
- avoiding the midday sun (between 11 a.m. and 3 p.m.), when the sun's rays are the strongest
- avoiding risky sexual practices
- avoiding known carcinogens in the environment or workplace

Certain drugs that are currently being used for treatment can also be suitable for prevention. For example, the drug tamoxifen, also called Nolvadex (a pill) or Soltamox (a liquid), has been very effective against breast cancer and is thought to be helpful in the prevention of breast cancer. As with all medications, the drug comes with side effects, which, according to the Cleveland Clinic, may include weight gain, leg swelling, fatigue, menopause-like symptoms (such as night sweats or hot flashes), fatigue, skin rash, and other possible side effects. The doctor should explain these potential side effects to the patient.

Prognosis

Most cancers are curable if detected and treated at their early stages. A cancer patient's prognosis is affected by many factors, particularly the type of cancer the patient has, the stage of the cancer, the extent to which it has metastasized, and the aggressiveness of the cancer. In addition, the patient's age and general health status and the effectiveness of the treatment being pursued are important factors.

To help predict the future outcome of cancer and the likelihood of recovery from the disease, five-year survival rates are used. Five-year survival rates vary widely

for different types of cancers. Suggest using statistics from the NCI's Annual Report to the Nation 2021: Overall Cancer Statistics, which can be found at https://seer.cancer.gov/report_to_nation/statistics.html. The web page includes some graphs that might be reproducible in GEGD. These people may be free of cancer, or they may be undergoing treatment. It is important to note that while this statistic can give some information about the average survival of cancer patients in a given population, it cannot be used to predict individual prognosis. No two patients are exactly alike. For example, the five-year survival rate does not account for differences in detection methods, types of treatments, additional illnesses, and behaviors.

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- American Cancer Society, 250 Williams Street NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org/index>

American Childhood Cancer Organization, 10920 Connecticut Avenue, Suite A, Kensington, MD 20895, (301) 962-3520 or (855) 858-2226, (301) 962-3521, <http://www.acco.org>
National Cancer Institute, BG 9609 MSC 9760, 9609 Medical Center Drive, Bethesda, MD 20892-9760. 800-4-CANCER, (800) 422-6237, <http://www.cancer.gov>

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Revised by Christine Adamec

Cancer genetics

Definition

Cancer genetics is the analysis of the multiple alterations in genetic material that transform normal cells into cancer cells. The cancer cells undergo uncontrolled division and proliferation to form tumors and metastasize (spread) to other parts of the body. The study of cancer genetics includes inherited gene mutations or versions of genes (alleles) that increase the risk of cells turning cancerous.

Description

Cancer is considered a genetic disease, or one caused by changes to genes that control how cells function. Spontaneous gene mutations occur frequently in cells throughout the body. In most cases, the cellular machinery either repairs the mutation or signals the cell to die through a process called apoptosis. However, occasionally certain “gatekeeper” mutations or genetic alterations escape these protections, as well as immune-system surveillance.

Most cancers originate from a series of two to eight significant genetic alterations that occur in a single cell over a period of 20 to 30 years. Each of these alterations increases the probability that the cell will grow and divide and transform into a cancer cell rather than die. Most of these mutations are not inherited from parents and are not passed on to offspring. Rather, they occur in somatic (non-germline) cells throughout a person’s lifetime. Even when people inherit genes that increase their susceptibility to certain types of cancer, environmental influences and lifestyle choices, such as smoking, interact with the genes to increase cancer risk.

A cell is more likely to become cancerous if a mutation or other change affects certain types of genes. These types include genes that normally control cell division and proliferation, genes involved in DNA repair, or genes that normally cause the induction of apoptosis in case of genetic damage. Such cancer-promoting genetic alterations most often result from point mutations that change

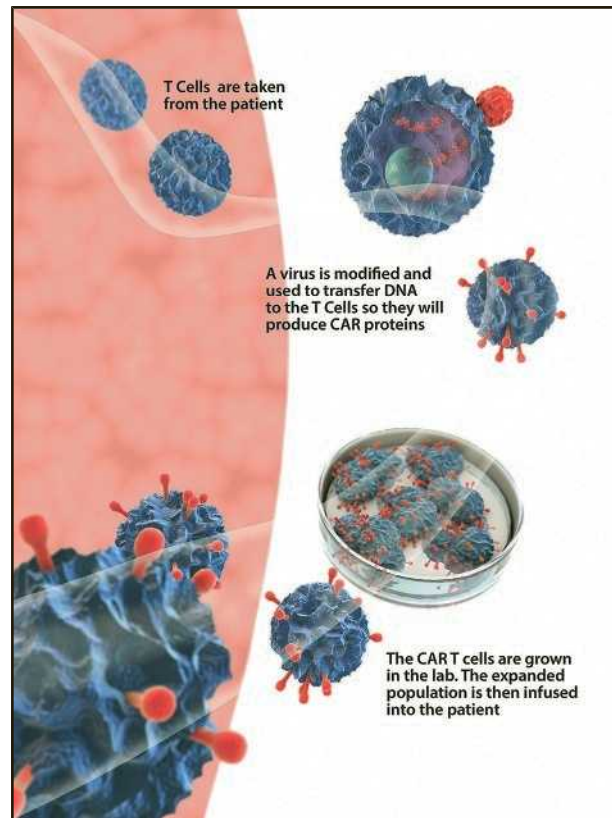


Illustration of the stages involved in CAR (chimeric antigen receptor) T cell immunotherapy, a process that is being developed to treat cancer. The sequence runs from top left to center right to lower left. The first stage (upper left) involves taking T cells (blue; a type of white blood cell) from the patient. These are then treated (upper right) with a virus (red) that transfers DNA (deoxyribonucleic acid, helical) to the T cells (a form of genetic engineering) that results in the production of chimeric antigen receptor (CAR) proteins. These proteins will be specific to the patient’s cancer. These modified T cells are then grown in the laboratory (Petri dish at lower right) and used to treat the patient (lower left). The technique is known as adoptive cell transfer (ACT). (Gunilla Elam/Science Source)

the DNA sequence of a gene. Other changes may be gene deletions or inversions (reversing the direction of the DNA sequence) or gene amplifications (the creation of multiple copies of a gene). The latter often arise from chromosome rearrangements, such as translocations that move portions of chromosomes to other chromosomes. Epigenetic changes that affect the expression of genes without changing their DNA sequence also are often involved in carcinogenesis, although these effects are not fully understood as of 2021.

Point mutations

DNA is a linear sequence of nucleotides. Each nucleotide is composed of phosphate, deoxyribose (a

Chromosomes and cancer

Cancer type	Associated gene mutation
Chronic myelocytic leukemia	translocation resulting in the Philadelphia chromosome (Ph ¹)
Burkitt's lymphoma	translocation involving the <i>c-myc</i> proto-oncogene
Retinoblastoma	mutation in chromosome 13; mutation can be inherited
Wilms' tumor	mutation in chromosome 11; mutation can be inherited
Colon cancer (occurs sporadically, but also occurs as a familial cancer syndrome)	mutation in adenomatous polyposis coli (APC) gene followed by further mutations
Breast cancer (occurs sporadically and also as a familial cancer syndrome)	mutation affecting the gene <i>BRCA1</i> , or mutation in <i>BRCA2</i>

Cancer genetics (Gale)

sugar), and one of four bases: adenine (A), guanine (G), cytosine (C), or thymine (T). These bases are paired (e.g., A-T and C-G) and form the “rungs” of the double helical structure of DNA. The order of the bases is the genetic code for producing specific proteins. The code for an amino acid in the protein (for example, glutamine-leucine-proline) is expressed as an order of each set of three bases (CAG-CTA-CCA). A point mutation is a single nucleotide change in the DNA sequence changing one or more amino acids in the protein. A point mutation in the thymine base of the second triplet in the sequence would produce CAG-CAA-CCA or glutamine-glutamine-proline in the protein. This mutation may alter the function or activity of the protein.

Chromosomal alterations

Whereas the rate of single-point mutations in cancer cells is similar to that in normal cells, rearrangements in chromosomes occur at a much higher rate in cancer cells and can affect multiple genes. Most solid tumors have numerous chromosome deletions, inversions, translocations, and duplications or other changes in the number of chromosomes. These large-scale alterations can make it difficult to identify the affected genes. However, chromosome translocations sometimes fuse together two genes to create a cancer gene called an oncogene, such as the *BCR-ABL* fusion gene in chronic myelogenous leukemia (CML). Occasionally, translocations inactivate a tumor-suppressor gene. Chromosome deletions can remove a tumor-suppressor gene.

Chromosome rearrangements can also cause gene amplifications, which are very common in human cancers. Gene amplifications producing 10 to 100 copies of a gene may lead to excessive amounts of a protein that can promote cancer cell proliferation.

Cancer genes

Proto-oncogenes, which are normal genes that can undergo mutations to become oncogenes that can turn a cell cancerous, were first discovered in the 1970s. Other classes of genes, such as tumor-suppressor and DNA-repair genes, normally protect against cancer. Mutations in these genes can eliminate that protection.

Oncogenes

Proto-oncogenes produce proteins that regulate cell division and help cells grow. When a proto-oncogene mutates so that it is continually activated (turned on) or is amplified so that there are multiple copies, it becomes an oncogene that overproduces proteins that lead to uncontrolled cell growth and division. Proto-oncogenes are generally converted into oncogenes by one of two mechanisms: a chromosomal rearrangement that moves the gene to a new position where it is constantly “on” or a gene amplification that produces too much of the encoded protein. Point mutations can also activate oncogenes. For example, point mutations in the *Ras* family of oncogenes are present in 15% of all human cancers.

Tumor-suppressor genes

Tumor-suppressor genes produce proteins that suppress or restrain cell growth and division, repair DNA mutations, or initiate apoptosis. When tumor-suppressor genes are mutated, they may fail to make the appropriate proteins. Cells can grow out of control, leading to cancer. While oncogenes are proto-oncogenes that have been activated, tumor-suppressor genes cause cancer when they are inactivated or “turned off.” For example, more than half of all cancers have acquired mutations in the tumor-suppressor gene *TP53* that codes for the tumor-suppressor protein p53.

Cancer genomics

The Human Genome Project, completed in 2003, revealed the entire DNA sequence of human cells and led to advanced sequencing technologies that have enabled researchers to sequence cancer genomes and compare them to the genome sequences of healthy cells. A Cancer Genome Atlas (CGA) was later developed. The landmark program characterized more than 20,000 samples of both cancer genes and normal matches for 33 cancer types. Over 12 years and with more than 11,000 patients contributing information, researchers compiled a huge set of data that is beginning to better show how cancer genetics work. For example, DNA alterations also can occur by fusion, alterations to copy numbers, or complex structural variations. One major finding has been a better understanding of how different tissues share the

KEY TERMS

Allele—Any of the alternative versions of a gene that are present in the population; some alleles increase the risk of specific cancers.

Apoptosis—Programmed self-destruction of a cell.

BRCA1 and BRCA2—Breast cancer susceptibility genes; specific inherited mutations in these genes greatly increase the risk of breast and ovarian cancers.

Cancer Genome Atlas (CGA)—A large multinational initiative for sequencing cancer genomes.

Chronic myelogenous leukemia (CML)—A type of leukemia caused by the *BCR-ABL* oncogene created by a gene fusion resulting from a chromosomal translocation.

Epigenetic—Gene modifications that are independent of the DNA sequence.

Exome—The protein-encoding DNA sequences of the genome.

Gene—A DNA sequence that contains the instructions for producing a specific protein; each gene is normally situated at a precise location on a chromosome.

Gene amplification—The creation of multiple copies of a gene, which can result in the production of excessive amounts of a specific protein.

Gene expression panel—A method for genetically characterizing specific types of cancer.

Genome—The entire DNA sequence of a cell or organism.

HER2—Human epidermal growth factor receptor 2 (EGFR2); also called HER2/neu or erbB-2; a protein overproduced in HER2-positive cancers.

Hereditary nonpolyposis colorectal cancer (HNPCC)—Lynch syndrome; the most common familial cancer syndrome that increases the risk of colorectal cancer; caused by inherited mutations in any of several genes, most of which are involved in DNA repair.

Li-Fraumeni syndrome—A rare familial cancer syndrome characterized by high risk for early-onset breast cancer and soft-tissue sarcomas.

Metastases—Cancers that have spread from the initial (primary) cancer site to other parts of the body.

Mutation—An inherited or spontaneous change in the DNA sequence of a gene.

Nucleotides—The building blocks of DNA and genes.

Oncogene—A proto-oncogene that has developed mutations that can transform a normal cell into a cancer cell; proto-oncogenes promote normal cell growth and division.

Polymerase chain reaction (PCR)—A method for making many copies of DNA or RNA; can be used to detect mutations in genes.

RB1—A cell-cycle control and tumor-suppressor gene; deletion or mutation of RB1 can lead to retinoblastoma.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division, which can create oncogenes, amplify oncogenes, or inactivate a tumor-suppressor gene.

Tumor-suppressor gene—A gene involved in controlling normal cell growth and preventing cancer; mutations in tumor-suppressor genes can promote cancer.

same genetic alterations and resemble one another in tumor biology. On the other hand, some specific cancer types react differently to similar genetic alterations.

Cancer genome sequencing has revealed about 140 genes that when mutated promote or “drive” carcinogenesis. A typical tumor contains 2–8 of these so-called driver gene mutations in oncogenes and tumor-suppressor genes. The driver genes are classified according to which of 12 different cell-signaling pathways they affect or interfere with. These signaling pathways regulate cell fate, cell survival, and genome maintenance. For example, the *APC* gene is most often the first “gatekeeper” or driver mutation in a cell that may eventually

develop into colon cancer. Mutations in the *APC* gene give the cell a growth advantage so that cells with the mutation slowly outgrow neighboring normal colon cells. The occurrence of a second mutation, often in the *KRAS* gene, enables the cell to proliferate much faster. Further mutations in other genes, usually over a period of years, eventually generate a malignant tumor.

Although cancer cells may have hundreds or thousands of point mutations and chromosome translocations, most of these are “passenger” mutations that have little effect on cancer development. Exome sequencing is used to identify mutations only in protein-coding regions of the DNA. Common solid breast, brain, colon, and

pancreatic tumors have an average of 33 to 55 gene mutations that are expected to alter protein products. Most of these are single-base (point) mutations in the DNA sequence. Some cancers, such as melanomas and lung tumors, contain about 200 different mutations, reflecting the effects on DNA of the mutagens ultraviolet light and cigarette smoke, respectively. Tumors with mutations in DNA repair genes can have thousands of mutations, reflecting the inability of the cells to carry out routine DNA repair. In contrast, leukemias and childhood tumors have far fewer mutations—an average of 9.6 per tumor—because the cancers develop over a much shorter period of time.

Tumor cells also have large numbers of epigenetic changes. These are modifications to DNA or histones (the proteins that surround DNA in chromosomes) that change gene expression—the amount of protein that a gene produces. Genome-wide sequencing has revealed previously unidentified driver genes that produce proteins for modifying DNA or histones. These epigenetic effects on gene expression can also promote the growth and proliferation of cancer cells. With advances in cancer genomics, testing can determine how many mutations are present in a tumor (tumor mutational burden) as well as the tumor's stability.

Genetic heterogeneity

In recent years, advanced genome sequencing has revealed that cancerous tumors can have hundreds or thousands of mutations. Furthermore, these mutations can differ significantly among the cells in a single tumor, as well as in tumor metastases—cancers that have spread to other parts of the body from the primary tumor. This means that not only is every cancer genetically unique, but that each cancer itself may contain several genetically distinct populations of cells. In recent years, research teams from around the world have sequenced breast tumor genomes and found that metastases differ genetically from the primary tumor. These metastases apparently evolved from subclones of different cells within the original primary breast tumor. Similar results have been found for pancreatic tumors and their metastases. In a study of large kidney tumors and their metastases, researchers identified 128 different mutations, only about one-third of which were present in all the samples from a single patient, although sometimes there were different mutations within the same cancer genes. Genome sequencing of leukemias has also identified multiple rare genetic subclones of cancer cells from individual patients.

This genetic heterogeneity among tumor cells and metastases has significant implications for diagnosis, treatment, and prognosis. For example, genetic analysis of a single biopsy from a tumor may fail to identify the

QUESTIONS TO ASK YOUR DOCTOR

- Will my cancer be tested for genetic mutations?
- What types of genetic tests will be performed?
- What information will the genetic tests provide?
- Will genetic test results affect my treatment choices?
- Will the genetics of my metastasized cancer be analyzed separately from my primary tumor?

genetic characteristics of all of the tumor cells. Genetic heterogeneity helps explain why cancer treatments are not necessarily effective in all patients with the same type of cancer. Furthermore, it helps explain why newer cancer drugs that target a specific gene mutation almost invariably stop working after a time. The drug may be effective against some, but not all, cancer cells in a tumor. Once the genetically susceptible cells are destroyed, the drug-resistant cells with different mutations can proliferate.

Diagnosis, treatment, and prognosis

Genetic changes in tumor cells can be used to diagnose specific cancers, determine appropriate treatments, and predict whether the cancer is likely to return after treatment. Although most tumors cannot be subjected to whole-genome or exome sequencing, there are various methods for identifying genetic alterations that are common in specific types of cancer. Gene expression panels are used for a number of cancer types, including breast, colon, and prostate cancers. These panels measure the activity (expression) of genes commonly involved in these cancers. The results help in selection of appropriate treatments. For example, the Oncotype Dx breast cancer panel measures the expression of 21 genes, using a method called reverse transcription-polymerase chain reaction (RT-PCR). This method can help predict which patients are most likely to benefit from certain treatments. A 70-gene panel called the MammaPrint is used to analyze breast cancer tumors for their risk of recurrence. Gene amplifications can be detected by cytological staining or by a fluorescent technique called comparative genomic hybridization (CGH).

PCR is used to detect the *BCR-ABL* fusion gene in CML and certain other leukemias. This fusion gene forms when the *ABL* gene from chromosome 9 breaks off and joins the *BCR* gene on chromosome 22 to form the Philadelphia chromosome. PCR is very sensitive—it can

detect the fusion gene, even when there are just a few CML cells among millions of normal cells. PCR is used to confirm diagnoses, monitor disease status, and guide treatment.

Cancer genetic testing is particularly useful for selecting treatments. Targeted therapies for cancer rely on this specific information to better manage the cancer. For example:

- *HER2* is a proto-oncogene that, when amplified to produce multiple copies, becomes an oncogene that causes cells to grow out of control. *HER2*-positive breast cancers do not respond well to some chemotherapy drugs, but specific drugs are available that destroy *HER2*-positive cells. Therefore, breast cancers are routinely tested for *HER2*. *HER2*-positive stomach cancers may also respond to these drugs.
- Specific drugs can target the tyrosine kinase protein produced by the *BCR-ABL* fusion gene in CML.
- Patients with acute myeloid leukemia cells with a mutation in the gene have a poorer prognosis than patients with mutations only in the *NPM1* gene, so a more aggressive treatment, such as a stem cell transplant, may be recommended for cancers with an *FLT3* mutation.
- *KRAS* gene mutations, which occur in 30% to 40% of colorectal tumors, do not respond to some drugs that are used to treat advanced colorectal cancer.
- Lung cancers with *ALK* gene mutations and melanomas and colorectal cancers with specific *BRAF* gene mutations can be targeted with specific drugs.

Hereditary cancer syndromes

Hereditary cancers are caused by genes that are passed down from parents to offspring and that increase the risk of developing specific types of cancer. More than 50 different hereditary cancer syndromes (familial cancers) have been identified. Although rare in the general population, they account for 5% to 10% of all cancers. In general, inheriting a familial cancer gene increases the risk of developing particular cancers, but it does not mean that the individual will necessarily develop cancer. However, familial cancer genes can cause cells to accumulate mutations more quickly and easily, which is why familial cancers tend to occur earlier in life.

Hereditary breast and ovarian cancers were among the first recognized familial cancers and led to the discovery of the *BRCA1* and *BRCA2* tumor-suppressor genes. Certain mutations in these genes confer a very high risk for breast, ovarian, and certain other cancers. However, fewer than 10% of breast and ovarian cancers are caused by these inherited mutations.

Various other familial cancer syndromes are also caused by mutations in tumor-suppressor genes. For example, Li-Fraumeni syndrome is a rare condition associated with many different cancers, most of which develop during childhood or young adulthood. Li-Fraumeni syndrome is most often caused by mutations in the *TP53* gene that encodes the p53 tumor-suppressor protein that normally halts the growth of abnormal cells. *TP53* was the most commonly mutated gene found in cancers as of 2021.

PTEN is a gene that produces a protein that can suppress the growth of cancerous tumors. Mutations in the gene are associated with Cowden syndrome, which is an inherited cancer syndrome associated with increased risk of breast, thyroid, endometrial, and other cancers.

Hereditary nonpolyposis colorectal cancer (HNPCC), or Lynch syndrome, is the most common familial cancer syndrome that increases the risk of colorectal cancer, usually before age 50. It is also associated with various other cancers and can be caused by mutations in various genes, most of which are involved in DNA repair.

Genetic testing

In addition to genetic testing of tumors, genome testing is available for hereditary cancer syndromes such as breast cancer, HNPCC, or mutations in the *RBI* gene that cause retinoblastoma. Individuals who test positive for increased cancer risk may choose to have frequent cancer screenings, make lifestyle changes to decrease their risk, or even undergo prophylactic procedures such as mastectomy (breast removal). Nevertheless, positive genetic tests do not mean that people will necessarily develop a particular cancer. Similarly, negative test results do not mean that they will not develop a particular cancer. Genetic counselors are trained in interpreting test results and in helping people decide whether to undergo genetic testing.

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American Cancer Society, 250 Williams Street NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org>

American Society of Clinical Oncology, 2318 Mill Road, Suite 800, Alexandria, VA 22314, (888) 282-2552, <https://www.asco.org/>

National Cancer Institute, 6116 Executive Boulevard, Suite 300, Bethesda, MD 20892-8322, (800) 422-6237, <http://www.cancer.gov>

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Cardiofaciocutaneous syndrome

Definition

Cardiofaciocutaneous syndrome is an extremely rare genetic condition present at birth characterized by intellectual disability, slow growth, and abnormalities of the heart, face, skin, and hair. There is no cure for cardiofaciocutaneous syndrome. Treatment centers on the

correction of heart abnormalities and strategies to improve the quality of life of the affected individual.

Description

Cardiofaciocutaneous syndrome was first identified and described in 1986 by J. F. Reynolds and colleagues at the Shodair Children's Hospital in Helena, Montana, and at the University of Utah. These physicians identified and described eight children with a characteristic set of mental and physical changes including abnormal skin conditions, an unusual face, sparse and curly hair, heart defects, and intellectual disability. These physicians named the syndrome based on the changes of the heart (cardio), face (facio), and skin (cutaneous). Since that time, physicians have used the descriptions originally put forth by Reynolds to identify other children with cardiofaciocutaneous syndrome.

Scientific research suggests that cardiofaciocutaneous syndrome is associated with a change in the genetic material. However, it is still not known precisely how this change in the genetic material alters growth and development in the womb to cause cardiofaciocutaneous syndrome.

Cardiofaciocutaneous syndrome can sometimes be confused with another genetic syndrome, Noonan syndrome. Children with Noonan syndrome have abnormalities in the same genetic material as those with cardiofaciocutaneous syndrome, and the two syndromes share some similar physical characteristics. Many scientists believe that the two diseases are different entities and should be regarded as separate conditions, while others believe that Noonan syndrome and cardiofaciocutaneous syndrome may be variations of the same disease.

Genetic profile

Recent research has shown that people with cardiofaciocutaneous syndrome have changes in one of four genes: *BRAF*, *MEK1*, *MEK2*, and *KRAS*. Some affected individuals do not have a mutation in one of these genes, suggesting that other genes are also associated with the syndrome.

In almost all cases of cardiofaciocutaneous syndrome, there is no family history of the disease. These cases are thought to represent new genetic changes that occur randomly and with no apparent cause and are termed sporadic. While the cause of the genetic change is still unclear, some studies suggest that the age of the father might be important in the genesis of the disease. In 20 cases for which information was available, scientists noted that fathers of affected children tended to be older (average age of 39 years) when the child was conceived. Therefore, it is believed that a change in the genetic material of the father's sperm may occur as the man ages, and that he

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Bitemporal constriction—Abnormal narrowing of both sides of the forehead.

Macrocephaly—A head that is larger than normal.

Noonan syndrome—A genetic syndrome that possesses some characteristics similar to cardiofaciocutaneous syndromes. It is unclear whether the two syndromes are different or two manifestations of the same disorder.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

may, in turn, pass this genetic change to the child, resulting in cardiofaciocutaneous syndrome.

Only one abnormal gene in a gene pair is necessary to display the disease. This is an example of a dominant gene (i.e., the abnormal gene of the gene pair dominates over the normal gene, resulting in the syndrome).

Demographics

Cardiofaciocutaneous syndrome is an extremely rare condition. Because the syndrome is relatively new and only a small number of physicians have actual first-hand experience with the diagnosis of the syndrome, some children with the syndrome may not be diagnosed, particularly if they are living in areas where sophisticated medical care is not available. As a result, it is difficult to know how many children are affected by cardiofaciocutaneous syndrome. However, scientists estimate that at least 800 children worldwide are affected by this condition as of 2021.

Because the syndrome is so rare, it is not known whether the disease is distributed equally among different geographic areas or whether different ethnic groups have higher incidences of the syndrome.

Signs and symptoms

Individuals with cardiofaciocutaneous syndrome have distinct malformations of the head and face. An unusually large head (macrocephaly), a prominent forehead, and abnormal narrowing of both sides of the forehead (bitemporal constriction) are typical. A short, upturned nose with a low nasal bridge and prominent external ears that are abnormally rotated toward the

back of the head are also seen. In most cases, affected individuals have downward slanting eyelid folds, widely spaced eyes, drooping of the upper eyelids, inward deviation of the eyes, and other eye abnormalities. In addition to having unusually dry, brittle, curly scalp hair, affected individuals may lack eyebrows and eyelashes.

Individuals with cardiofaciocutaneous syndrome may also have a range of skin abnormalities, varying from areas of skin inflammation to unusually dry, thickened, scaly skin over the entire body. Most affected individuals also have congenital heart defects, particularly obstruction of the normal flow of blood from the right chamber of the heart to the lungs and/or an abnormal opening in the wall that separates two of the heart chambers.

In addition, most individuals with the disorder experience growth delays, mild to severe intellectual disability, and abnormal delays in the acquisition of skills requiring the coordination of muscular and mental activity. Other abnormalities encountered in children with cardiofaciocutaneous syndrome include seizures, abnormal movements of the eye, poor muscle tone, and poor digestion. In some cases, additional abnormalities may be present.

Diagnosis

The diagnosis of cardiofaciocutaneous syndrome relies on a physical exam by a physician familiar with the condition and radiographic evaluation, such as the use of x-rays or ultrasound to define abnormal or missing structures that are consistent with the criteria for the condition. Although a diagnosis may be made in a newborn, most often the features do not become fully evident until early childhood.

There is no laboratory blood test that can be used to identify people with cardiofaciocutaneous syndrome. However, because the condition is so rare, molecular genetic testing is available for mutations in the four genes known to cause CFC syndrome.

Cardiofaciocutaneous syndrome can be differentiated from Noonan syndrome by the presence of nervous system abnormalities, such as low muscle tone, seizures, and abnormal movements of the eye, as well as by typical changes in the hair and skin.

Treatment and management

There is no cure for cardiofaciocutaneous syndrome. The genetic change responsible for cardiofaciocutaneous syndrome is present in every cell of the body and, as of 2021, there was no means of correcting this genetic abnormality.

Treatment of the syndrome is variable and centers on correcting the different manifestations of the condition. For

QUESTIONS TO ASK YOUR DOCTOR

- What do we know about the genetic basis of cardiofaciocutaneous syndrome?
- How soon after birth can a child with cardiofaciocutaneous syndrome be diagnosed, and on what basis is that diagnosis made?
- What early treatments are available for cardiofaciocutaneous syndrome?
- What is the average lifespan for a child born with cardiofaciocutaneous syndrome, and what factors affect that prognosis?

children with heart defects, surgical repair is often necessary. This may take place shortly after birth if the heart abnormality is life threatening, but often physicians will prefer to attempt a repair once the child has grown older and the heart is more mature. For children who experience seizures, lifelong treatment with antiseizure medications is often necessary. Oral or topical medications may also be used to treat the inflammatory skin conditions and provide some symptomatic and cosmetic relief.

During early development and progressing into young adulthood, children with cardiofaciocutaneous syndrome should be educated and trained in behavioral and mechanical methods to adapt to their disabilities. This program is usually initiated and overseen by a team of healthcare professionals including a pediatrician, physical therapist, and occupational therapist. A counselor specially trained to deal with issues of disabilities in children is often helpful in assessing problem areas and encouraging healthy development of self-esteem. Support groups and community organizations for people with cardiofaciocutaneous syndrome or other disabilities often prove useful to the affected individual and their families. Specially equipped schools or enrichment programs should also be sought.

Children with cardiofaciocutaneous syndrome should be seen regularly by a team of healthcare professionals, including a pediatrician, medical geneticist, pediatric cardiologist, dermatologist, and neurologist. Consultation with a reconstructive surgeon may be of use if some of the physical abnormalities are particularly debilitating.

Prognosis

The prognosis of children with cardiofaciocutaneous syndrome depends on the severity of the symptoms and

the extent to which appropriate treatments are available. In addition to the physical disabilities, the intellectual disability and other nervous system effects can be severe. Since cardiofaciocutaneous syndrome was discovered relatively recently, very little is known regarding the level of functioning and the average lifespan of individuals affected with the condition.

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- "Cardiofaciocutaneous Syndrome." National Organization for Rare Disorders. Last updated 2017. <https://rarediseases.org/rare-diseases/cardiofaciocutaneous-syndrome/> (accessed August 8, 2021).

ORGANIZATIONS

- CFC International, 8720 W. Bent Tree Drive, Peoria, AZ 85383, (623) 248-7992, info@cfcsyndrome.org, <http://www.cfcsyndrome.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Oren Traub, MD, PhD

Carnitine palmitoyltransferase deficiency

Definition

Carnitine palmitoyltransferase (CPT) deficiency refers to two separate hereditary diseases of lipid metabolism, CPT-I deficiency and CPT-II deficiency. CPT-I

deficiency affects lipid metabolism in the liver, with serious physical symptoms including coma and seizures. Two types of CPT-II deficiency are similar in age of onset and type of symptoms to CPT-I deficiency. The third most common type of CPT-II deficiency involves intermittent muscle disease in adults, with a potential for myoglobinuria, a serious complication affecting the kidneys. Preventive measures and treatments are available for CPT-I deficiency and the muscle form of CPT-II deficiency.

Description

Carnitine palmitoyltransferase (CPT) is an important enzyme required by the body to use (metabolize) lipids (fats). CPT speeds up the transport of long-chain fatty acids across the inner mitochondria membrane. This transport also depends on carnitine, also called vitamin B₇.

Until the 1990s, discussion centered on whether defects in a single CPT enzyme were responsible for all the conditions resulting from CPT deficiency. Careful chemical and genetic analysis eventually pointed to two different enzymes: CPT-I and CPT-II. Both CPT-I and CPT-II were shown to play an important role in the metabolism of lipids. CPT deficiency of any type affects the muscles, so these disorders are considered to be metabolic myopathies (muscle diseases), or more specifically, mitochondrial myopathies, meaning myopathies that result from abnormal changes occurring in the mitochondria of the cells as a result of excessive lipid buildup.

Understanding the symptoms of CPT requires some familiarity with the basics of lipid metabolism in muscle cells. Fatty acids (FAs) are the major component of lipids. FAs contain a chain of carbon atoms of varying length. Long-chain fatty acids (LCFAs) are the most abundant type, and have at least 12 carbon atoms. Lipids and glucose (sugar) are the primary sources of energy for the body. Both are converted into energy (oxidized) inside mitochondria, structures within each cell where numerous energy-producing chemical reactions take place. Each cell contains many mitochondria.

A single mitochondrion is enclosed by a double-layer membrane. LCFAs are unable to pass through the inner portion of this membrane without first being bound to carnitine, a type of amino acid. CPT-I chemically binds carnitine to LCFAs, allowing transfer through the inner membrane. However, LCFAs cannot be oxidized inside the mitochondrion while still attached to carnitine, so CPT-II reverses the action of CPT-I and removes carnitine. Once accomplished, LCFAs can proceed to be metabolized. Therefore, deficiency of either CPT-I or CPT-II results in improper transfer and utilization of LCFAs in the mitochondria.

CPT-I is involved in lipid metabolism in several tissues, most importantly the liver. There, LCFAs are broken down and ketone bodies are produced. Like lipids and glucose, ketone bodies are used by the body as fuel, especially in the brain and muscles. Deficiency of CPT-I in the liver results in decreased levels of ketone bodies (hypoketosis), as well as low blood sugar levels (hypoglycemia). Hypoketosis combined with hypoglycemia in a child can lead to weakness, seizures, and coma. Symptoms can be reversed by glucose infusions, as well as supplementation with medium-chain fatty acids, which do not require CPT-I to produce energy.

As noted, glucose and fatty acids are important energy sources for the body. During exercise, the muscles initially use glucose as their primary fuel. After some time, however, glucose is depleted and the muscles switch to using fatty acids by a chemical process called oxidation. CPT-II deficiency results in a decrease in LCFAs that can be used by the mitochondria, and the muscles eventually exhaust their energy supply. This explains why prolonged exercise may cause an attack of muscle fatigue, stiffness, and pain in people with CPT-II deficiency. The ability to exercise for short periods is not affected. Infections, stress, muscle trauma, and exposure to cold also put extra demands on the muscles and can trigger an attack. Fasting or a diet high in fats and low in carbohydrates (complex sugars) deplete glucose reserves in the muscles and are risk factors as well.

In some cases, CPT deficiency results in the breakdown of muscle tissue, a process called rhabdomyolysis, and it causes some components of muscle cells to “leak” into the bloodstream. Myoglobin, the muscle-cell equivalent of hemoglobin in the blood, is one of these components. Myoglobin is filtered from the blood by the kidneys and deposited in the urine, causing myoglobinuria. Dark-colored urine is the typical sign of myoglobinuria. Severe and/or repeated episodes of rhabdomyolysis and myoglobinuria can cause serious kidney damage.

Genetic profile

CPT-I deficiency is caused by defects in the *CPT1* gene located on chromosome 11. CPT-II deficiency results from mutations in the *CPT2* gene on chromosome 1.

Both CPT-I and CPT-II deficiency are considered autosomal recessive conditions. This means that both parents of an affected person carry one defective *CPT* gene, but also have a normal gene of that pair. Carriers of a single recessive gene typically do not express the deficiency because the second normal functioning gene is able to compensate. A person with two mutated genes has no normal gene to make up for the deficiency and thus

KEY TERMS

Carnitine—An amino acid necessary for metabolism of the long-chain fatty acid portion of lipids. Also called vitamin B₇.

Fatty acids—The primary component of fats (lipids) in the body. Carnitine palmitoyl transferase (CPT) deficiency involves abnormal metabolism of the long-chain variety of fatty acids.

Hypoglycemia—An abnormally low glucose (blood sugar) concentration in the blood.

Hypoketosis—Decreased levels of ketone bodies.

Ketone bodies—Products of fatty acid metabolism in the liver that can be used by the brain and muscles as an energy source.

Metabolic myopathies—A broad group of muscle diseases whose cause is a metabolic disturbance of some type.

Mitochondria (singular, mitochondrion)—Organelles within the cell responsible for energy production.

Myoglobinuria—The abnormal presence of myoglobin, a product of muscle disintegration, in the urine. Results in dark-colored urine.

Myopathy—Any abnormal condition or disease of the muscle.

Rhabdomyolysis—Breakdown or disintegration of muscle tissue.

expresses the disease. Parents who are both carriers for the same autosomal recessive condition face a 25% chance in each pregnancy that they will both pass on the defective gene and have an affected child.

Several individuals proven to be carriers of CPT-II deficiency have had mild symptoms of the disorder. Measurement of CPT-II enzyme levels (the protein coded for by *CPT2*) in most of the carriers tested show lower levels, as would be expected when one gene is mutated and the other is not. It is not yet clear why some carriers show mild symptoms, but this phenomenon occasionally occurs in other autosomal recessive conditions.

Demographics

CPT-I deficiency is rare, with fewer than 50 cases having been reported. CPT-II deficiency is more common, with more than 300 reported cases, but its true occurrence is unknown. Muscle CPT-II deficiency makes up the majority of cases that have been reported; liver and multiorgan CPT-II deficiency are both quite rare. There

seems to be no geographic area or ethnic group that is at greater risk for either type of CPT deficiency.

Approximately equal numbers of males and females with CPT-I deficiency have been seen, which is typical of autosomal recessive inheritance. However, about 80% of those individuals diagnosed with CPT-II deficiency are male. Males and females do have an equal likelihood of inheriting a defective *CPT2* gene from a parent, but the effects of the gene in each sex can be different. Hormonal differences between males and females may have some effect—a clue being the tendency of an affected woman to have more symptoms while pregnant.

Signs and symptoms

CPT-I deficiency

The CPT-I enzyme has two forms, coded for by different genes. CPT-IA is the form present in liver, skin, kidney, and heart cells, while CPT-IB functions in skeletal muscle, heart, fat, and testis cells. CPT-I deficiency refers to the CPT-IA form since a defective CPT-IB enzyme has not yet been described in humans. CPT-I deficiency has always been diagnosed in infants or children.

The brain and muscles use ketone bodies as a source of energy. The brain especially relies heavily on ketone bodies for energy during times of stress, such as after fasting when low sugar levels (hypoglycemia) occur. In fact, children with CPT-I deficiency are usually first diagnosed after they have fasted due to an illness or diarrhea. Hypoketosis and hypoglycemia in CPT-I deficiency can become severe, and result in lethargy (lack of physical energy), seizures, and coma.

CPT-II deficiency

CPT-II deficiency is divided into three subtypes. Muscle CPT deficiency is the most common form of the condition. Onset of symptoms is usually in adolescence or adulthood, but varies. Hepatic CPT-II deficiency is rare and is diagnosed in childhood. The remaining cases are classified as multiorgan CPT-II deficiency, and have been diagnosed in infants. Differences in the severity of symptoms between the groups, as well as within each group, are due in part to different mutations in the *CPT2* gene. Environmental factors may assist the triggering of attacks and thus may contribute to the variety of observed symptoms.

MUSCLE CPT-II DEFICIENCY. Muscle fatigue, stiffness, and pain are typically caused by prolonged exercise or exertion. Other possible triggers include fasting, infection, muscle injury, exposure to cold, and even emotional stress. Cases of adverse reactions to certain types of general anesthesia have also been reported.

These muscle attacks after a triggering event are the classic physical signs of muscle CPT-II deficiency. When an attack is associated with the breakdown of muscle tissue (rhabdomyolysis), myoglobinuria is the other classic sign. Unlike other metabolic myopathies, there are no obvious signs of an impending attack, and resting will not stop the symptoms once they have begun. Muscle symptoms may begin during or up to several hours after prolonged exercise or other triggering events. A specific muscle group may be affected, or generalized symptoms may occur. Muscle weakness between attacks is not a problem, unlike some other metabolic myopathies. In addition, muscle cells examined under the microscope typically appear normal. Some people with muscle CPT deficiency have only had a few attacks in their lifetime, while others may experience several attacks per week. Renal failure due to repeated episodes of myoglobinuria occurs in about 25% of individuals with muscle CPT deficiency.

HEPATIC CPT-II DEFICIENCY. Symptoms and age of onset in hepatic CPT-II deficiency are similar to CPT-I deficiency, primarily coma and seizures associated with hypoketotic hypoglycemia. However, unlike CPT-I deficiency, most infants with liver CPT-II deficiency have had heart problems and have died.

MULTIORGAN CPT-II DEFICIENCY. This type of CPT-II deficiency has only been reported a few times and involves the liver, skeletal muscles, and heart. Infants with this type have all died.

Diagnosis

The symptoms of CPT-I deficiency can be dramatic, but the rare nature of the disease means that some time may elapse while other more common diseases are ruled out. Definitive diagnosis of CPT-I deficiency is made by measuring the activity of the CPT enzyme in fibroblasts, leukocytes, or muscle tissue. Abnormal results on several blood tests are also typical of CPT-I deficiency, but the most important finding is hypoketotic hypoglycemia. Analysis of the *CPT1* gene on chromosome 11 may be possible, but is not yet considered a diagnostic test.

CPT-II deficiency is somewhat more common than CPT-I deficiency. However, the milder symptoms of muscle CPT deficiency and their similarity to other diseases often leads to a wrong diagnosis (misdiagnosis). For example, the symptoms of CPT-II deficiency are sometimes initially diagnosed as fibromyalgia or chronic fatigue syndrome. Misdiagnosis is a special concern for people with muscle CPT-II deficiency, since the use of available preventive measures and treatment are then delayed.

QUESTIONS TO ASK YOUR DOCTOR

- Can you explain the name of this disorder?
- How do the two types of carnitine palmitoyltransferase deficiency differ from each other?
- What forms of treatment for the disorder are available, and how effective are these treatments?
- What is the prognosis for a child born with each type of carnitine palmitoyltransferase deficiency?

Analysis of the CPT-II enzyme levels can confirm the diagnosis, but must be done carefully if performed on any tissue other than a muscle specimen. Direct testing of the *CPT2* gene is available and is probably the easiest method (simple blood sample) of making the diagnosis. If genetic testing shows two mutated *CPT2* genes, the diagnosis is confirmed. However, not all disease-causing mutations in the gene have been discovered, so demonstration of only one mutated *CPT2* gene, or a completely negative test, does not exclude the diagnosis. In those individuals in whom genetic testing is not definitive, the combination of clinical symptoms and a laboratory finding of low levels of CPT-II enzyme activity should be enough to confirm the diagnosis.

Treatment and management

While CPT-I and CPT-II deficiency differ in their typical age of onset and in the severity of their symptoms, treatment of both conditions is similar. Attacks may be prevented by avoiding those situations that lead to them. Someone undergoing surgery should discuss the possibility of alternative anesthetics with their doctor. Most people with CPT deficiency find it necessary to carry or wear some type of identifying information about their condition such as a Medic-Alert bracelet.

Those who find that they cannot avoid a situation known to be a trigger for them should try to supplement their diet with carbohydrates. Since medium-chain fatty acids do not require carnitine to enter the mitochondrion, use of a dietary supplement containing them results in significant improvement in people with CPT-I deficiency and also helps prevent attacks in most people with CPT-II deficiency. The use of carnitine supplements (vitamin B₇) is also helpful for some individuals diagnosed with the deficiency.

Anyone diagnosed with CPT deficiency, or anyone concerned about a family history of CPT deficiency, should

be offered genetic counseling to discuss the most up-to-date treatment and testing options available to them.

Prognosis

Children with CPT-I deficiency improve significantly with treatment. So far, however, all have had some lasting neurological problems, possibly caused by damage to the brain during their first attack. The outlook at this point for infants and children with liver and multiorgan CPT-II deficiency is still poor.

Once a person with muscle CPT-II deficiency is correctly diagnosed, the prognosis is good. While it is impossible for many patients to completely avoid attacks, most people with the condition eventually find the right mix of preventive measures and treatments. CPT-II deficiency then has much less of a harmful impact on their lives. A number of excellent sources of information are available for families affected by CPT deficiency. Any new treatments in the future would likely attempt to directly address the enzyme deficiency, so that normal metabolism of lipids might occur.

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ORGANIZATIONS

- Fatty Oxidation Disorders (FOD) Family Support Group, PO Box 54, Okemos, MI 48805-0054, (517) 381-1940, (866) 290-5206, deb@fodsupport.org, <http://www.fodsupport.org>

Genetic Alliance, 26400 Woodfield Road #189, Damascus, MD 20872, (202) 966-5557, info@geneticalliance.org, <http://www.geneticalliance.org>

March of Dimes, 1550 Crystal Dr, Suite 1300, Arlington, VA 22202, (888)-MODIMES (888-663-4637), <http://www.modimes.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

United Mitochondrial Disease Foundation, 8085 Saltsburg Road, Suite 201, Pittsburgh, PA 15239, (412) 793-6477 or (888) 317-8633, (412) 793-6477, info@umdf.org, <http://www.umdf.org>

Scott J. Polzin, MS, CGC

Carpenter syndrome

Definition

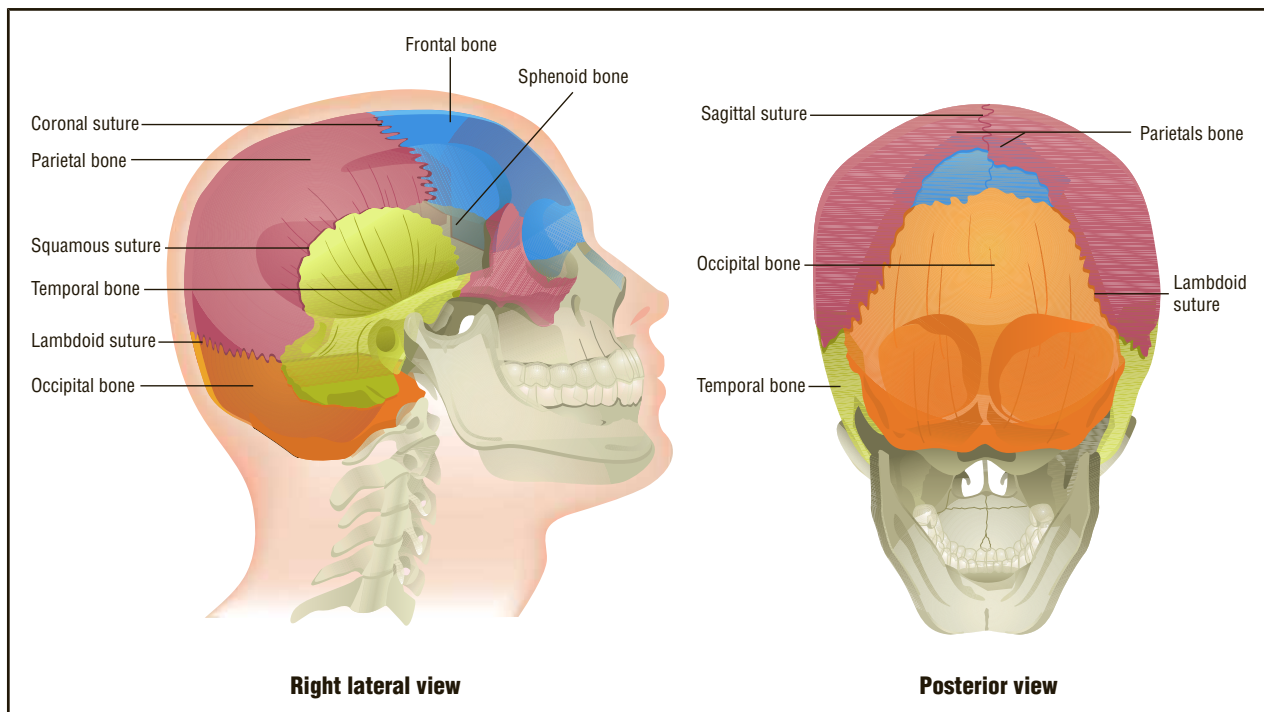
Carpenter syndrome is a rare hereditary disorder resulting in the premature closing of the cranial sutures, which are the line joints between the bones of the skull, and in syndactyly, a condition characterized by the webbing of fingers and toes. The syndrome is named after G. Carpenter, who first described this disorder in 1901.

Description

Carpenter syndrome is a subtype of a family of genetic disorders known as acrocephalopolysyndactyly (ACPS) disorders. Carpenter syndrome is also called acrocephalopolysyndactyly type II (ACPS II). There were originally five types of ACPS. This number has decreased in recent years because some of these conditions have been recognized as being similar to each other or to other genetic syndromes. For example, it is now agreed that ACPS I, or Noack syndrome, is the same as Pfeiffer syndrome. Researchers have also concluded that the disorders formerly known as Goodman syndrome (ACPS IV) and Summitt syndrome are variants (slightly different forms) of Carpenter syndrome.

All forms of ACPS are characterized by premature closing of the cranial sutures and malformations of the fingers and toes. Individuals diagnosed with Carpenter syndrome have short and broad heads (brachycephaly), the tops of which appear abnormally cone-shaped (acrocephaly). Webbing or fusion of the fingers or toes (syndactyly) and/or the presence of extra fingers or toes (polydactyly) are also characteristic signs of Carpenter syndrome.

The human skull consists of several bony plates separated by a narrow fibrous joint that contains stem cells. These fibrous joints are called cranial sutures. There are



Graphic of human skull (Gale)

six sutures: the sagittal, which runs from front to back across the top of the head; the two coronal sutures, which run across the skull parallel to and just above the hairline; the metopic, which runs from front to back in front of the sagittal suture; and the two lambdoid sutures, which run from side to side across the back of the head. The premature closing of one or more of these cranial sutures leads to skull deformations, a condition called *craniosynostosis*. There are seven types of *craniosynostosis* depending on which cranial suture or sutures are affected: sagittal, bicoronal (both coronal sutures), unicoronal (one coronal suture), coronal and sagittal, metopic, lambdoid and sagittal, and total, in which all the cranial sutures are affected. Individuals affected with Carpenter syndrome show sagittal and bicoronal types of skull malformations.

Genetic profile

Carpenter syndrome is inherited as a recessive non-sex linked (autosomal) condition. The gene responsible for the syndrome has not yet been identified, but it is currently believed that all ACPS syndromes may be the result of genetic mutations—changes occurring in the genes. Genetic links to other syndromes that also result in *craniosynostosis* have been identified. Sixty-four distinct mutations in seven different genes have been linked to *craniosynostosis*. Three of these genes, one located on the short arm of chromosome 8 (8p11), one on the long arm of chromosome 10 (10q26), and another on the short

arm of chromosome 4 (4p16), are related to fibroblast growth factor receptors (FGFRs), which are molecules that control cell growth. Other implicated genes are the *TWIST* gene located on chromosome 7, the *MSX2* gene on chromosome 5, and the *FBN1* gene on the long arm of chromosome 15.

Demographics

Carpenter syndrome and the other ACPS disorders have an occurrence of approximately one in every one million live births. It is rare because both parents must carry the gene mutation in order for their child to have the disease. Therefore, Carpenter syndrome has been observed in cases where the parents are related by blood, though in most cases parents are not related. Parents with one child affected by Carpenter syndrome have a 25% likelihood that their next child will also be affected with the disorder.

Signs and symptoms

Individuals diagnosed with Carpenter syndrome show various types of malformations and deformities of the skull. The two main examples are sagittal and bicoronal *craniosynostosis*. Sagittal *craniosynostosis* is characterized by a long and narrow skull (*scaphocephaly*). This is measured as an increase in the A-P or anterior-to-posterior diameter, which indicates that

KEY TERMS

Acrocephalopolysyndactyly syndromes—A collection of genetic disorders characterized by a cone-shaped abnormality of the skull and partial fusing of adjacent fingers or toes.

Acrocephaly—An abnormal cone shape of the head.

Autosome—Any chromosome not involved in specifying sex.

Brachycephaly—An abnormal thickening and widening of the skull.

Cranial suture—Any one of the seven fibrous joints between the bones of the skull.

Craniosynostosis—Premature, delayed, or otherwise abnormal closure of the sutures of the skull.

Cutaneous syndactyly—Fusion of the soft tissue between fingers or toes resulting in a webbed appearance.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Hydrocephalus—The excess accumulation of cerebrospinal fluid around the brain, often causing enlargement of the head.

Polydactyly—The presence of extra fingers or toes.

Scaphocephaly—An abnormally long and narrow skull.

Syndactyly—Webbing or fusion between the fingers or toes.

looking down on the top of the skull, the diameter of the head is greater than normal in the front-to-back orientation. Individuals affected with sagittal craniosynostosis also have narrow but prominent foreheads and a larger than normal back of the head. The so-called soft spot found just beyond the hairline in a normal baby is very small or absent in a baby affected with sagittal craniosynostosis.

The other type of skull malformation observed, bicoronal craniosynostosis, is characterized by a wide and short skull (brachycephaly). This is measured as a decrease in the A-P diameter, which indicates that looking down on the top of the skull, the diameter of the head is less than normal in the front-to-back orientation. Individuals affected with this condition have poorly formed

eye sockets and foreheads. This causes a smaller than normal sized eye socket that can cause eyesight complications. These complications include damage to the optic nerve, which can cause a loss of visual clarity; bulging eyeballs resulting from the shallow orbits (exophthalmos), which usually damage the eye cornea; widely spaced eyes; and a narrowing of the sinuses and tear ducts that can cause inflammation of the mucous membranes that line the exposed portion of the eyeball (conjunctivitis).

A further complication of bicoronal craniosynostosis is water on the brain (hydrocephalus), which increases pressure on the brain. Most individuals affected with this condition also have an abnormally high and arched palate that can cause dental problems and protrusion, the thrusting forward of the lower jaw. Coronal and sagittal craniosynostosis are characterized by a cone-shaped head (acrocephaly). The front soft spot characteristic of an infant's skull is generally much larger than normal and it may never close without surgical intervention. Individuals with these skull abnormalities may also have higher than normal pressure inside the skull.

Individuals with Carpenter syndrome often have webbed fingers or toes (cutaneous syndactyly) or partial fusion of their fingers or toes (syndactyly). These individuals also tend to have unusually short fingers (brachydactyly) and sometimes exhibit extra toes, or more rarely, extra fingers (polydactyly).

Approximately one third of Carpenter syndrome individuals have heart defects at birth. These may include: narrowing of the artery that delivers blood from the heart to the lungs (pulmonary stenosis); blue baby syndrome, due to various defects in the structure of the heart or its major blood vessels; transposition of the major blood vessels, meaning that the aorta and pulmonary artery are inverted; and the presence of an extra-large vein called the superior vena cava, that delivers blood back to the heart from the head, neck, and upper limbs.

In some persons diagnosed with Carpenter syndrome, additional physical problems are present. Individuals are often short or overweight, with males having a disorder in which the testicles fail to descend properly (cryptorchidism). Another problem is caused by parts of the large intestine coming through an abnormal opening near the navel (umbilical hernia). In some cases, mild mental retardation has also been observed.

Diagnosis

The diagnosis of Carpenter syndrome is made based on the presence of the bicoronal and sagittal skull

QUESTIONS TO ASK YOUR DOCTOR

- What are the most important physiological characteristics of Carpenter syndrome?
- How is Carpenter syndrome diagnosed?
- What types of treatments are available for Carpenter syndrome, and at what point in a child's life should they be used?
- What kind of lifestyle adjustments may be necessary for a family with a Carpenter syndrome child?

malformation, which produces a cone-shaped or short and broad skull, accompanied by partially fused or extra fingers or toes (syndactyly or polydactyly). Skull x-rays and/or a CT scan may also be used to diagnose the skull malformations correctly. Other genetic disorders are also characterized by the same types of skull deformities and some genetic tests are available for them. Thus, positive results on these tests can rule out the possibility of Carpenter syndrome.

Before birth, ultrasound imaging, a technique used to produce pictures of the fetus, is generally used to examine the development of the skull in the second and third months of pregnancy, but the images are not always clear enough to properly diagnose the type of skull deformity, if present. New ultrasound techniques are being used in Japan, however, that can detect skull abnormalities in fetuses with much higher image clarity.

Treatment and management

Operations to correct the skull malformations associated with Carpenter syndrome should be performed during the first year of the baby's life. This is because modifying the skull bones is much easier at that age and new bone growth—as well as the required bone reshaping—can occur rapidly. Also, the facial features are still highly undeveloped, so a greatly improved appearance can be achieved. Follow-up support by pediatric, psychological, neurological, surgical, and genetic specialists may be necessary.

Individuals with Carpenter syndrome may have vision problems that require consultation with an ophthalmologist, or doctor specialized in the treatment of such problems. Speech and hearing therapy may also be necessary if the ears and the brain have been affected. If the palate is severely malformed, dental consultation may also be necessary. In the most severe cases of Carpenter

syndrome, it may be necessary to treat feeding and respiratory problems that are associated with the malformed palate and sinuses. Obesity is associated with Carpenter syndrome, and dietary management throughout the patient's lifetime may also be recommended.

Webbed fingers or toes (cutaneous syndactyly) may be easily corrected by surgery. Extra fingers or toes (polydactyly) may often be surgically removed shortly after birth.

Surgical procedures also exist to correct some of the heart defects associated with Carpenter syndrome, as well as the testicular disorder of affected males. The abnormal opening of the large intestine near the navel (umbilical hernia or omphalocele) can also be treated by surgery. Additionally, intervention programs for developmental delays are available for affected patients.

Prognosis

Carpenter syndrome is not usually fatal if immediate treatment for the heart defects and/or skull malformations is available. In all but the most severe and inoperable cases of craniosynostosis, it is possible that the affected individual may attain a greatly improved physical appearance. Depending on damage to the nervous system, the rapidity of treatment, and the potential brain damage from excess pressure on the brain caused by skull malformation, certain affected individuals may display varying degrees of developmental delay. Some individuals will continue to have vision problems throughout life. These problems will vary in severity depending on the initial extent of their individual skull malformations, but most of these problems can now be treated.

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Children's Craniofacial Association, 13140 Coit Road, Suite 517, Dallas, TX 75240, (214) 570-9099 or (800) 535-3643, (214) 570-8811, contactCCA@ccakids.com, <http://www.ccakids.com>

Paul A. Johnson

Cat cry syndrome see **Cri du chat syndrome**

Caudal dysplasia

Definition

Caudal dysplasia is a total or partial failure of development of the lower vertebrae, including the sacrum (tailbone), which results in associated abnormalities of the lower extremities (legs), spine, kidneys, and gastrointestinal and genitourinary tracts.

Description

Caudal dysplasia is also known as sacral agenesis, sacral regression, caudal aplasia, caudal regression sequence, and sirenomelia. Caudal dysplasia results from a failure of the caudal, or lower, region of the spinal column to form correctly. This abnormal development of the lower spine causes a wide spectrum of other abnormalities. On the mild end of the spectrum, there may be a partial absence of the tailbone with no associated symptoms (sometimes picked up accidentally on x-ray), but on the severe end of the spectrum, there can be complete absence of the kidneys, openings on the spinal cord, and genitourinary, limb, and bowel abnormalities. Some of these more serious abnormalities can be life-threatening. Most infants with caudal dysplasia fall in between the two ends of the spectrum. They may have kidney malformations, gastrointestinal malformations, spinal cord problems, heart abnormalities, and problems with their lower limbs.

Sirenomelia, sometimes called mermaid syndrome, is a rare condition that was once thought to represent the most severe end of the caudal dysplasia sequence. Infants with sirenomelia may have complete fusion of the lower limbs, complete or partial renal agenesis, and severe bowel problems. There is often oligohydramnios, or a low amount of amniotic fluid, during pregnancy. Because of the severity of the defects in this condition, it is generally lethal. As of 2021, sirenomelia was declared to be a separate syndrome.

Caudal dysplasia is caused by a problem with the formation of certain tissues early in pregnancy. The lower spine is usually completely formed by the seventh week of pregnancy. Caudal dysplasia is a primary defect of

formation of the tissues that will become the sacrum, spinal cord, kidneys, and gastrointestinal system.

Genetic profile

Although the genetics of caudal dysplasia are not well understood, two genes are associated with it: *VANGLI*, which is located on the short arm of chromosome 1 (1p13), and *HLXB9*, which causes a rare form of caudal dysplasia known as Currarino syndrome. Some families have shown autosomal dominant inheritance, but more research will be necessary before the exact pattern of inheritance of this disorder is clear. In most cases, it occurs as an isolated event. In some families, there is evidence of an increased incidence of mild scoliosis and spina bifida occulta (opening on one or more of the vertebra without any physical effect) in the parents of children affected with caudal agenesis.

Demographics

Estimates of the incidence of caudal dysplasia range from approximately 1 to 2.5 per 100,000 newborns. Caudal dysplasia occurs equally in males and females. There is an increased rate of caudal dysplasia among infants of diabetic mothers. As many as 16%–22% of infants with caudal dysplasia are born to diabetic mothers, and the risk for a diabetic woman (with poor glucose control) to have an infant with caudal dysplasia is 200 times higher than the average population risk. Diabetes or impaired glucose metabolism is a common problem in pregnancy, with 3%–10% of all pregnancies affected by abnormal glucose metabolism. The exact mechanism by which diabetes causes caudal dysplasia is not well understood.

Caudal dysplasia is a defect of the mesodermal tissue, which develops early in the first trimester of pregnancy. Poor glucose control during the first trimester can lead to an increased risk for the fetus to develop caudal dysplasia. The interaction between poor glucose control and the defects that lead to problems in the mesodermal tissues is not yet well understood.

Most women with an increased risk to have a child with caudal regression have diabetes (often undiagnosed) prior to pregnancy. Gestational diabetes (or diabetes that develops during pregnancy) is a separate entity and should not be confused with diabetes in the first trimester. Gestational diabetes is not associated with an increased risk for caudal dysplasia.

Signs and symptoms

In order to understand the signs and symptoms of caudal dysplasia, it is important to understand early embryonic development. Very early in pregnancy, the cells that will develop into the embryo are organized as

a small round ball. These cells eventually separate into three distinct layers: the endoderm, the mesoderm, and the ectoderm. The endoderm can be thought of as the inside layer. Cells from the endoderm will eventually form into the lining of the digestive tract and the respiratory tract. The mesoderm can be thought of as the middle layer, and the cells of the mesoderm will eventually become the muscles, bones, kidney, heart, and blood vessels. The ectoderm can be thought of as the outside layer. The cells of the ectoderm will eventually become the skin, hair, nails, brain, and nervous system. Caudal dysplasia is the result of an early insult to the tissues of the mesoderm. Since the mesoderm is the tissue that forms the bones, muscles, kidneys, and other tissues, individuals with caudal dysplasia will have problems with these tissues. Any disruption of the development of the mesoderm will lead to disruption of the organs formed from this layer. Impaired glucose metabolism early in pregnancy can lead to an insult that results in the infant having caudal dysplasia. However, since only 16%–22% of mothers of infants with caudal dysplasia have diabetes, there must be other factors that also cause caudal dysplasia. These other factors were not well understood as of 2021.

Caudal dysplasia is a disorder with a wide spectrum of defects. Some individuals are very mildly affected, and some are much more severely affected. Individuals with caudal dysplasia can have some or all of the signs and symptoms.

Spinal cord abnormalities in infants affected with caudal dysplasia include:

- missing or malformed sacrum
- abnormal vertebrae
- cerebellum agenesis
- hydrocephalus
- spina bifida
- scoliosis

Kidney abnormalities include:

- hydronephrosis
- renal failure
- agenesis of the kidney
- hypoplasia of the kidney

Gastrointestinal abnormalities include:

- imperforate anus
- malformed or rotated gut

Heart abnormalities include:

- atrial septal defect
- coarctation of the aorta
- stenosis of the pulmonary valve

Lower limb abnormalities include:

- clubfeet
- missing reflexes
- paralysis or numbness of the legs

Neurological abnormalities include:

- neurogenic bladder (impaired bladder control)
- neurogenic bowel (impaired bowel control)
- motor and sensory nerve abnormalities

Other abnormalities include:

- cleft lip/palate
- diaphragmatic hernia
- hypoplastic lungs
- low-set ears
- tracheo-esophageal fistula (abnormal connection between the trachea and esophagus)

Diagnosis

The diagnosis of caudal dysplasia can be made during pregnancy, at birth, and during childhood, depending on the severity of the defects present.

Prenatal diagnosis

The diagnosis of caudal dysplasia can be made prenatally (during pregnancy) by prenatal ultrasound (a sonogram). Sonograms use sound waves to provide an image of a fetus. The structural abnormalities of caudal dysplasia, including absence of vertebrae, kidney malformations, other spinal cord malformations, and limb abnormalities, can be seen during the second trimester of pregnancy. Because the bones of the sacrum do not ossify, or harden, until approximately 22 weeks of pregnancy, it may be difficult to diagnose caudal dysplasia before this time.

The diagnosis of caudal dysplasia can also be made by physical examination after birth. Physical signs can include flattening of the buttocks, shortening of the gluteal cleft, scoliosis, spina bifida, and hydrocephalus. X-rays should be taken to look at the formation of the underlying bones and tissues.

Treatment and management

Pregnancy management

When caudal dysplasia is diagnosed by prenatal ultrasound, the mother should be tested for diabetes. Pregnancy termination may be an option. If the pregnancy continues, the parents may wish to consult with specialists to get more specific information about prognosis.

KEY TERMS

Aplasia—Defective development resulting in absence of all or part of an organ or tissue.

Caudal—Pertaining to the tail (bone).

Dysplasia—Abnormal development of tissues, organs, or cells.

Sacrum—Triangular bone at the base of the spinal column.

Delivery management

Because of the abnormalities seen and the possible complications, delivery should be at a tertiary care center or hospital able to provide specialized pediatric care. It is likely that an infant with caudal dysplasia will spend a significant amount of time in the hospital as a newborn. If the tertiary care center is not located near the family, this can increase the burden of care for the family.

There is no cure for caudal dysplasia. Treatment is governed by the abnormalities present. If the abnormalities are severe (life-threatening), corrective surgery is not an option. The main goals of treatments include maintaining and improving kidney, lung, and gastrointestinal function. Orthopedic surgeries are done to correct malformation, and physical therapy is used to avoid secondary complications, such as scoliosis.

Many of the defects of caudal dysplasia can be surgically treated but not cured. For example, an opening on the spine (spina bifida) can be surgically closed, but if the nerves in that opening have been damaged, there is nothing that can be done to reverse this damage. Other surgeries include orthopedic surgeries to correct bone malformations and improve limb function. Surgery can also be done to correct hydrocephalus or imperforate anus.

Other treatments involve orthopedic devices and treatments for neurogenic bladder. Orthopedic devices may be used to help with problems of the hip, back, and legs. Neurogenic bladder is one of the more serious and debilitating problems in caudal dysplasia. Long-term bladder dysfunction can result in kidney damage and failure.

The treatments for caudal dysplasia often require lifelong medical attention. It is important to prepare the family for this and to stress the need for preventive care (that is, prevention of infections) and vigilance in detecting complications.

Prognosis

The prognosis for caudal dysplasia is highly dependent on the severity of the malformation present. Those

with extremely mild abnormalities may have no or few symptoms. Infants with more serious symptoms may require extensive urologic and orthopedic assistance, including multiple surgeries and lifelong therapies. Neurogenic bladder is one of the more serious and debilitating problems in caudal dysplasia. Long-term bladder dysfunction can result in kidney damage and failure, and intensive efforts may be required to avoid this problem. Some infants with caudal dysplasia are born with lethal abnormalities that are incompatible with life. Infants that do survive generally have normal mental function.

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- National Institute of Arthritis and Musculoskeletal and Skin Diseases, 1 AMS Circle, Bethesda, MD 20892-3675, (301) 495-4484, (301) 718-6366, NIAMSinfo@mail.nih.gov, <http://www.niams.nih.gov>

Kathleen A. Fergus, MS, CGC

CECR1 gene-recurrent fevers and strokes in children

Definition

The *CECR1* gene produces a protein called adenosine deaminase 2 (ADA2). Mutations (changes) in the *CECR1* gene can cause a condition known as deficiency

KEY TERMS

Adenosine deaminase 2 (ADA2)—The enzyme produced by the *CECR1* gene and required for blood-vessel and immune-system development and maintenance; *CECR1* gene mutations that result in little or no ADA2 can cause recurrent fevers and strokes in children and other syndromes in children and adults.

Aneurysm—A blood-filled stretching of a blood vessel, usually an artery, that can lead to stroke.

Autosomal dominant—A pattern of genetic inheritance in which only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance in which two copies of a mutated gene, one from each parent, must be present for the child to develop the trait or disorder.

Deficiency of adenosine deaminase 2 (DADA2)—Syndromes caused by mutations in the *CECR1* gene.

Inflammation—An immune-system response, usually resulting from irritation, infection, or injury and causing redness, swelling, and pain.

Livedo reticularis—Bluish net-like patterns of skin discoloration caused by blood-vessel abnormalities; usually present in children with recurrent fevers and strokes caused by *CECR1* gene mutations.

Macrophages—Immune-system cells derived from monocytes that both promote and inhibit inflammation, among other activities, and whose normal development is affected by *CECR1* gene mutations.

Polyarteritis nodosa (PAN)—An inflammatory disease that affects all layers of blood vessel walls and may be caused by *CECR1* gene mutations.

Sneddon syndrome—Adenosine deaminase 2 deficiency that may be caused by mutations in the *CECR1* gene, with symptoms usually developing later than those of polyarteritis nodosa.

Stroke—An obstruction (ischemic) or rupture (hemorrhagic) of a blood vessel in the brain, causing death of brain tissue and potentially affecting physical and mental functioning.

Vasculitis—Blood vessel inflammation.

of ADA2 (DADA2). DADA2 is characterized by inflammation in various tissues throughout the body, but especially in the blood vessels, resulting in a condition known as vasculitis. DADA2 can be severely disabling or life threatening and has recently been identified as a cause of recurrent fevers and strokes in children.

Description

Adenosine deaminases 1 and 2 are very important enzymes that regulate the levels of the signaling molecule adenosine, which is critical for controlling a variety of cellular functions. ADA1 has long been known to activate immune system cells, but the structure and functions of the very similar ADA2 have only recently begun being elucidated. ADA2, encoded by the *CECR1* gene, is essential for maintaining the integrity of blood vessel walls. ADA2 also functions as a growth factor that is involved in the growth and development of immune system cells, especially the differentiation of monocytes into macrophages and the proliferation of macrophages. Macrophages have critical roles in both promoting and inhibiting inflammation.

Inflammation is the immune system's response to injury and to pathogens such as bacteria. Researchers

have found that ADA2 deficiency (DADA2) causes monocytes/macrophages to attack the body's own blood vessels, leading to uncontrolled inflammation that can damage organs, including the skin, digestive system, kidneys, and nervous system. In particular, blood vessel damage from DADA2 can cause a variety of problems, including stroke, the narrowing or blockage of blood vessels in the brain that can damage and destroy brain tissue by starving it of its blood supply.

With the discovery of mutations in the *CECR1* gene, researchers have realized that DADA2 may be responsible for a variety of previously unexplained syndromes affecting both children and adults. These include recurrent intermittent fevers and recurrent strokes in children that begin in the first years of life. These strokes affect deep-brain structures and may cause permanent brain damage. In children, as in adults, strokes can affect physical, intellectual, and emotional functioning and cause blindness or deafness. The syndrome of recurrent fevers and strokes in children has often been classified as a type of polyarteritis nodosa (PAN). Childhood-onset PAN is a rare autosomal recessive genetic disorder. In addition to recurrent fevers and ischemic stroke in the small blood vessels of the brain, which can cause neurologic dysfunction, PAN is characterized by areas of net-like mottled

skin discoloration called livedo reticularis. PAN and other types of DADA2 can also result in systemic vasculitis-inflamed blood vessels throughout the body, as well as muscle pain, high blood pressure, or aneurysms (dangerous blood-filled pouches in blood vessel walls that can block vessels or burst and hemorrhage). Some patients with PAN or other forms of DADA2 have an enlarged liver and spleen, as well as immune system deficiencies. PAN in children usually begins before the age of ten and varies greatly in its severity. However, PAN in both adults and children probably has other causes in addition to ADA2 deficiency and/or *CECR1* gene mutations. Other forms of DADA2 also vary greatly in symptoms and severity, as well as in the age of onset.

Genetic profile

The *CECR1* gene that produces ADA2 is named for “cat eye syndrome chromosome region, candidate 1” Cat eye syndrome, also called Schmid-Fraccaro syndrome, is a rare abnormality of chromosome 22 that is unrelated to DADA2. *CECR1* is located on the long arm (q) of chromosome 22 at position 11.2 (22q11.2). In 2014, researchers identified mutations in the *CECR1* gene that were responsible for recurrent fevers and strokes beginning in early childhood, as well as *CECR1* mutations that result in blood vessel inflammation. These mutations seriously reduce or eliminate ADA2. In the original study, researchers identified eight different mutations that eliminated the production of ADA2; three of these mutations were present in multiple patients. These early patients had either inherited mutated *CECR1* genes from both parent or had a DNA deletion that knocked out the normal copy of the *CECR1* gene. Subsequently, researchers identified a different *CECR1* mutation that, if present in both copies of the *CECR1* gene (one inherited from each parent), resulted in PAN. As of 2015, at least 15 *CECR1* mutations that result in ADA2 deficiency had been identified.

Conditions associated with *CECR1* mutations are inherited in an autosomal recessive manner, meaning that both copies of the *CECR1* gene (one inherited from each parent) must have mutations in order for DADA2 symptoms to develop. Thus, parents of individuals with DADA2 typically do not have signs or symptoms of ADA2 deficiency. However, there is evidence that adults with a single mutated *CECR1* may have a predisposition to adult-onset stroke.

Furthermore, cases of Sneddon syndrome, a progressive condition characterized by livedo reticularis and neurological abnormalities, have also been found to be caused by *CECR1* gene mutations. Sneddon syndrome may be inherited not only in an autosomal recessive pattern, but also in an autosomal dominant manner that

QUESTIONS TO ASK YOUR DOCTOR

- Could my child’s recurrent fevers and strokes be a result of adenosine deaminase 2 deficiency?
- Should my child have genetic testing for *CECR1* gene mutations?
- Should other family members be tested for *CECR1* mutations?
- What treatments are available for my child?
- What is my child’s prognosis?

requires only one defective copy of the *CECR1* gene to result in signs and symptoms of the disorder.

Demographics

Although only a few dozen cases of DADA2 have appeared in the medical literature, it is suspected that ADA2 deficiency may be much more common than previously recognized. Researchers suspect that *CECR1* mutations may be responsible for more common forms of vasculitis and stroke, as well as PAN and Sneddon syndrome. Furthermore, the *CECR1* mutations that can result in PAN are not uncommon in Middle Eastern and Pakistani populations.

Signs and symptoms

The signs and symptoms of ADA2 deficiency caused by *CECR1* gene mutations vary greatly in severity, even among affected patients from the same family. Early-onset recurrent fevers and strokes usually begin between the ages of five months and four years. However, in some cases symptoms do not develop until adulthood. Some patients have hemorrhagic strokes, in which blood vessels in the brain burst and bleed profusely (hemorrhage), as well as ischemic strokes caused by blockage of small blood vessels deep in the brain or brainstem. The neurologic symptoms of stroke can include paralysis, headache, blindness, and altered mental status. Livedo reticularis or other skin rashes affect most children with *CECR1* gene mutations. Some children have blockages of blood vessels in the fingers and toes, leading to cell death. Other symptoms may include aneurysms, blood vessel problems throughout the body, high blood pressure, other neurologic problems, and abdominal pain. Symptoms depend on the organ damage caused by defective blood vessels. In addition to the heart, skin, and nervous system, joints, muscles, the gastrointestinal tract, and the kidneys may be affected. Because DADA2

affects maturation of the immune system, some patients have poorly regulated or deficient immune systems. DADA2 can also cause anemia (red blood cell deficiency) and other blood disorders. At the mildest end of the DADA2 spectrum, individuals may have no symptoms until the development of leg ulcers after age 59.

Signs and symptoms of Sneddon syndrome are neurological abnormalities including headache and dizziness, high blood pressure, heart disease, and/or stroke. Intellectual impairment, memory loss, and other neurologic symptoms may be caused by reduced blood flow to the brain. Sneddon syndrome generally has a later onset than PAN.

Diagnosis

PAN and other blood vessel disorders may be diagnosed by symptoms including fevers, stroke, and skin rashes, as well as complete blood counts, blood vessel studies called arteriography, and tissue biopsy. Blood tests and skin biopsies may reveal immune system deficiencies and other abnormalities. Other than recurrent fevers and strokes in children, diagnosis of ADA2 deficiency may be difficult because the symptoms are so variable, and ADA2 deficiency now appears to underlie multiple symptoms and syndromes that were not previously recognized as related. Genetic testing is available for known *CECR1* mutations.

Treatment and management

There is no specific treatment for recurrent fevers and strokes caused by *CECR1* gene mutations. Some patients respond better than others to immunosuppressive therapies. However, steroid medications, cyclophosphamide, and immune system inhibitors that can reduce inflammation have proved only partially effective in controlling fever, rash, and other symptoms. ADA2 is produced and functions within the bone marrow, and bone marrow transplantation with blood-cell-producing (hematopoietic) stem cells appears to restore ADA2 levels and resolve symptoms of DADA2 in the few patients who have undergone the procedure.

Prognosis

Prognosis for recurrent fevers and strokes in children caused by *CECR1* gene mutations depends on the severity of symptoms. Strokes and other symptoms of DADA2 can cause permanent disability or death, although some abilities lost to stroke—such as walking—can be relearned. Steroids and other immunosuppressive drugs can improve symptoms and increase long-term survival of patients with PAN. However, with so few cases yet identified as *CECR1*-associated, the likeliest prognosis is unknown.

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ORGANIZATIONS

- National Institute of Neurological Disorders and Stroke, NIH Neurological Institute, PO Box 5801, Bethesda, MD 20824, (301) 496-5751 or (800) 496-5751, <http://www.ninds.nih.gov>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>
- Office of Rare Diseases Research, National Center for Advancing Translational Sciences, National Institutes of Health, 6701 Democracy Blvd., Suite 1001, MSC 4874, Bethesda, MD 20892, (301) 402-4336, (301) 480-9655, ordr@nih.gov, <https://rarediseases.info.nih.gov>
- YoungStroke, PO Box 692, Conway, SC 29528, (843) 655-2835, info@youngstroke.org, <http://youngstroke.org>

Margaret Alic, PhD

Celiac disease

Definition

Celiac disease is a disease of the digestive system that damages the small intestine and interferes with the absorption of nutrients from food.

Description

Celiac disease occurs when the body reacts abnormally to gluten, a protein found in wheat, rye, barley, and possibly oats. When someone with celiac disease eats foods containing gluten, that person's immune system causes an inflammatory response in the small intestine, which damages the tissues and results in an impaired ability to absorb nutrients from foods. The inflammation and malabsorption create wide-ranging problems in many systems of the body. Since the body's own immune system causes the damage, celiac disease is classified as an autoimmune disorder. Celiac disease may also be called sprue, nontropical sprue, gluten sensitive enteropathy, celiac sprue, and adult celiac disease.

Each person with celiac disease is affected differently. When food containing gluten reaches the small intestine, the immune system begins to attack a substance called gliadin, which is found in the gluten. The resulting inflammation causes damage to the delicate finger-like structures in the intestine called villi, where food absorption actually takes place. This damage is referred to as villus atrophy. The patient may experience a number of symptoms related to the inflammation and the chemicals it releases, and/or the lack of ability to absorb nutrients from food, which can cause malnutrition.

Risk factors

People with autoimmune disorders are more at risk for celiac disease. Since it can run in families, risk is also increased if there is a family history of the condition.

Many disorders are associated with celiac disease, though the nature of the connection is unclear. One type of epilepsy is linked to celiac disease. Once their celiac disease is successfully treated, a significant number of these patients have fewer or no seizures. Patients with alopecia areata, a condition in which hair loss occurs in sharply defined areas, have been shown to have a higher risk of celiac disease than the general population. There appears to be a higher percentage of celiac disease among people with Down syndrome, but the link between the conditions is unknown.

Several conditions attributed to a disorder of the immune system have been associated with celiac disease. People with insulin dependent diabetes (type 1) have a much higher incidence of celiac disease. One source estimates that as many as 1 in 10 insulin-dependent diabetics may have celiac disease. Patients with juvenile chronic arthritis, some thyroid diseases, and IgA deficiency are also more likely to develop celiac disease.

There is an increased risk of intestinal lymphoma, a type of cancer, in individuals with celiac disease.

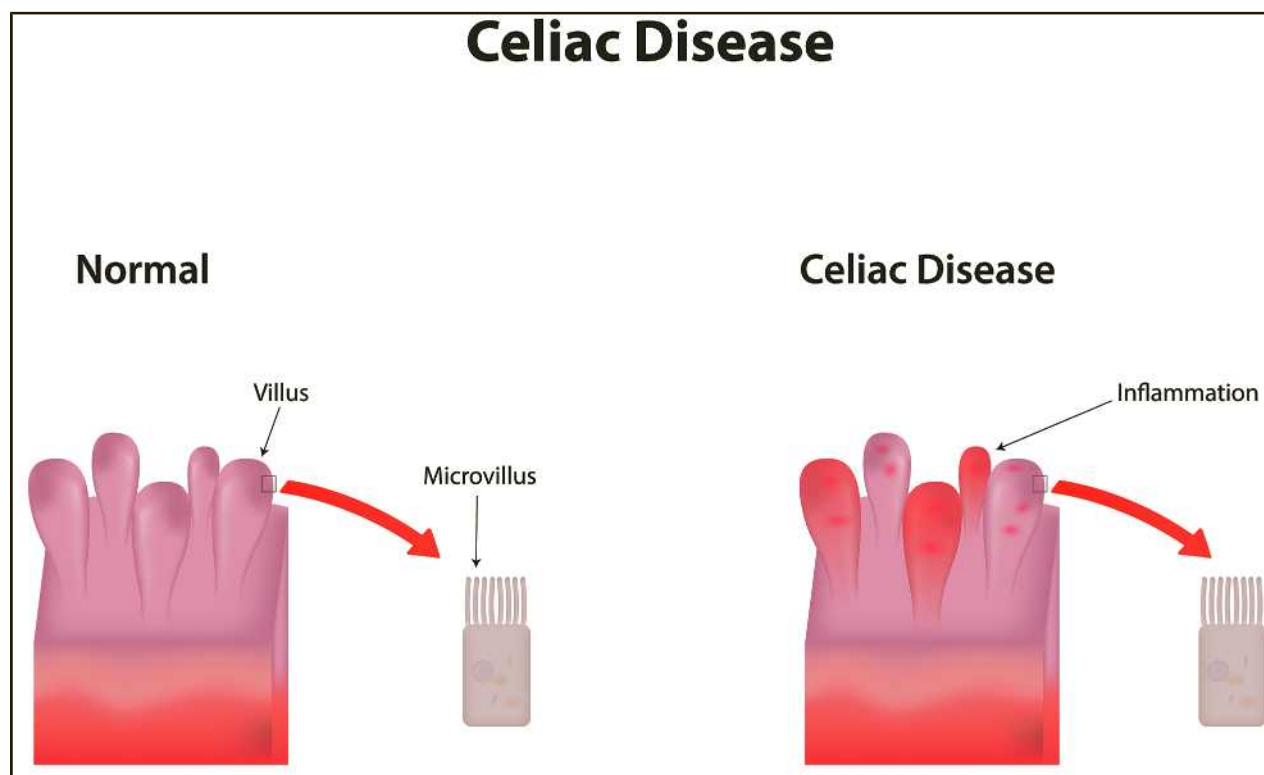


Illustration of healthy villi (left) and inflamed villi affected by celiac disease (right). When people with celiac disease eat foods or use products containing gluten, their immune system responds by damaging the villi. (joshya/Shutterstock)

Successful treatment of celiac disease seems to decrease the chance of developing lymphoma.

Genetic profile

The exact cause of celiac disease is unknown. It can run in families and has a genetic basis, but the pattern of inheritance is complicated. The type of inheritance pattern that celiac disease follows is called multifactorial (caused by many factors, both genetic and environmental). Researchers think that several factors must exist in order for the disease to occur. First, the patient must have a genetic predisposition to develop the disorder. Then, something in their environment acts as a stimulus to trigger their immune system, causing the disease to become active for the first time. For conditions with multifactorial inheritance, people without the genetic predisposition are less likely to develop the condition with exposure to the same triggers. Or, they may require more exposure to the stimulus before developing the disease than someone with a genetic predisposition. Several factors may provoke a reaction; these include surgery, especially gastrointestinal surgery; a change to a low-fat diet, which has an increased number of wheat-based foods; pregnancy; childbirth; severe emotional stress; or a viral infection. This combination of genetic susceptibility and an outside agent leads to celiac disease.

Demographics

Celiac disease may be discovered at any age, from infancy through adulthood. The disorder is more commonly found among white Europeans or in people of European descent. It is very unusual to find celiac disease in African or Asian people. The exact incidence of the disease is uncertain. Estimates vary from 1 in 5,000, to as many as 1 in every 300 individuals with this background. The prevalence of celiac disease seems to be different from one European country to another and between Europe and the United States. This may be due to differences in diet and/or unrecognized disease. A recent study of random blood samples tested for celiac disease in the United States showed 1 in 250 testing positive. It is clearly underdiagnosed, probably because of the symptoms being attributed to another problem or lack of knowledge about celiac disease by physicians and laboratories.

Because celiac disease has a hereditary influence, close relatives (especially first-degree relatives, such as children, siblings, and parents) have a higher risk of being affected with the condition. The chance that a first-degree relative of someone with celiac disease will have the disease is about 10%.

As more is learned about celiac disease, it becomes evident that there are many variations that may not produce typical symptoms. It may even be clinically “silent,” where no obvious problems related to the disease are apparent.

Signs and symptoms

The most commonly recognized symptoms of celiac disease relate to the improper absorption of food in the gastrointestinal system. Many patients with gastrointestinal symptoms will have diarrhea and fatty, greasy, unusually foul-smelling stools. The patient may complain of excessive gas (flatulence), distended abdomen, weight loss, and generalized weakness. Not all people have digestive system complications; some people only have irritability or depression. Irritability is one of the most common symptoms in children with celiac disease.

Not all patients have these problems. Unrecognized and untreated celiac disease may cause or contribute to a variety of other conditions. The decreased ability to digest, absorb, and utilize food properly (malabsorption) may cause anemia (low red blood count) from iron deficiency or easy bruising from a lack of vitamin K. Poor mineral absorption may result in osteoporosis, or “brittle bones,” which may lead to bone fractures. Vitamin D levels may be insufficient and bring about a softening of bones (osteomalacia), which produces pain and bony deformities, such as flattening or bending. Defects in the tooth enamel characteristic of celiac disease may be recognized by dentists. Celiac disease may be discovered during medical tests performed to investigate failure to thrive in infants, or lack of proper growth in children and adolescents. People with celiac disease may also experience lactose intolerance because they do not produce enough of the enzyme lactase, which breaks down the sugar in milk into a form the body can absorb. Other symptoms can include muscle cramps, fatigue, delayed growth, tingling or numbness in the legs (from nerve damage), pale sores in the mouth (called aphthous ulcers), tooth discoloration, or missed menstrual periods (due to severe weight loss).

A distinctive, painful skin rash called dermatitis herpetiformis may be the first sign of celiac disease. Approximately 10% of patients with celiac disease have this rash, but it is estimated that 85% or more of patients with the rash have the disease.

Diagnosis

Examination

Because of the variety of ways celiac disease can manifest itself, it is often not diagnosed promptly. Its symptoms are similar to many other conditions, including

irritable bowel syndrome, Crohn's disease, ulcerative colitis, diverticulosis, intestinal infections, chronic fatigue syndrome, and depression. The condition may persist without diagnosis for so long that the patient accepts a general feeling of illness as normal. This leads to further delay in identifying and treating the disorder. It is not unusual for the disease to be identified in the course of medical examinations for seemingly unrelated problems.

Tests

If celiac disease is suspected, a blood test can be ordered. This test looks for the antibodies to gluten (called antigliadin, anti-endomysium, and antireticulin) that the immune system produces in celiac disease. Antibodies are chemicals produced by the immune system in response to substances that the body perceives to be threatening. Some experts advocate not just evaluating patients with symptoms, but using these blood studies as a screening test for high-risk individuals, such as those with relatives (especially first-degree relatives) known to have the disorder. An abnormal result points toward celiac disease, but further tests are needed to confirm the diagnosis. Because celiac disease affects the ability of the body to absorb nutrients from food, several tests may be ordered to look for nutritional deficiencies. For example, doctors may order a test of iron levels in the blood because low levels of iron (anemia) may accompany celiac disease. Doctors may also order a test for fat in the stool, since celiac disease prevents the body from absorbing fat from food.

Procedures

If celiac disease is suspected, a biopsy (removal of a tiny piece of tissue surgically) of the small intestine can be performed. This is usually done by a gastroenterologist, a physician who specializes in diagnosing and treating bowel disorders. It is generally performed in the office, or in a hospital's outpatient department. The patient remains awake but is sedated. A narrow tube called an endoscope is passed through the mouth, down through the stomach, and into the small intestine. A small sample of tissue is taken and sent to the laboratory for analysis. If it shows a pattern of tissue damage characteristic of celiac disease, the diagnosis is established.

The patient is then placed on a gluten-free diet (GFD). The physician will periodically recheck the level of antibodies in the patient's blood. After several months, the small intestine is biopsied again. If the diagnosis of celiac disease was correct (and the patient followed the rigorous diet), healing of the intestine will be apparent. Most experts agree that it is necessary to follow these steps in order to be sure of an accurate diagnosis.

QUESTIONS TO ASK YOUR DOCTOR

- What does gluten do to people with celiac disease?
- What caused my celiac disease?
- How can I manage my celiac disease?
- What are the treatment options?
- What kinds of tests will I need to confirm that I have celiac disease?
- Where can I get information about maintaining a gluten-free diet?
- Is my condition likely to improve over time, stay the same, or get worse?
- What is the likelihood that my disorder will be transmitted to any children I may have in the future?

Treatment and management

Traditional

The only treatment for celiac disease is a gluten-free diet. This may be easy for the doctor to prescribe but difficult for the patient to follow. For most people, adhering to this diet will stop symptoms and prevent damage to the intestines. Damaged villi can be functional again in three to six months. This diet must be followed for life. For people whose symptoms are cured by the gluten-free diet, this is further evidence that their diagnosis is correct.

Gluten is present in any product that contains wheat, rye, barley, or oats. It helps make bread rise and gives many foods a smooth, pleasing texture. In addition to the many obvious places gluten can be found in a normal diet, such as breads, cereals, and pasta, there are many hidden sources of gluten. These include ingredients added to foods to improve texture or enhance flavor and products used in food packaging. Gluten may even be present on surfaces used for food preparation or cooking.

Fresh foods that have not been artificially processed, such as fruits, vegetables, and meats, are permitted as part of a GFD. Gluten-free foods can be found in health food stores and in some supermarkets. Mail-order food companies often have a selection of gluten-free products. Help in dietary planning is available from dietitians (health-care professionals specializing in food and nutrition) or from support groups for individuals with celiac disease. There are many cookbooks on the market specifically for those on a GFD.

Treating celiac disease with a GFD is almost always completely effective. Gastrointestinal complaints and other symptoms are alleviated. Secondary complications, such as anemia and osteoporosis, resolve in almost all patients. People who have experienced lactose intolerance related to their celiac disease usually see those symptoms subside as well. Although there is no risk and much potential benefit to this treatment, it is clear that avoiding all foods containing gluten can be difficult.

Experts emphasize the need for lifelong adherence to the GFD to avoid the long-term complications of this disorder. They point out that although the disease may have symptom-free periods if the diet is not followed, silent damage continues to occur. Celiac disease cannot be “outgrown” or cured, according to medical authorities.

Prevention

There is no way to prevent celiac disease. However, the key to decreasing its impact on overall health is early diagnosis and strict adherence to the prescribed gluten-free diet.

Prognosis

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Patients with celiac disease must adhere to a strict GFD throughout their lifetime. Once the diet has been followed for several years, individuals with celiac disease have mortality rates similar to those of the general population. However, about 10% of people with celiac disease develop a cancer involving the gastrointestinal tract (both carcinoma and lymphoma).

There are a small number of patients who develop a refractory type of celiac disease, where the GFD no longer seems effective. Once the diet has been thoroughly assessed to ensure no hidden sources of gluten are causing the problem, medications may be prescribed. Steroids or immunosuppressant drugs are often used to try to control the disease. It is unclear whether these efforts meet with much success.

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- Celiac Disease Foundation, 20350 Ventura Boulevard, Suite 240, Woodland Hills, CA 91364, (818) 716-1513, (818) 267-5577, cdf@celiac.org, <http://celiac.org>
- Celiac Support Association, 1941 S 42nd St, Suite 522, Omaha, NE 68105, (402) 558-1347 or (877) 272-4272, <http://www.csaceliacs.org>
- Gluten Intolerance Group, 31214 124th Ave. SE, Auburn, WA 98092, (253) 833-6655, (253) 833-6675, customerservice@gluten.net, <https://www.gluten.org>
- National Foundation for Celiac Awareness (NFCA), PO Box 544, Ambler, PA 19002-0544, (215) 325-1306 or (844) 856-6692, (215) 643-1707, info@celiaccentral.org, <http://www.celiaccentral.org>
- North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, 714 N. Bethlehem Pike, Suite 300, Ambler, PA 19002, (215) 641-9800, (215) 641-1995, naspghan@naspghan.org, <http://www.naspghan.org>

Judith Sims, MS
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Cell-free DNA test

Definition

Cell-free DNA testing is a procedure for identifying fragments of disintegrated DNA in blood serum that have been released from dying cells or tumor cells, amplifying

the fragments by polymerase chain reaction (PCR), and using next-generation sequencing methods to identify genetic mutations in the targeted DNA.

Cell-free DNA is also referred to as cfDNA or circulating DNA. Such specific subtypes of cfDNA as cell-free fetal DNA, cell-free tumor DNA, and donor-derived cell-free DNA are abbreviated as cffDNA, ctDNA, and ddcfDNA, respectively.

Description

All living cells in humans actively release fragments of DNA and other nucleic acids into the blood. This release has been variously attributed to apoptosis, or programmed cell death; cell lysis; or spontaneous mechanisms of DNA release that are not yet fully understood. Apoptosis is characterized by the activation of certain enzymes that cut or cleave the DNA in the dying cell into smaller units about 180 base pairs (bp) in length. This process, known as DNA fragmentation, is a consequence rather than a cause of apoptosis. Cell lysis occurs when the membrane of a cell breaks down as the result of osmotic pressure or the activity of a virus or an enzyme. The average level of cfDNA in a healthy adult human varies between 10 and 30 nanograms per milliliter (ng/mL), which is a low concentration that presents an ongoing challenge to current recovery methods.

Cell-free fetal DNA is produced by cells in the trophoblast, the collection of cells that surrounds the embryo from the time it implants in the wall of the mother's uterus. The trophoblast cells eventually form the placenta, the organ that allows for exchange of nutrients and waste products between the fetus's blood circulation and the mother's. As early as seven weeks of gestation, microparticles from the trophoblast cells containing fragmented DNA from the fetus are shed into the mother's bloodstream. The fragments of cell-free fetal DNA are significantly smaller (about 200 bp) than the DNA fragments in the mother's blood, so they can be separated from the mother's cell-free DNA on the basis of size. The proportion of cffDNA in the mother's blood increases over the course of the pregnancy up until childbirth.

Whether from DNA fragmentation following apoptosis, cell lysis, or spontaneous release from living cells, cell-free DNA has only a brief half-life in blood plasma. It is estimated that the half-life of cell-free DNA ranges from 15 minutes to several hours. It is cleared from the blood by the liver and kidneys. In the case of cell-free fetal DNA, cffDNA is cleared from the mother's blood within 2 hours of delivery.

Cell-free nucleic acids (cfNAs) were first identified in human blood plasma in 1948 by two French scientists, but it was not until the late 1970s that cancer patients

were found to have higher levels of circulating DNA than healthy persons, and not until the 1990s that genetic mutations in the cell-free DNA of cancer patients were identified. In 1997, cell-free fetal DNA was first detected in maternal blood, but the trophoblast was not identified as the source of the cffDNA until 2007. The introduction of so-called high-throughput or next-generation sequencing methods in 2005 has allowed for the detection of mutations in cell-free DNA with a very high degree of specificity and accuracy and for the introduction of the first noninvasive screening test for fetal chromosomal abnormalities in 2011.

Purpose

Cell-free DNA testing had only one clinical application as of 2015, which was as a noninvasive screening test using cell-free fetal DNA to look for genetic abnormalities in high-risk pregnancies without the risk of causing loss of the pregnancy. Cell-free fetal DNA testing can also be used for paternity testing and early identification of fetal sex, but it is not presently used as a diagnostic test. If the cffDNA screening test indicates the possibility of a chromosomal abnormality in the fetus, the mother is asked to return for additional tests that are considered definitively diagnostic.

Cell-free DNA testing is presently being used in research in other areas of medicine, particularly cancer therapy, organ transplantation, and inflammatory conditions and disorders. Cell-free DNA testing is presently used in cancer diagnostics to provide genetic profiles of cancers and monitor the results of treatment.

Method

Cell-free DNA is obtained from samples of the patient's blood. It is considered a noninvasive test because it does not require surgical removal of tissue, as in a biopsy, or the insertion of endoscopes or similar instruments into the patient's body cavities. No special preparation on the patient's part is required for the blood test.

After the blood is withdrawn by venipuncture into a test tube containing an anticoagulant, the tube is sent to the laboratory, where it is first centrifuged to separate the blood cells from the plasma (the liquid portion of blood). The cell-free DNA is in the plasma and must be isolated and purified; this process is usually done with commercially available kits. The separation of the plasma from the cells in the blood sample must be done quickly before the white cells in the blood disintegrate and release genomic DNA into the sample.

In the case of cell-free fetal DNA testing, the fetal DNA must be separated from the mother's DNA. To

prevent the further release of maternal DNA from any blood cells in the sample, formaldehyde is added to the plasma. The DNA fragments are then separated by size to increase the proportion of fetal DNA in the final sample. Most laboratories consider a fetal cell-free DNA content of 4% or higher within the cell-free maternal DNA to be necessary to obtain an accurate result; between 2% and 6% of cell-free fetal DNA tests are unsuccessful because the fetal fraction is too low. The results of the test are usually available within 7–10 days after the blood is drawn.

Uses

Cell-free DNA testing has a growing number of uses.

Noninvasive prenatal testing (NIPT)

Cell-free fetal DNA testing has been used since 2011 as a noninvasive prenatal test, or NIPT. Ultrasound is the other form of NIPT. The cffDNA test is performed during or after the tenth week of pregnancy, when measurable amounts of cell-free fetal DNA can be detected in the mother's blood. Between 3% and 13% of cell-free DNA in the mother's blood at ten weeks gestation is of fetal origin. As of 2021, the American College of Obstetricians and Gynecologists (ACOG) recommended the test only as a screener for women at high risk of a chromosomal disorder in their pregnancy. Women are considered to be at high risk if they meet any of the following criteria:

- are age 35 or older
- have had a positive result on a first- or second-trimester maternal serum screening test
- have had an ultrasound that indicates the possibility of a chromosomal abnormality in the fetus
- have had a previous pregnancy with a trisomy
- have a known balanced chromosome translocation in either father or mother linked to trisomies 13, 18, or 21

The patient should receive genetic counseling prior to the test.

As of mid-2021, ACOG did not recommend cell-free fetal DNA testing as routine screening for women with low-risk pregnancies because the accuracy of the results has not yet been adequately tested. In addition, cffDNA testing is not recommended for women carrying twins, triplets, or other multiple pregnancies. The organization also notes the limitations of cffDNA testing: While it is effective in screening for the most common trisomies—trisomy 13 (Patau syndrome), trisomy 18 (Edwards syndrome), and trisomy 21 (Down syndrome)—it will not detect such abnormalities as neural tube defects or defects of the ventral abdominal wall.

Because the cffDNA test is considered a screener and not a diagnostic test, women who receive abnormal findings should undergo an invasive diagnostic test (usually chorionic villus sampling or amniocentesis) to confirm the diagnosis of a chromosomal abnormality. An important reason for this precaution is that the screening test in its present form yields some false-positive results, and many women do not wait for confirmation but terminate their pregnancies immediately. An article published in the *Boston Globe* in December 2014 described the limitations of present cffDNA screening tests and the importance of closer Food and Drug Administration (FDA) regulation of the companies offering these tests. The ACOG states that any decisions about further management of a pregnancy should never be based on the results of the screening test alone.

Cancer detection and monitoring

Another major area of investigation using cell-free DNA is in cancer diagnosis and therapy. It has been known since the late 1970s that cell-free DNA levels are significantly higher in patients with cancer than in healthy persons and that these increased levels include the patient's normal cell-free DNA as well as cell-free tumor DNA. The level of cell-free tumor DNA (ctDNA) in the patient's blood is broadly proportional to the extent of the disease and increases still further when the cancer metastasizes. The size of ctDNA fragments varies somewhat, but most are between 70 and 200 bp in length.

The amount of ctDNA detected in cancer patients varies somewhat depending on the type of tumor. Cancers of the ovaries and liver, as well as metastatic cancers of the pancreas, urinary bladder, colon, stomach, breast, esophagus, or throat produce measurable amounts of ctDNA, whereas cancers of the central nervous system are less likely to produce detectable amounts; it is thought that the existence of the blood/brain barrier explains this difference.

Cell-free tumor DNA, sometimes referred to as liquid biopsy, is presently used in cancer research for several purposes:

- Diagnosing the genotype of the tumor. Liquid biopsy has an advantage over tissue biopsy not only because it is less invasive but also because it is more accurate. Many solid tumors are genetically heterogeneous, which means that different portions of the tumor have different genetic profiles, and a tissue biopsy may fail to sample some of the evolving mutations within the cancer. A liquid biopsy, on the other hand, would collect cell-free tumor DNA from all parts of the tumor.
- Monitoring the presence of residual disease in patients who have undergone surgery; ctDNA testing could spare

KEY TERMS

Aneuploidy—A condition in which an abnormal number of chromosomes exists in the nucleus of a cell. Trisomy 18 and trisomy 13 are examples of aneuploid conditions.

Apoptosis—The normally programmed cell death process in which cells die in order to be replaced with new cells.

Base pair (bp)—Any of the complementary nucleotide bases (adenine-thymine and cytosine-guanine in DNA; adenine-uracil and cytosine-guanine in RNA) held together by weak hydrogen bonds. Base pairs form links between the two strands of DNA.

Biomarker—In medicine, any substance or other indicator that can be measured to identify the presence or severity of a disease.

Half-life—The amount of time that it takes for a drug, cell, or other component of blood to drop to half of its initial value.

Histocompatibility—The degree to which two people's genetically determined human leucocyte antigen (HLA) alleles (tissue types) match. The higher the level of histocompatibility, the greater the likelihood of successful organ transplantation.

Liquid biopsy—An informal term used to describe the use of cell-free tumor DNA in identifying the presence of cancer, staging it, evaluating its risk of metastasis, and monitoring the effects of treatment on the cancer's progression.

Next-generation sequencing—A general term for massively parallel sequencing of large portions of DNA base pairs, performed by first fragmenting the DNA, reading the individual fragments in parallel, and then reassembling the reads to obtain the sequence of the entire genome.

Noninvasive prenatal testing (NIPT)—Prenatal testing that does not involve methods or techniques that increase the mother's risk of miscarriage. Present forms of NIPT include ultrasound imaging and cell-free fetal DNA testing.

Plasma—The liquid portion of blood and lymphatic fluid that contains antibodies and other proteins.

Polymerase chain reaction (PCR)—A laboratory process used to make a large number of copies of specific genetic information from small amounts of DNA.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosomal material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

Trisomy—The condition of having three identical chromosomes, instead of the normal two, in a cell.

some patients unnecessary chemotherapy or radiotherapy by indicating that the surgery was successful in curing the patient.

- Measuring the effectiveness of chemotherapy and radiotherapy in treating the cancer; this measurement is possible because the levels of ctDNA will drop if the patient is responding to these therapies.
- Identifying new mutations in the tumor and the development of genetic resistance to anticancer drugs. This application of cell-free tumor DNA promises to advance the development of personalized medicine (the use of a patient's genetic information to devise highly individualized therapy for his or her cancer).

Transplantation medicine

Researchers have discovered that cell-free DNA produced by a donated organ—called donor-derived cell-free DNA, or ddcfDNA—can be identified in the transplant

recipient's blood and urine during acute rejection of the donated organ. It is thought that improving the ability to measure ddcfDNA in transplant recipients might allow its use as an early noninvasive biomarker of organ rejection.

As with other applications of cell-free DNA measurement, the use of next-generation sequencing techniques makes ddcfDNA a simpler and more accurate way to assess the degree of histocompatibility between organ donor and recipient before transplantation as well as an effective technique for monitoring the success of the transplant. Of the 419 clinical research studies of cell-free DNA registered with the National Institutes of Health as of late summer 2021, two were studies of the use of ddcfDNA as a biomarker in heart and kidney transplantation.

Other biomarker research

Measurement of cell-free DNA is presently used in sports medicine research to evaluate the effects of

QUESTIONS TO ASK YOUR DOCTOR

- What do you think the future holds for cell-free DNA testing?
- What is your opinion of extending the use of cell-free fetal DNA testing to routine pregnancies as well as high-risk ones?
- Do you think personalized medicine for cancer patients will become a reality in the near future?
- What do you see as the possible drawbacks of widespread cell-free DNA testing (issues of confidentiality, potential loss of health insurance, etc.)?

overtraining on skeletal muscle as well as the changes in a subject's immune response following exercise. It is known that intense exercise temporarily raises a person's levels of cfDNA, although the mechanism behind the active cellular release of cfDNA during exercise is still not fully understood.

Inflammation is another biological process that is known to raise the levels of cfDNA in humans. Researchers are presently measuring cell-free DNA levels in burn patients as a marker of the extent and severity of tissue injury and in patients with autoimmune diseases such as systemic lupus erythematosus (SLE) to evaluate response to therapy.

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- American College of Obstetricians and Gynecologists (ACOG), 409 12th Street SW, Washington, DC 20024, (202) 638-5577 or (800) 673-8444, resources@acog.org, <http://www.acog.org>
- International Society for Prenatal Diagnosis (ISPD), 154 Hansen Road, Suite 201, Charlottesville, VA 22911, (434) 979-4773, (434) 977-1856, info@ispdhome.org, <http://ispdhome.org>
- National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, (301) 402-2218, <http://www.genome.gov>
- National Society of Genetic Counselors (NSGC), 330 N. Wabash Ave., Suite 2000, Chicago, IL 60611, (312) 321-6834, [nsgc@nsgc.org](http://www.nsgc.org), <http://www.nsgc.org>
- Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

Rebecca J. Frey, PhD

Cenani-Lenz syndrome

Definition

Cenani-Lenz syndrome is a rare genetic disorder characterized by syndactyly, a condition in which two or more digits (fingers or toes) are joined together either by webs of skin or by fusion of the bones of adjoining digits. The word "syndactyly" comes from two Greek words that mean "together" and "finger." The syndrome is also known as Cenani-Lenz syndactyly syndrome (CLSS), Cenani syndactylism, syndactylism type VII, and syndactyly type 7.

The syndrome is named for the two geneticists who first identified it in 1967, Asim Cenani and Widukind Lenz. The two researchers were able to determine that their first patients had a previously unknown disorder rather than a form of Apert syndrome, a type of syndactyly recognized since 1906.

Description

Children with CLSS are born with complex syndactyly of the hands, as well as other skeletal malformations. "Complex syndactyly" refers to fusion of the bones in the fingers (synostosis), as distinct from simple syndactyly, in which the fingers are connected by soft tissue only. In children with CLSS, the syndactyly includes attachment of the thumb to the four fingers, giving the child's hand a

KEY TERMS

Anonychia—The absence or abnormal development of the fingernails and toenails.

Apert syndrome—A genetic syndrome characterized by syndactyly as well as malformations of the skull and face. It is named for Eugène Apert, the French physician who first described it in 1906.

Autosomal recessive—A pattern of inheritance in which two copies of a defective gene on a nonsex chromosome must be present for a disease or inherited trait to develop in an individual.

Autosome—Any human chromosome other than a sex chromosome.

Congenital—Present at birth.

Consanguinity—The property of belonging to the same blood kinship as another person. In genetics, marriages between two people who are second cousins or closer are regarded as consanguineous unions.

Frontal bossing—The medical term for an unusually prominent forehead, often associated with an abnormally heavy brow ridge.

Hypertelorism—A birth defect in which the child's eyes are spaced abnormally far apart.

Hypothyroidism—A condition in which the patient's thyroid gland does not produce enough thyroid hormone.

Oligodactyly—The absence of one or more fingers on a hand or toes on a foot.

Scoliosis—Abnormal curvature of the spine, usually defined as greater than 10 degrees to the right or left as the doctor faces the patient.

Spoon hand—A type of syndactyly in which the thumb is joined to the four fingers as well as the fingers being fused together. It is also known as "mitten hand."

Syndactyly—A birth defect in which the fingers or toes are joined either by webs of soft tissue (simple syndactyly) or by fusion of the bones (complex syndactyly). Syndactyly may occur either as an isolated birth defect or as part of a genetic syndrome like CLSS.

Synostosis (plural, synostoses)—The medical term for the fusion of two bones.

mitten- or spoon-shaped appearance. This malformation is sometimes referred to as "mitten hand" or "spoon hand."

In addition to complex syndactyly, children with CLSS typically have abnormally short forearm bones; these bones may also be fused together. Malformations of the feet and toes are also common, as are scoliosis and other deformities of the spinal column. In some cases, some of the child's fingers or toes are completely missing (oligodactyly) and facial features are deformed.

Genetic profile

Most known cases of Cenani-Lenz syndrome have been traced to mutations in the *LRP4* gene on chromosome 11 at 11p12–p11.2. At least two families with histories of CLSS, however, were found to not have *LRP4* mutations, suggesting that mutations in at least one other gene might also produce the syndrome. In May 2015, a team of geneticists based in Saudi Arabia reported tracing a new group of CLSS cases to mutations in the *APC* gene located on chromosome 5 at 5q22. This finding is the first time that mutations of this gene have been linked to a syndrome unrelated to cancer. Defects in the *APC* gene have long been associated with colorectal cancer, as the

gene normally codes for a protein that acts as a tumor suppressor.

CLSS is inherited in an autosomal recessive pattern, meaning that two copies of a defective gene, one from each parent, are required in order to produce the syndrome. Parents of one child with CLSS have a 25% chance of having another child with the syndrome in each successive pregnancy.

Consanguinity, or intermarriage among blood relatives, increases the risk of inheriting an autosomal recessive mutation. Most geneticists regard marriages contracted between two persons who are second cousins or closer as consanguineous unions. Worldwide, the most common form of consanguineous marriage is between first cousins, in which husband and wife share one-eighth of their genetic material derived from one common ancestor. It is noteworthy that most of the known cases of Cenani-Lenz syndrome were identified in consanguineous families from Turkey, eastern Asia, Pakistan, and Saudi Arabia.

Demographics

Syndactyly, by itself, is a relatively common birth defect, occurring in 1 of every 2,000–3,000 live births,

and it is associated with nearly 30 different genetic disorders. Cenani-Lenz syndrome, however, is very rare, with only about 30 cases reported worldwide as of 2021. It is estimated to affect less than one person per million. Although the syndrome appears to be most common in countries that allow marriages between first cousins, there is no evidence as of 2021 that race or ethnicity by itself is a risk factor for CLSS.

Signs and symptoms

In addition to syndactyly, the typical symptoms of Cenani-Lenz syndrome include the following:

- absence of fingernails or toenails (anonychia; 90% of patients)
- syndactyly of toes as well as fingers (90%)
- frontal bossing (50%)
- fusion of the forearm bones (50%)
- abnormally widely spaced eyes (hypertelorism; 50%)
- underdevelopment of the forearm bones (50%)
- underdevelopment or abnormal location of the kidneys (7.5%)
- abnormally shaped ribs (7.5%)
- eye cataracts (7.5%)
- impaired hearing (7.5%)
- dislocation of the elbow (7.5%)
- reduced number of teeth (7.5%)
- underactive thyroid gland (7.5%)

Diagnosis

Ultrasound imaging during pregnancy, which will reveal the presence of syndactyly and malformations of the child's bones, can suggest the presence of CLSS. Genetic testing, however, is required to confirm the diagnosis. In the United States, laboratory testing is available for mutations of the *LRP4* and *APC* genes. These tests involve deletion or duplication analysis and sequencing of the entire coding region.

The diagnosis of CLSS after birth is usually made on the basis of the child's clinical appearance and confirmed by genetic testing. X-ray studies are performed in order to detect the precise location and extent of the malformations of the limbs and spine prior to corrective surgery.

Treatment and management

There is no cure for Cenani-Lenz syndrome. Treatment of the syndactyly requires surgery, which can be performed on infants as young as six months of age. In general, complex syndactyly should be treated as soon as possible to release the fingers and minimize permanent

QUESTIONS TO ASK YOUR DOCTOR

- My older child was born with complex syndactyly. Does that mean that he has Cenani-Lenz syndrome?
- There is a history of first-cousin marriage in the older generations on my father's side of the family. Should I be tested for mutations in the *LRP4* gene?
- How effective is surgical treatment for CLSS?
- Have you ever referred a patient to the Limb Study group in San Francisco for evaluation?

deformity of the hand and forearm. Children whose malformations are not corrected before they reach school age are at risk of losing function in the affected hands or feet, suffering developmental delays, and developing psychological problems, particularly if their facial features are deformed. The surgery should be performed by a specialist in hand surgery to lower the risk of postoperative complications and the recurrence of the syndactyly.

Children diagnosed with Cenani-Lenz syndrome (or any other genetic syndrome characterized by syndactyly) must be evaluated by the anesthesiologist prior to surgery to make sure that any spinal or rib cage deformities will not cause breathing difficulties under general anesthesia.

Physical therapy is necessary after surgery to maximize the child's use of the hands and ability to walk, even though the lower limbs are usually less seriously affected in CLSS than the hands and lower arms.

Research into CLSS and other genetic syndromes affecting the hands, feet, arms, and legs is carried out in the Limb Study conducted at the University of California, San Francisco. Persons with limb defects caused by genetic disorders who are interested in participating in the study can contact the University of California Department of Bioengineering and Therapeutic Sciences for more information.

Prognosis

The prognosis of children with Cenani-Lenz syndrome varies somewhat according to the severity of the syndactyly, oligodactyly, and other skeletal defects. It also varies according to whether the skeletal malformations are accompanied by kidney disorders, misshapen facial features, hypothyroidism, and dental abnormalities. At least one *LRP4* mutation has been identified as causing the prenatal death of the fetus.

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- "Syndactyly Cenani Lenz Type." GARD. <https://rarediseases.info.nih.gov/diseases/5084/syndactyly-cenani-lenz-type> (accessed May 26, 2021).

ORGANIZATIONS

- American Society for Surgery of the Hand (ASSH), 822 W. Washington Blvd., Chicago, IL 60607, (312) 880-1900, (847) 384-1435, info@assh.org, <http://www.assh.org>
- Limb Study, Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, Rock Hall, 1550 Fourth St., Room RH584C, San Francisco, CA 94158, (415) 476-1838, (415) 502-0720, bts.limbstudy@ucsf.edu, <http://pharm.ucsf.edu/limb-study>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>
- Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS), 6701 Democracy Blvd., Suite 1001, MSC 4874, Bethesda, MD 20892, (301) 402-4336, (301) 480-9655, ordr@nih.gov, <https://rarediseases.info.nih.gov>

Rebecca J. Frey, PhD

Central core disease

Definition

Central core disease (CCD) is an inherited muscle disorder that causes weakness of many of the voluntary muscles necessary for movement. The shoulders, hips, pelvis, and upper arms and legs are particularly affected.

Description

First described in 1956, central core disease is one of a group of muscle disorders, or myopathies, named for

certain abnormalities found in the muscle biopsies of people with the syndrome. In CCD, abnormal rounded areas, or cores, of certain muscle cells are present when viewed under the microscope. These core areas lack two particular organelles: mitochondria, which produce energy for the cell, and sarcoplasmic reticulum. The sarcoplasmic reticulum is involved with calcium release when muscle cells contract and calcium absorption when the cells relax. Changes in a particular protein on the muscle cells (the ryanodine receptor 1 protein) coupled with the absence of the sarcoplasmic reticulum causes the muscle cells to have an abnormal increase in the amount of calcium. The increased calcium leads to changes in muscle excitation and contraction leading to muscle weakness. These changes may be an abnormality or absence of this protein necessary for normal function of a muscle cell. The changes result from an altered gene (the *RYR1* gene).

Genetic profile

Central core disease is most often inherited as a dominant trait; that is, an alteration in one gene is enough to cause the condition. In dominant inheritance, an individual with CCD has a 50% chance of passing the disorder on to each child and an affected person usually has one affected parent. There are also occurrences of sporadic inheritance, which means that a gene alters spontaneously to cause the disorder in a person with no family history of the disease. Less often, CCD is inherited in a recessive pattern of inheritance, meaning that two copies of an altered gene are needed for a person to have the condition. In recessive inheritance, both parents of the affected person are unaffected carriers of an altered gene and the affected person usually has a low chance of having an affected child. In 1993, researchers identified the abnormal gene on chromosome 19q13 that leads to the disease. Many different changes in the gene have been documented in individuals with CCD. In general, it appears that the recessive form of CCD results in a more severe clinical presentation than the dominant form.

Demographics

The incidence of CCD is unknown. It is considered a rare disorder, with perhaps a higher incidence in Japan.

Signs and symptoms

Symptoms of central core disease are variable, even within the same family. Some individuals with the condition have an absence of noticeable features while others can be significantly more severely affected. Most often, the condition is not severe; however, the disease can be disabling. A mild general symmetric weakness of proximal muscles and hip displacement are key characteristics

KEY TERMS

Dominant trait—A genetic trait in which one copy of the gene is sufficient to yield an outward display of the trait; dominant genes mask the presence of recessive genes; dominant traits can be inherited from only one parent.

Malignant hyperthermia—A condition in which a person's body temperature may rise dangerously high in response to certain anesthetic drugs during surgery. If not recognized and treated quickly, this condition can lead to kidney failure and be fatal.

Mitochondria (singular, mitochondrion)—Organelles within the cell responsible for energy production.

Myopathy—Any abnormal condition or disease of the muscle.

Sarcoplasmic reticulum—A system of tubules surrounding muscle fibers that release calcium when muscle cells contract and absorb calcium when muscle cells relax.

Scoliosis—An abnormal curvature of the spine. In this condition, the curvature is usually side to side.

Sporadic inheritance—A situation in which a gene mutates spontaneously, or for the first time, to cause the disorder in a person with no family history of the disorder.

of the disease. Occasionally, the facial muscles show weakness. The disease often becomes noticeable in early childhood, when muscle cramps are present after exercising or performing other physical activities. Individuals with CCD have delayed motor skills, such as walking and jumping. Other features of the condition include scoliosis, muscle cramps, breathing difficulty, and, in some cases, malignant hyperthermia. In the more rare severe presentation, a newborn baby may have floppiness followed by periods of persistent muscle weakness, joint contractures, and breathing difficulty. Intelligence is not usually affected.

Diagnosis

The diagnosis of central core disease is made after several tests are completed. A neurological test involves checking an individual's coordination, tendon reflexes such as the knee-jerk reaction, walking ability, and the ability to rise from a sitting position. In addition, a muscle biopsy can be performed to look for the histopathological changes in the cell seen under the microscope. Molecular genetic testing is also available.

Sequencing of the DNA code that makes up the *RYR1* gene as well as looking for deletions or duplications in the gene detects over 90% of mutations. Once the mutation in a family has been identified, other relatives who may be at risk for the condition can also be tested for the condition, and prenatal diagnosis would be available for the family if desired.

Treatment and management

There is no cure for CCD. Treatment measures greatly depend on the severity of the individual's symptoms, especially the degree of muscle weakness that is involved. Treatment measures include surgical procedures, pain management, muscle stimulation therapy, and physical therapy. Individuals with CCD may need assistive devices like wheelchairs, respiratory support like a ventilator, or a feeding tube, and should inform physicians of the increased risk for malignant hyperthermia before any surgery so that an appropriate anesthetic can be used to prevent the condition. Individuals with CCD should wear a medical alert bracelet indicating the risk for malignant hyperthermia.

Prognosis

Although CCD is not a progressive illness, different people experience varying degrees of muscle weakness. Some children with CCD show mildly delayed motor milestones, then catch up and appear only slightly uncoordinated. Others have more severe delays, but also catch up somewhat and are able to walk and move about, although with more limitations. While most are able to walk independently, some children use braces for walking, and a few use wheelchairs.

Fortunately, the outlook for children with this disease is generally positive. Although children with central core disease start their life with some developmental delays, many improve as they get older and stay active throughout their lives. Lifespan is not usually shortened.

Related disorders

The clinical, microscopic, and genetic changes found in CCD can also be found in some other conditions. For instance, isolated cases of malignant hyperthermia (where no other clinical features are present) appear to be linked to the same gene on chromosome 19. Some other conditions such as multiminiore disease show similar muscle weakness and microscopic changes. In addition, other similar clinical conditions are known to be caused by changes in other genes. Therefore, an evaluation with a neurologist as well as a medical geneticist is recommended.

QUESTIONS TO ASK YOUR DOCTOR

- Please explain the bodily changes that take place in a person with central core disease.
- Are there symptoms by which central core disease can be recognized in infants and young children?
- What tests are available for confirming a diagnosis of central core disease?
- What is the prognosis for a child who has been diagnosed with central core disease?

Family support

There are several organizations that families with CCD can turn to for support. The Muscular Dystrophy Association (MDA) sponsors national events and provides information about various myopathies. They also raise money to fund research for cures, provide information to find local clinicians, and organize other family support events. The Muscular Dystrophy Campaign is a similar organization located in the United Kingdom. The Malignant Hyperthermia Association of the United States also assists families in finding information, medical help, and support.

Resources

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"Central Core Disease." Muscular Dystrophy Australia. June 28, 2018. <https://www.mda.org.au/disorders/congenitalmd/ccd/> (accessed May 26, 2021).

ORGANIZATIONS

Malignant Hyperthermia Association of the United States, PO Box 1069, Sherburne, NY 13460, (607) 674-7901, <http://www.mhaus.org>

Muscular Dystrophy Association, 161 N. Clark, Suite 3550, Chicago, IL 60601, (800) 572-1717, <https://www.mda.org/>

Muscular Dystrophy UK, 61 Southwark Street, London, UK SE1 0HL, 0800 652 6352, info@muscular dystrophyuk.org, <https://www.muscular dystrophyuk.org/>

Sonja Higgins, MS

Central core disease of muscle see **Central core disease**

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

Definition

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, or CADASIL, is an inherited condition that can lead to strokes and impairments caused by thickened blood vessel walls in the brain.

Other names for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, or CADASIL, include:

- Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy
- Hereditary multi-infarct dementia
- Chronic familial vascular encephalopathy
- Lacunar dementia
- Agnogenic medial arteriopathy

Demographics

Age of onset varies, but symptoms of CADASIL normally do not appear until people are between the ages of 40 and 60 years old, although they can appear as early as age 20 in rare cases. A general age spread for the condition ranges from 30 to 60 years of age. CADASIL has been reported in people throughout the world. As of 2021, the prevalence of CADASIL was estimated to be between 2 and 4 persons per 100,000.

Description

Understanding CADASIL may be easier if its complex name—cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy—is considered word by word:

- *Cerebral* describes anything related to the brain.
- *Autosomal dominant* describes the type of genetic inheritance involved. It takes only one copy of the altered gene in each cell to cause CADASIL.

- *Arteriopathy* describes a disease of the body's arteries.
- *Subcortical* refers to a specific portion of the brain below the cerebral cortex. Nerve centers in this region control important functions such as reasoning and memory.
- *Infarcts* are areas of tissue in which the cells have died because of lost blood supply.
- *Leukoencephalopathy* refers to any disease that affects the brain's white matter, which contains nerve fibers.

CADASIL is then an inherited disorder caused by a mutation (pathogenic variant) in the *NOTCH3* gene. The gene provides instructions for producing a receptor protein of the same name. This protein is important for normal function of certain cells. Through a complex process at the molecular level, the receptors send signals to the nuclei of cells that normally activate genes within the smooth muscle cells of veins. *NOTCH3* gene mutations cause the protein to accumulate abnormally and affect the function and survival of cells, mainly in the brain's vasculature (blood veins) blood vessels and some tissue arteries. Eventually, the cells self-destruct.

The damaged blood vessels eventually cause a reduction or total loss of blood flow to the affected areas. Sometimes, migraines and other symptoms are the first indications of CADASIL, but eventually the blood vessel damage leads to stroke. As many as 85% of people with symptoms of CADASIL have strokes or transient ischemic attacks (strokes that come and go quickly). Most people with CADASIL have repeated strokes, which eventually lead to other problems, such as dementia.

The only known risk factor for CADASIL is inheritance of the genetic mutation responsible for the disorder. As of 2021, research had not shown a link between risk behaviors such as smoking, high blood pressure, or high cholesterol and the onset of CADASIL. The only link seems to be between current smoking in an adult who has CADASIL and likelihood of stroke.

Genetic profile

CADASIL is an autosomal dominant disease. It develops due to the presence of a mutated gene on one of the two copies of the *NOTCH3* gene that each individual has. One mutated copy of the *NOTCH3* gene is all that is needed for expression of the disease. All humans have two copies of the *NOTCH3* gene but a single mutated copy of the *NOTCH3* gene can override a normal copy of the gene. As a result, CADASIL is a disease that is inherited from an affected parent and is seen in multiple generations of a family. Each child of a parent who carries the mutation has a 50% chance of having CADASIL. For the most part, there is little

KEY TERMS

Dementia—A condition that affects memory and other cognitive abilities and that is usually progressive. Alzheimer's disease is a common form of dementia.

Migraine—A condition marked by severe headaches, often on one side of the head and accompanied by nausea, light and sound sensitivity, and other symptoms. Migraines are believed to involve the nerves and blood vessels of parts of the brain and head.

Nuclei—Plural for nucleus, a special part of the cell that is essential for cell function.

Phenotype—Observable characteristics that result from presentation of a gene. In the case of CADASIL, this includes the observable signs, symptoms, and characteristics of the disease in individuals.

Transient ischemic attack (TIA)—A neurologic dysfunction that comes and goes quickly and is similar to a stroke.

variation among the phenotypes (external characteristics of this genetic disorder), but a few have been observed. For example, some people may have strokes in their 20s and others may not have strokes until they are in their 60s.

The symptoms of CADASIL generally do not appear until mid-life and include the following:

- Stroke or transient ischemic attacks before age 60. Often multiple strokes occur.
- Migraine with aura. A migraine is a headache that involves the nerves and blood vessels in the head. An aura is an abnormal sensation, usually visual, that signals the headache is going to occur.
- Cognitive problems regarding memory and attention. These problems usually worsen with the disease and memory loss is progressive.
- Psychiatric or mood disorders, including depression or abnormal behavior.

Other symptoms may occur but are reported less frequently, including the following:

- Epileptic seizures
- Dementia
- Problems with vision
- Paralysis on one side of the body.

Not everyone who has CADASIL will have every symptom. Some symptoms are less common. For

example, a study found that some women with CADASIL are more likely to have a stroke during pregnancy or soon after childbirth, especially if they are over age 30. Migraines that begin later in life than is typical and strokes that occur earlier than is typical, as well as recurring strokes, are the most common symptoms of CADASIL.

Signs and symptoms

The only known cause of CADASIL is the inherited genetic mutation in the *NOTCH3* gene.

Diagnosis

There is no set clinical guideline for diagnosing CADASIL. The most common way to diagnose CADASIL is by taking a biopsy (sample of muscle or skin tissue) that is viewed under a special microscope. The granular material, called granular osmiophilic material (GOM), is deposited in smooth muscle cells. Pathologists can view the sample and detect GOM accumulation of *NOTCH3* with the help of a technique called electron microscopy. The method is not always exact, as it depends on the accuracy of the sample and the skill of the pathologist. Therefore, a negative result from the biopsy does not necessarily clear the patient of having CADASIL.

If CADASIL is suspected based on symptoms, family history, or biopsy results, DNA testing of the *NOTCH3* gene can confirm the diagnosis. DNA testing is done primarily by DNA sequencing of the *NOTCH3* gene. DNA sequencing is the molecular determination of the precise sequence of nucleotides in a sample of DNA. By looking at the coding regions (exons) of the *NOTCH3* gene and the junctions between these coding regions, mutations or changes in the sequence of nucleotides can be found. If no mutations are detected, then deletion/duplication testing which looks for copy number variants is performed. Using these two testing approaches, it is estimated that greater than 96% of the mutations responsible for CADASIL will be detected.

Procedures

Magnetic resonance imaging (MRI) can be used to look for white matter changes in the brain that are characteristic of CADASIL. A radiologist is a physician who is trained to interpret MRI exams; he or she also will look for lesions where the white matter and gray matter of the brain meet. There may be other causes for these changes, so reviewing the family medical history helps in diagnosis. The family medical history would look for

QUESTIONS TO ASK YOUR DOCTOR

- What can I do to minimize my risk of stroke?
- How can I find out about clinical trials that exist for CADASIL treatment or management?
- If my family has a history of CADASIL, how can I determine the likelihood of passing CADASIL to my children?
- How can I delay the onset of dementia?
- Is there a support group in this community I can turn to?

occurrences of CADASIL, as well as possible CADASIL symptoms.

Tests

There are genetic tests available that can confirm CADASIL by finding the *NOTCH3* mutation in DNA coding regions. Genetic tests to predict whether a person has CADASIL seldom are performed, but they might be used to confirm a diagnosis. The genetic tests are reliable, correctly diagnosing CADASIL in about 96% of cases.

Treatment and management

There is no known treatment that can halt or slow CADASIL. Various treatments can be used to manage the symptoms of the disorder.

Migraine management

Many medications can help manage migraines. A neurologist may prescribe prophylactic (preventive) medications such as antiseizure drugs to help control the frequency and severity of migraine attacks. Medications also are available to help manage the pain and other symptoms of migraine attacks once they occur.

Stroke care

Some neurologists prescribe salicylates to help prevent strokes. Use of aspirin therapy also may help prevent strokes.

Supportive care

Patients with CADASIL may receive a number of supportive care services. For example, services may be offered to help deal with the effects of stroke and cognitive decline or dementia. Patients may receive counseling or other therapies.

Prevention

As of 2021, there was no way to prevent CADASIL or its onset in those who are born with the mutation. Some steps can be taken to prevent the number of strokes or delay onset of stroke. Studies have shown that smoking increases stroke attacks in people who have CADASIL, so people with the disease are advised to quit smoking. Patients with CADASIL also may be advised not to take anticoagulants (medicines that thin the blood) because they may increase the risk of accidents in the brain's vessels. They also may be advised to avoid angiography procedures for the same reason.

Prognosis

The disease progresses slowly, but most people with CADASIL have severe cognitive problems and dementia by the time they reach age 65. The multiple strokes they experience may lead to inability to walk or care for themselves. Some clinicians have suggested that people with hypertension and other heart problems have a worse prognosis. As of 2021, research only seemed to support that smoking leads to more rapid onset of stroke.

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ORGANIZATIONS

CADASIL Together We Have Hope Non-Profit, 3605 Monument Drive, Round Rock, TX 78681-3707, (877) 519-HOPE, (512) 608-1611, info@cadasilfoundation.org, <http://www.cadasilfoundation.org/index.html>
National Institute of Neurological Disorders and Stroke, PO Box 5801, Bethesda, MD 20824, (800) 352-9424, <http://www.ninds.nih.gov>
United Leukodystrophy Foundation, 224 N. Second St., Suite 2, DeKalb, IL 60115, (800) 728-5483, (815) 895-2432, office@ulf.org, <http://www.ulf.org>

Teresa G. Odle
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Cerebral giantism see **Sotos syndrome**

Cerebral palsy

Definition

Cerebral palsy (CP) is the term used for a group of nonprogressive disorders of movement and posture caused by abnormal development of (or damage to) motor control centers of the brain. CP is caused by events before, during, or after birth. The abnormalities of muscle control that define CP are often accompanied by other neurological and physical abnormalities.

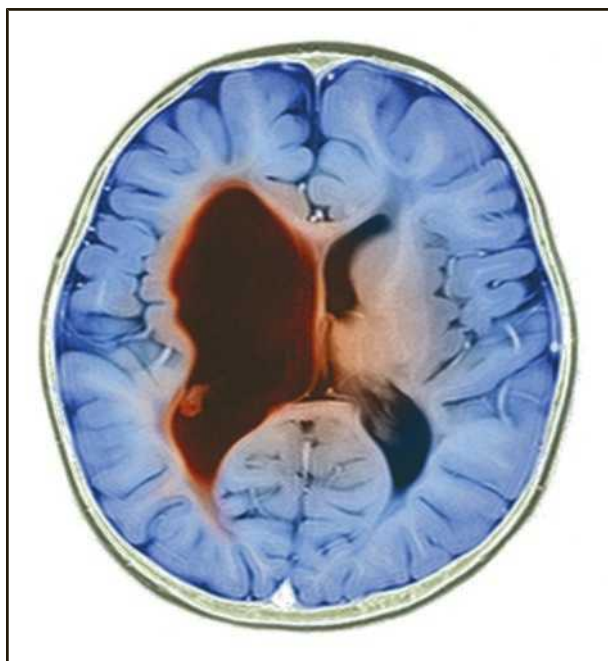
Description

CP is not a specific diagnosis. It is more accurately considered a description of a broad but defined group of neurological and physical problems.

Voluntary movement (walking, grasping, chewing, for example) is primarily accomplished using muscles that are attached to bones, known as the skeletal muscles. Control of the skeletal muscles originates in the cerebral cortex, the largest portion of the brain. *Palsy* means paralysis, but may also be used to describe uncontrolled muscle movement or tension (hypertonia). Therefore, cerebral palsy encompasses any disorder of abnormal movement and paralysis caused by abnormal function of the cerebral cortex. In truth, however, CP does not include conditions due to progressive disease or degeneration of the brain. For this reason, CP is also referred to as static (nonprogressive) encephalopathy (disease of the brain). Also excluded from CP are any disorders of muscle control that arise in the muscles themselves and/or in the peripheral nervous system (nerves outside the brain and spinal cord).

The symptoms of CP and their severity are quite variable. Those with CP may have only minor difficulty with fine motor skills, such as grasping and manipulating items with their hands. A severe form of CP could involve significant muscle problems in all four limbs, mental disability, seizures, and difficulties with vision, speech, and hearing.

Muscles that receive abnormal messages from the brain may be constantly contracted and tight (spastic), exhibit involuntary writhing movements (athetosis), or have difficulty with voluntary movement (dyskinesia). There can also be a lack of balance and coordination with unsteady movements (ataxia). A combination of any of these problems may also occur. Spastic CP and mixed CP constitute the majority of cases. Effects on the muscles can range from mild weakness or partial paralysis (*paresis*) to complete loss of voluntary control of a muscle or group of muscles (*plegia*). CP is also designated by the number of limbs affected. For instance, having



Colored magnetic resonance imaging (MRI) scan of an axial (horizontal) section through the head of a child with cerebral palsy. The front of the head is at top. A right frontal porencephalic cyst can be seen (dark red), which is an abnormal cyst or cavity filled with cerebrospinal fluid (CSF). In this case it has resulted in left-sided weakness of the child. Cerebral palsy is a developmental abnormality caused by damage to the brain during late pregnancy, childbirth, or early childhood. (Simon Fraser/Science Source)

affected muscles in one limb is monoplegia; having affected muscles in both arms or both legs is diplegia; having affected muscles in both limbs on one side of the body is hemiplegia; and having affected muscles in all four limbs is quadriplegia. Muscles of the trunk, neck, and head may be affected as well.

CP can be caused by a number of different mechanisms at various times—from several weeks after conception through birth, and into early childhood. For many years, it was accepted that most cases of CP were due to brain injuries received during a traumatic birth, known as birth asphyxia. However, extensive research in the 1980s showed that only 5%–10% of CP can be attributed to birth trauma. Other possible causes include abnormal development of the brain, prenatal factors that directly or indirectly damage neurons in the developing brain, premature birth, and brain injuries that occur in the first few years of life.

Genetic profile

As noted, CP has many causes, making a discussion of the genetics of CP complicated. About 2% of all cases

of CP were thought to result from genetic mutations as of 2021. In addition, a number of hereditary or genetic syndromes have signs and symptoms similar to CP, but they usually also have associated problems that are not typical of CP. Put another way, some hereditary conditions mimic CP. Isolated CP, meaning CP that is not a part of some other syndrome or disorder, is usually not inherited.

It might be possible to group the causes of CP into those that are genetic and those that are non-genetic, but most would fall somewhere in between. Grouping the causes according to the time of injury is preferable to a genetic and nongenetic classification. The time-related classification of causes would be those that occur during pregnancy (prenatal), those that happen around the time of birth (perinatal), and those that occur after birth (post-natal). Classifying CP related to premature birth and multiple-birth pregnancies (e.g., twins or triplets) is somewhat different and considered separately.

Prenatal causes

Although much has been learned about human embryology in the last several decades, a great deal remains unknown. Studying prenatal human development is difficult because the embryo and fetus develop in a closed environment—the mother’s womb. However, the relatively recent development of a number of prenatal tests has opened a window on the process. Add to that more accurate and complete evaluations of newborns, especially those with problems, and a clearer picture of what can go wrong before birth is possible.

The complicated process of brain development before birth is susceptible to many chance errors that can result in abnormalities of varying degrees of severity. Some of these errors will result in structural anomalies of the brain, while others may cause undetectable but significant abnormalities in the “wiring” of the cerebral cortex. An abnormality in structure or function is sometimes hereditary but is most often due to chance or a cause unknown at this time. Recognizing the degree to which genetic factors play a role in a particular brain abnormality depends on the type of anomaly and the form of CP it causes.

GENETIC. As noted above, genetic mutations are thought to account for about 2% of all cases of CP. As of 2015, two genes had been identified that are associated with specific subtypes of cerebral palsy. Both genetic mutations are inherited in an autosomal recessive pattern. In 2004, a mutation in the *GAD1* gene on chromosome 2 at 2q31 was identified as the cause of a form of spastic cerebral palsy. The *GAD1* gene codes for an enzyme called glutamate decarboxylate-1, which is important in

neurotransmission. Mutations in this gene have been implicated in insulin-dependent (type 1) diabetes and bipolar disorder as well as CP.

The other gene associated with CP is the *CPAT1* gene on chromosome 9 at 9p12-q12. This gene, which was incompletely understood as of 2021, has been linked to ataxic cerebral palsy, which accounts for 5%–10% of all forms of CP. About 50% of cases of ataxic CP are thought to be inherited as an autosomal recessive trait.

It is likely that more candidate genes associated with CP will be discovered or confirmed in the near future. A group of researchers at the University of California, San Francisco, reported in 2013 that a single nucleotide polymorphism (SNP) in the *IL6* gene increases a child's risk of CP. This gene regulates the levels of the IL-6 protein in amniotic fluid and within brain lesions. An international team of American, Australian, and Dutch geneticists reported in early 2015 that whole-exome sequencing of 183 cases of CP indicated that as many as 14% of cases may have a genetic component. The team's findings underscore the complexity of the genetic contribution to CP.

INFECTIOUS. Several maternal-fetal infections are known to increase the risk of CP, including rubella (German measles, now rare in the United States), cytomegalovirus (CMV), and toxoplasmosis. Each of these infections is considered a risk to the fetus only if the mother contracts it for the first time during that pregnancy. Even in those cases, though, most babies will be born normal. Most women are immune to all three infections by the time they reach childbearing age, but a woman's immune status can be determined using the TORCH (toxoplasmosis, rubella, cytomegalovirus, and herpes) test before or during pregnancy.

CARDIOVASCULAR. Just as a stroke can cause neurologic damage in an adult, so too can this type of event occur in the fetus. A burst blood vessel in the brain followed by uncontrolled bleeding (coagulopathy), known as intracerebral hemorrhage, could cause a fetal stroke, as could a cerebral blood vessel obstructed by a clot (embolism). Infants who later develop CP, along with their mothers, are more likely than other mother-infant pairs to test positive for factors that put them at increased risk of bleeding episodes or blood clots. Some coagulation disorders are strictly hereditary, but most have a more complicated origin.

ENVIRONMENTAL. A teratogen is any substance to which a woman is exposed that has the potential to harm the embryo or fetus. Links between a drug or other chemical exposure during pregnancy and an increased risk of CP are difficult to prove. However, any substance that might affect fetal brain development directly or indirectly

could increase the risk of CP. Furthermore, any substance that increases the risk of premature delivery and low birth weight, such as alcohol, tobacco, or cocaine, may indirectly increase the risk of CP.

The fetus receives all nutrients and oxygen from blood circulating through the placenta. Therefore, anything that interferes with normal placental function may adversely affect the brain development of the fetus or may increase the risk of premature delivery. Structural abnormalities of the placenta, premature detachment of the placenta from the uterine wall (abruptio placentae), and placental infections (chorioamnionitis) are thought to pose some risk of CP.

IMMUNOLOGIC. Certain conditions in the mother during pregnancy may pose a risk to fetal development leading to CP. Women with autoimmune antithyroid or antiphospholipid (APA) antibodies are at slightly increased risk of CP in their children. A potentially important clue points toward high levels of cytokines in the maternal and fetal circulation as a possible risk for



Young boy with cerebral palsy using a walker. (Jaren Jai Wicklund/Shutterstock)

CP. Cytokines are proteins associated with inflammation, such as inflammation caused by infection or autoimmune disorders. These cytokines may be toxic to neurons in the fetal brain. More research is needed to determine the exact relationship, if any, between high levels of cytokines in pregnancy and CP. A woman has some risk of developing the same complications in more than one pregnancy, slightly increasing the risk of bearing more than one child with CP.

Serious physical trauma to the mother during pregnancy may result in direct trauma to the fetus as well. Furthermore, injuries to the mother may compromise the availability of nutrients and oxygen to the developing fetal brain.

Perinatal causes

Birth asphyxia significant enough to result in CP is now uncommon in developed countries. A tight nuchal cord (umbilical cord around the baby's neck) and prolapsed cord (cord delivered before the baby) are possible causes of birth asphyxia, as are bleeding and other complications associated with placental abruption and placenta previa (placenta lying over the cervix).

Infection in the mother is sometimes not passed to the fetus through the placenta, but is transmitted to the baby during delivery. Some examples include chlamydia, gonorrhea, CMV, human papilloma virus (HPV), and Group B streptococci (GBS). Any such infection that results in serious illness in the newborn has the potential to produce some neurological damage.

Postnatal causes

The remaining 15% of CP is due to neurological injury sustained after birth. CP that has a postnatal cause is sometimes referred to as acquired CP, but this name is accurate only for those cases caused by infection or trauma.

Incompatibility between the Rh blood types of mother and child (mother Rh negative, baby Rh positive) can result in severe anemia in the baby (erythroblastosis fetalis). This incompatibility may lead to other complications, including severe jaundice, which can cause CP. Rh disease in the newborn is now rare in developed countries due to routine screening of maternal blood type and treatment of at-risk pregnancies. The routine effective treatment of jaundice due to other causes has also made it an infrequent cause of CP in developed countries. Rh blood type poses a risk for recurrence of Rh disease if treatment is not provided.

Such serious infections that affect the brain directly as meningitis and encephalitis may cause irreversible damage to the brain, leading to CP. A seizure disorder

early in life may cause CP, or may be the product of a hidden problem that causes CP in addition to seizures. Unexplained (idiopathic) seizures are hereditary in only a small percentage of cases. Although rare in infants born healthy at or near term, intracerebral hemorrhage and brain embolism, like fetal stroke, are sometimes genetic.

Physical trauma to an infant or child resulting in brain injury, such as from abuse, accidents, or near drowning/suffocation, may cause CP. Likewise, ingestion of such toxic substances as lead, mercury, poisons, or certain chemicals may cause neurological damage. Accidental overdose of certain medications may also cause similar damage to the central nervous system.

Prematurity and multiple-birth pregnancy

Advances in the medical care of premature infants in the last 20 years have dramatically increased the rate of survival of these fragile newborns. However, as gestational age at delivery and birth weight of a baby decrease, the risk of CP increases dramatically. A term pregnancy is delivered at 37–41 weeks' gestation. The risk of CP in a preterm infant (32–37 weeks) is increased about fivefold over the risk for an infant born at term. Survivors of extremely preterm births (less than 28 weeks) face as much as a fiftyfold increase in risk. About 50% of all cases of CP now being diagnosed are in children who were born prematurely.

Two factors are involved in the risk of CP associated with prematurity. First, premature babies are at higher risk of CP-associated medical complications, such as intracerebral hemorrhage, infection, and difficulty in breathing. Second, the onset of premature labor may be induced in part by complications that have already caused neurologic damage in the fetus. A combination of both factors almost certainly plays a role in a number of cases of CP. The tendency toward premature delivery tends to run in families, but the genetic mechanisms are far from clear.

An increase in multiple birth pregnancies in recent years, especially in the United States, is attributed to the increased use of fertility drugs. As the number of fetuses in a pregnancy increases, the risks of abnormal development and premature delivery also increase. Children from twin pregnancies have four times the risk of developing CP as those from singleton pregnancies, owing to the fact that more twin pregnancies are delivered prematurely. The risk of CP in a triplet is up to 18 times greater. Furthermore, recent evidence suggests that a baby from a pregnancy in which its twin died before birth is at increased risk of CP.

KEY TERMS

Asphyxia—Lack of oxygen. In the case of cerebral palsy, lack of oxygen to the brain.

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Athetosis—A condition marked by slow, writhing, involuntary muscle movements.

Cerebral palsy—Movement disability resulting from nonprogressive brain damage.

Coagulopathy—A disorder in which blood is either too slow or too quick to coagulate (clot).

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Cytokine—A protein associated with inflammation that, at high levels, may be toxic to nerve cells in the developing brain.

Diplegia—Paralysis affecting like parts on both sides of the body, such as both arms or both legs.

Dorsal rhizotomy—A surgical procedure that cuts nerve roots to reduce spasticity in affected muscles.

Dyskinesia—Impaired ability to make voluntary movements.

Hemiplegia—Paralysis of one side of the body.

Hypotonia—Reduced or diminished muscle tone.

Quadriplegia—Paralysis of all four limbs.

Serial casting—A series of casts designed to gradually move a limb into a more functional position.

Single nucleotide polymorphism (SNP)—A DNA sequence variation in which a single nucleotide in the genome differs between two individuals of the same species or between two paired chromosomes. SNPs affect individuals' susceptibility to diseases.

Spastic—Referring to a condition in which the muscles are rigid, posture may be abnormal, and fine motor control is impaired.

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

Static encephalopathy—A disease of the brain that does not get better or worse.

Tenotomy—A surgical procedure that cuts the tendon of a contracted muscle to allow lengthening.

Demographics

As of 2019, over 760,000 people in the United States were living with CP. For every 1,000 babies born in the United States, approximately 3 will be diagnosed with some type of CP by the time they are 8 years old. This results in 10,000 babies born with CP every year. Thus, CP is the most widespread cause of childhood disability. It is more common among boys than girls, and more common among African American children than white children, with Asians having the lowest rates. In addition, around 1,200–1,500 preschool-age children are recognized each year to have CP.

Signs and symptoms

By definition, the defect in cerebral function causing CP is nonprogressive. However, the symptoms of CP often change over time. Most of the symptoms of CP relate in some way to the aberrant control of muscles. To review, CP is categorized first by the type of movement/postural disturbance(s) present; then, by a description of which limbs are affected; and finally, by the severity of motor impairment. For example, spastic diplegia refers to continuously tight muscles that have no voluntary control in both legs, while athetoid quadriplegia describes uncontrolled

writhing movements and muscle weakness in all four limbs. These three-part descriptions are helpful in providing a general picture, but cannot give a complete description of any one person with CP. In addition, the various forms of CP do not occur with equal frequency—spastic diplegia is seen in more individuals than is athetoid quadriplegia. CP can also be loosely categorized as mild, moderate, or severe. However, these are very subjective terms with no firm boundaries among them.

A muscle that is tensed and contracted is hypertonic, while excessively loose muscles are hypotonic. Spastic, hypertonic muscles can cause serious orthopedic problems, including scoliosis (spine curvature), hip dislocation, or contractures. A contracture is shortening of a muscle, aided sometimes by a weak opposing force from a neighboring muscle. It may become permanent, or “fixed,” without some intervention. Fixed contractures may cause postural abnormalities in the affected limbs. Clenched fists and contracted feet (equinus or equinovarus) are common in people with CP. Spasticity in the thighs causes them to turn in and cross at the knees, resulting in an unusual method of walking known as a scissors gait. Any of the joints in the limbs may be stiff (immobilized) due to spasticity of the attached muscles.

Athetosis and dyskinesia often occur with spasticity, but do not often occur alone. The same is true of ataxia. It is important to remember that “mild CP” or “severe CP” refers not only to the number of symptoms present, but also to the level of involvement of any particular class of symptoms.

Mechanisms that can cause CP are not always restricted to motor-control areas of the brain. Other neurological symptoms may include:

- mental and learning disabilities (about 50%)
- behavioral disorders
- seizure disorders (about 28%)
- visual impairment (about 42%)
- hearing loss
- speech impairment (dysarthria; about 58%)
- abnormalities of sensation and perception

These problems may have a greater impact on a child’s life than the physical impairments of CP, although not all children with CP are affected by other problems. Many infants and children with CP have growth impairment. About one-third of individuals with CP have moderate to severe mental disability, about one-third have mild mental disability, and the remainder have normal intelligence.

Diagnosis

Diagnosis of CP is based on the child’s clinical presentation rather than laboratory or imaging tests. The signs of CP are not usually noticeable at birth. Children normally progress through a predictable set of developmental milestones through the first 18 months of life. Children with CP, however, tend to develop these skills more slowly because of their motor impairments. Therefore, delays in reaching milestones are usually the first symptoms of CP. Babies with more severe cases of CP are normally diagnosed earlier than others.

Selected developmental milestones and the ages for normally acquiring them are given below. If a child does not acquire the skill by the age shown in parentheses, there is some cause for concern.

- Sits well unsupported—6 months (8–10 months)
- Babbles—6 months (8 months)
- Crawls—9 months (12 months)
- Finger-feeds, holds bottle—9 months (12 months)
- Walks alone—12 months (15–18 months)
- Uses one or two words other than dada/mama—12 months (15 months)
- Walks up and down steps—24 months (24–36 months)

QUESTIONS TO ASK YOUR DOCTOR

- How certain is your diagnosis of cerebral palsy for my child?
- What confirmatory tests can be performed to increase the reliability of this diagnosis?
- What type of cerebral palsy does my child have?
- Given your diagnosis, what is the long-term prognosis for my child?
- What types of treatment and/or care are available for a child with cerebral palsy?
- Does my child have one of the rare forms of CP related to gene mutations?
- Can you recommend support groups for CP patients and their family members in our area?

- Turns pages in books; removes shoes and socks—24 months (30 months)

Children do not consistently favor one hand over the other before 12 to 18 months, and doing so may be a sign that the child has difficulty using the other hand. This same preference for one side of the body may show up as asymmetric crawling, or later on, favoring one leg while climbing stairs.

Children normally progress at somewhat different rates; slow beginning accomplishment is often followed by normal development. Other causes for developmental delay—some benign, some serious—should be excluded before considering CP as the answer. CP is nonprogressive, so continued loss of previously acquired milestones indicates that CP is not the cause of the problem.

There is no single diagnostic test for CP as of 2015, but certain factors increase suspicion. The Apgar score measures a baby’s condition immediately after birth. Babies who have low Apgar scores are at increased risk of CP. Presence of abnormal muscle tone or movements may indicate CP, as may the persistence of infantile reflexes. Imaging of the brain using ultrasound, x-rays, MRI, and/or CT scans may reveal a structural anomaly. Evidence of some brain lesions associated with CP include scarring, cysts, expansion of the cerebral ventricles (hydrocephalus), periventricular leukomalacia (an abnormality of the area surrounding the ventricles), areas of dead tissue (necrosis), and signs of an intracerebral hemorrhage or blood clot. Blood and urine biochemical tests, as well as genetic tests, may be used to rule out other possible causes, including muscle and

peripheral nerve diseases, mitochondrial and metabolic diseases, and other inherited disorders. Evaluations by a pediatric developmental specialist and a geneticist may be beneficial.

Treatment and management

Cerebral palsy cannot be cured, but many of the disabilities it causes can be managed through planning and timely care. Treatment for a child with CP depends on the severity, nature, and location of the primary muscular symptoms, as well as any associated problems that might be present. Optimal care of a child with mild CP may involve regular interaction with only a physical therapist and occupational therapist. Care for a more severely affected child may include visits to multiple medical specialists throughout life. With proper treatment and an effective plan, most people with CP can lead productive, happy lives.

Importance of early intervention

Data of limited quantity and quality suggest benefit from early interventions, with medium effect size for motor development. If implemented as part of an early intervention program while the child is still developing, certain therapies for CP can lessen the impact of impairment and minimize the child's potential for developing associated conditions.

Therapy

Spasticity, muscle weakness, coordination, ataxia, and scoliosis are all significant impairments that affect the posture and mobility of a person with CP. Physical and occupational therapists work with the patient and the family to maximize the ability to move affected limbs, develop normal motor patterns, and maintain posture. Assistive equipment such as wheelchairs, walkers, shoe inserts, crutches, and braces is often required. A speech therapist and such high-tech aids as computer-controlled communication devices can make a tremendous difference in the life of someone who has speech impairments.

Medications

Before fixed contractures develop, such muscle relaxants as diazepam (Valium), dantrolene (Dantrium), and baclofen (Lioresal) may be prescribed. Botulinum toxin (Botox), a newer and highly effective treatment, is injected directly into the affected muscles. Alcohol or phenol injections into the nerves controlling the muscle are other options. Multiple medications are available to control seizures. Athetosis can be treated using medications such as trihexyphenidyl HCl (Artane) and benzotropine (Cogentin).

Surgery

Fixed contractures are usually treated with either serial casting or surgery. The most commonly used surgical procedures are tenotomy, tendon transfer, and dorsal rhizotomy. In tenotomy, the tendons of the affected muscle are cut and the limb is cast in a more normal position while the tendon regrows. Alternatively, tendon transfer involves cutting and reattaching a tendon at a different point on the bone to enhance the length and function of the muscle. A neurosurgeon performing dorsal rhizotomy carefully cuts selected nerve roots in the spinal cord to prevent them from stimulating the spastic muscles. Neurosurgical procedures in the brain, such as implanting tiny electrodes directly into the cerebellum or cutting a portion of the hypothalamus, have very specific uses and have had mixed results.

Education

Parents of a child newly diagnosed with CP are not likely to have the necessary expertise to coordinate the full range of care their child will need. Although knowledgeable and caring medical professionals are indispensable for developing a care plan, a potentially more important source of information and advice is other parents who have dealt with the same set of difficulties. Support groups for parents of children with CP can be significantly effective sources of both practical advice and emotional support. Many cities have support groups that can be located through the United Cerebral Palsy Association. Furthermore, most large medical centers have special multidisciplinary clinics for children with developmental disorders.

Clinical trials

Many clinical trials for the treatment of cerebral palsy are currently sponsored by the National Institutes of Health (NIH) and other agencies. In 2021, the NIH reported 920 recruiting, ongoing, or recently completed studies. Current clinical trials include studies of robotic wheelchairs and other robotic assistive devices for children with CP. Other studies include investigational medications, and the use of hyperbaric oxygen therapy. Experimental treatments include functional electrical stimulation (FES) as a form of treatment for CP, and prenatal administration of magnesium sulfate as a preventive measure.

Clinical trial information is constantly updated by NIH. The most recent information on CP trials can be found at: <https://clinicaltrials.gov/ct2/home>

Prognosis

Cerebral palsy can affect every stage of maturation from childhood through adolescence, and into adulthood. At each stage, those with CP, along with their caregivers,

must strive to achieve and maintain the fullest range of experiences and education consistent with their abilities. The advice and intervention of various professionals remains crucial for many people with CP. Although CP itself is not considered a terminal disorder, it can affect a person's lifespan by increasing the risk of certain medical problems like osteoarthritis, depression, chronic pain, high blood pressure, and urinary incontinence. People with mild cerebral palsy may have near-normal lifespans, but the lifespan of those with more severe forms may be shortened. However, over 90% of infants with CP survive into adulthood.

The cause of most cases of CP remains unknown, but it has become clear in recent years that birth difficulties are not to blame in most cases. Rather, developmental problems before birth, usually unknown and generally undiagnosable, are responsible for most cases. The rate of survival for preterm infants has leveled off in recent years. Furthermore, methods to improve the long-term health of these at-risk babies are now being sought. Current research is also focusing on the possible benefits of recognizing and treating coagulopathies and inflammatory disorders in the prenatal and perinatal periods. The use of magnesium sulfate in pregnant women with preeclampsia or threatened preterm delivery may reduce the risk of CP in very preterm infants. Finally, the risk of CP can be decreased through good maternal nutrition, avoidance of drugs and alcohol during pregnancy, and prevention or prompt treatment of infections.

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ORGANIZATIONS

- American Academy of Pediatrics (AAP), 345 Park Boulevard, Itasca, IL 60413, (847) 434-4000 or (800) 433-9016, (847) 434-8000, <https://www.aap.org/en-us/Pages/Contact.aspx> <https://services.aap.org/en/support-center/>
- Cerebral Palsy International Research Foundation (CPIRF), 3 Columbus Circle, 15th Floor, New York, NY, United States 10019, (212)520-1686, info@yourcpf.org, <https://www.yourcpf.org/>
- March of Dimes, 1550 Crystal Drive, Suite 1300, Arlington, VA 22202, (888) 663-4637, <http://www.marchofdimes.org/contact-us.aspx>, <http://www.marchofdimes.org>
- National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, (301) 402-2218, nhgripressoffice@nih.gov, <http://www.genome.gov/10005049> <http://www.genome.gov>
- Society for Maternal-Fetal Medicine (SMFM), 409 12th Street, SW, Washington, D.C. 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>
- United Cerebral Palsy (UCP), 1825 K Street NW, Suite 600, Washington, DC 20006, (202) 776-0406, (800) 872-5827, info@ucp.org, <http://ucp.org>

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Revised by Bharati K. Hegde, BE, MS, PhD

Cerebral sclerosis see **Adrenoleukodystrophy (ALD)**

Cerebrohepatorenal syndrome see **Zellweger spectrum**

CFC syndrome see **Cardiofaciocutaneous syndrome**

Channelopathies

Definition

Channelopathies are inherited diseases caused by defects in cell proteins called ion channels. These diseases appear as episodes of epilepsy, headache disorders, and movement disorders (dyskinesias).

Channelopathies include a wide range of neurologic diseases, including periodic paralysis, congenital myasthenic syndromes, malignant hyperthermia, a form of Charcot-Marie-Tooth disease, cystic fibrosis, and long Q-T syndrome.

Description

Channelopathies are a diverse group of disorders resulting from the dysfunction of proteins, called ion channels, that transport materials across the cell membrane. Ion channels are found in every cell of the body. These cells, including nerve and muscle cells, are surrounded by thin coverings called membranes. Embedded in these membranes are a large and varied set of proteins that control the movement of materials across the membrane, in and out of the cell. One major type of material that crosses through such proteins includes ions. The proteins that transport these proteins are called ion channels.

Ions perform many different functions in cells. In neurons (nerve cells), they help transmit the electrical messages that allow neurons to communicate not only with each other, but also with muscle cells. In muscle cells, they allow the muscle to contract. When the ion channels are defective, these activities may be disrupted.

When these ion channels malfunction, many diseases throughout the body may occur. Among conditions caused by channelopathies are:

- Diseases of the nervous system: Generalized epilepsy with febrile seizures, familial hemiplegic migraine, episodic ataxia, and hyperkalemic and hypokalemic periodic paralysis.
- Diseases of the cardiovascular system: Long QT syndrome, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia.
- Diseases of the respiratory system: Cystic fibrosis.
- Diseases of the endocrine system: Neonatal diabetes mellitus, familial hyperinsulinemic hypoglycemia, thyrotoxic hypokalemic periodic paralysis, and familial hyperaldosteronism.
- Diseases of the urinary system: Bartter syndrome, nephrogenic diabetes insipidus, autosomal-dominant polycystic kidney disease, and hypomagnesemia with secondary hypocalcemia.

- Diseases of the immune system: Myasthenia gravis, neuromyelitis optica, Isaac syndrome, and anti-NMDA (N-methyl-D-aspartate) receptor encephalitis.

Inheritance

The proteins responsible for channelopathies are made by genes, and defects in these genes cause diseases. Genes are inherited from both parents. Many unique gene mutations have been identified that cause ion channelopathies. These mutations are specific to the genes that relate to the affected body part of the system. If a disease follows a recessive inheritance pattern, two defective copies of a gene are needed in order for a person to develop the disease. Two parents, each of whom carry one defective copy, have a 25% chance with each pregnancy of having a child with the disease.

If a disease follows a dominant inheritance pattern, only one defective copy of the gene is needed in order to develop the disease. When only one parent carries the disease gene (and likely has the disease as well), there is a 50% chance with each pregnancy of having a child with the disease.

Types of channelopathies

Periodic paralysis

A person with periodic paralysis experiences sudden onset of weakness, which gradually subsides, only to return again later. Two forms of periodic paralysis exist, termed “hyperkalemic,” referring to the excessively high levels of potassium in the blood that can trigger attacks, and “hypokalemic,” in which excessively low levels of potassium are the culprit. Each is caused by different genetic mutations of a potassium ion channel. Both exhibit the dominant inheritance pattern. Onset is usually in childhood for the hyperkalemic form, and childhood to adulthood for the hypokalemic form. Dietary restrictions can reduce the frequency of attacks of both forms, with a high-carbohydrate, low-potassium diet for the hyperkalemic form, and a low-carbohydrate, high-potassium diet for the hypokalemic form.

Congenital myasthenic syndromes

Congenital myasthenic syndromes are a group of related disorders caused by inherited defects in the acetylcholine receptor. This protein sits on the surface of muscle cells. When a nearby neuron releases the chemical acetylcholine, it binds to the receptor, causing the muscle to contract. Defects cause myasthenia (“muscle weakness”) and fatigue and may be life threatening in some individuals. Most forms display the recessive inheritance pattern. Mutations in the *CHRNE* gene are responsible for

more than half of all cases. A large number of cases are also caused by mutations in the *RAPSN*, *CHAT*, *COLQ*, and *DOK7* genes.

Malignant hyperthermia

Malignant hyperthermia is caused by mutations of the *CACNA1S* and *RYR1* genes. These genes contain instructions for creating the membrane protein inside the muscle cell, called the ryanodine receptor, which controls calcium ion movement within the muscle and a different muscle protein controlling calcium. Malignant hyperthermia is usually triggered by exposure to certain kinds of anesthetics or muscle relaxants. It causes a dangerous increase in the rate of activity within the muscle and a sharp rise in temperature, leading to a variety of threats. These threats may include severe damage to muscle cells, heart malfunction, swelling of tissues (including the brain), and death. Scientists have identified at least six other genetic mutations that may cause this condition.

Charcot-Marie-Tooth disease

Charcot-Marie-Tooth disease is a group of progressive disorders that affect the nerves linking the brain and spinal cord to muscles and sensory cells. These nerves detect sensations such as touch, pain, heat, and sound. Charcot-Marie-Tooth disease can result in loss of sensation and wasting of muscles in the feet, legs, and hands. Charcot-Marie-Tooth disease is caused by mutations in many different genes. These genes provide instructions for making proteins that are involved in the function of nerves in the feet, legs, and hands. It is suspected that the gene mutations that cause Charcot-Marie-Tooth disease likely impair axons, which transmit nerve impulses, or affect the specialized cells that produce myelin. As a result, these nerve cells slowly lose the ability to stimulate the muscles and to transmit signals to the brain. The list of genes associated with Charcot-Marie-Tooth disease continues to grow as researchers study this disorder.

Resources

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Charcot-Marie-Tooth Association, PO Box 105, Glenolden, PA 19036, (800) 606-2682, (610) 499-9264, 610-499-9267, info@cmtausa.org, <http://cmtausa.org/>

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Charcot-Marie-Tooth disease

Definition

Charcot-Marie-Tooth disease (CMT) is the name of a group of inherited disorders of the nerves in the peripheral nervous system causing weakness and loss of sensation in the limbs.

Description

CMT is named for the three neurologists who first described the condition in the late 1800s. It is also known as hereditary motor and sensory neuropathy. It is sometimes called peroneal muscular atrophy, referring to the muscles in the leg that are often affected. The age of onset of CMT can vary anywhere from young childhood to middle adulthood. Symptoms typically begin by the age of 20. For reasons yet unknown, the severity in symptoms can also vary greatly, even among members of the same family.

Although CMT has been described for many years, it has only been since the early 1990s that the genetic causes of many types of CMT have become known. Knowledge about CMT has accordingly increased dramatically within the two past decades as a result of the significant advances in genetics.

The peripheral nerves

CMT affects the peripheral nerves, those groups of nerve cells carrying information to and from the spinal

cord. It decreases their ability to carry motor commands to muscles, especially those furthest from the spinal cord located in the feet and hands. As a result, the muscles connected to these nerves eventually weaken. CMT also affects the sensory nerves that carry information from the limbs to the brain. Therefore, people with CMT also have sensory loss. This causes symptoms such as difficulties with balance, or not being able to tell if something is hot or cold.

Although multiple types of CMT may be grouped together based on the types of nerve problems of clinical findings, the disease often is classified according to several specific types. The types are distinguished by how CMT affects nerve function and by the genetic cause. Type X CMT is caused by mutations in a gene on the X chromosome, one of the two sex chromosomes. Type 1 CMT is characterized by abnormalities in myelin, the protective substance that covers nerve cells. Type 2 CMT is characterized by abnormalities in the axon fiber that extends from a nerve cell and transmits nerve impulses. Intermediate forms of CMT display abnormalities in both axons and myelin. Type 4 CMT affects either the axon or myelin. Types 1, 2, 4, and intermediate forms are further categorized by subtypes (such as 1A, 2A, 4A), distinguished by the specific gene that is altered. No universal system has yet been adopted to classify types of CMT, and other names are used to describe this disorder. For example, Roussy-Levy syndrome is a form of type 1 CMT, type 1B. Dejerine-Sottas syndrome is a severe early childhood form of CMT that may be type 1 or type 4 depending on the specific gene that is altered.

Genetic profile

CMT is caused by changes (mutations) in any one of a number of genes that carry the instructions to make the peripheral nerves. Genes contain the instructions for how the body grows and develops before and after a person is born. As of 2021, mutations in 88 genes had been identified as responsible for one of the many types of CMT. These include the *AARS*, *BSCL2*, *DNM2*, *EGR2*, *FGD4*, *GARS*, *GDAP1*, *GJB1*, *HSPB1*, *KIAA0274*, *KIF1B*, *LITAF*, *LMNA*, *MFN2*, *MPZ*, *MTMR2*, *NDRG1*, *NEFL*, *PMP22*, *PRX*, *RAB7A*, *SBF2*, *SH3TC2*, and *YARS* genes, along with others.

Increasingly, CMT is categorized by the specific gene that is altered. Type 1 is caused by mutations in the following genes: *PMP22* (subtypes 1A and 1E), *MPZ* (subtype 1B), *LITAF* (subtype 1C), *EGR2* (subtype 1D), and *NEFL* (subtype 1F). Alterations in the following genes cause type 2 CMT disease: *KIF1B* and *MFN2* (subtype 2A), *RAB7A* (subtype 2B), *LMNA* (subtype 2B1), *TRPV4* (subtype 2C), *BSCL2* and *GARS* (subtype 2D), *NEFL* (subtype 2E), *HSPB1* (subtype 2F), *MPZ*

(subtypes 2I and 2J), *HSPB5* (subtype 2L), and *GDAP1* (subtype 2K). Type 4 CMT is caused by mutations in the following genes: *GDAP1* (subtype 4A), *MTMR2* (subtype 4B1), *SBF2* (subtype 4B2), *SH3TC2* (subtype 4C), *NDRG1* (subtype 4D), *EGR2* (subtype 4E), *FGD4* (subtype 4H), *FIG4* (subtype 4J), and *PRX* (subtype 4F). Intermediate CMT is caused by mutations in the *DNM2*, *YARS*, *MPZ*, and *GDAP1* genes. Type X CMT disease is caused by a mutation in the *GJB1* and *PRPS1* genes.

CMT1

The most common type of CMT is called CMT1A. It is often caused by a mutation in a gene called peripheral myelin protein 22 (*PMP22*) located on chromosome 17. The function of this gene is to make a protein (*PMP22*) that makes up part of the myelin. In most people who have CMT, the mutation that causes the condition is a duplication (doubling) of the *PMP22* gene. Instead of having two copies of the *PMP22* gene (one on each chromosome), there are three copies. It is not known how this extra copy of the *PMP22* gene causes the observed symptoms. A small percentage of people with CMT1A do not have a duplication of the *PMP22* gene, but rather have a point mutation in the gene. A point mutation is a misprint in the gene that causes it to work incorrectly.

CMT1B is caused by a mutation in a gene called myelin protein zero (*MPZ*) located on chromosome 1. The function of this gene is to make the layers of myelin stick together as they are wrapped around the axon. The mutations in this gene are point mutations because they involve a change (either deletion, substitution, or insertion) at one specific component of a gene.

Hereditary neuropathy with liability to pressure palsies (HNPP)

HNPP is a condition that is also caused by a mutation in the *PMP22* gene. The mutation is a deletion resulting in only one copy of the *PMP22* gene instead of two. People who have HNPP may have some of the signs of CMT. However, they also have episodes where they develop weakness and problems with sensation after compression of certain pressure points, such as the elbows or knee. These symptoms will often resolve after a few days or weeks, but sometimes they are permanent.

CMT2

CMT2 results from abnormalities in the axon of the peripheral nerve cell rather than the myelin sheath. There are many subtypes of CMT2, designated by the letters from A–L. Each subtype is characterized by the mode of inheritance and associated clinical features. As of 2021, the genetic loci have been identified for some subtypes.

KEY TERMS

Axon—Very thin, wire-like extension of nerve cells.

Myelin—A fatty sheath surrounding nerves in the peripheral nervous system that helps them conduct impulses quickly.

Nerve conduction testing—Procedure that measures the speed at which impulses move through the nerves.

Neuropathy—A condition caused by nerve damage. Major symptoms include weakness, numbness, paralysis, or pain in the affected area.

Peripheral nerves—Nerves throughout the body that that communicate motor and sensory information to and from the spinal cord.

CMTX

Another type of CMT, called CMTX, is usually considered a subtype of CMT1 because it affects the myelin, but it has a different type of inheritance than type 1 or type 2. In CMTX, the CMT-causing gene is located on the X chromosome and is called connexin 32 (*Cx32*). The function of this gene is to code for a class of protein called connexins that form tunnels between the layers of myelin.

CMT3

In the past a condition called Dejerine-Sottas disease was referred to as CMT3. This is a severe type of CMT in which symptoms begin in infancy or early childhood. It is now known that this is not a separate type of CMT. People who have onset in infancy or early childhood often have mutations in the *PMP22* or *MPZ* genes.

CMT4

CMT4 consists of several different subtypes of autosomal recessive demyelinating motor and sensory neuropathies. Each neuropathy subtype is caused by a different genetic mutation, may affect a particular ethnic population, and produces distinct physiologic or clinical characteristics. Patients with CMT4 generally develop symptoms of leg weakness in childhood and by adolescence they may not be able to walk.

Inheritance

Autosomal dominant inheritance

CMT1A and 1B, HNPP, and all of the subtypes of CMT2 have autosomal dominant inheritance. Autosomal refers to the first 22 pairs of chromosomes that are the

same in males and females. Therefore, males and females are affected equally in these types. In a dominant condition, only one gene of a pair needs to have a mutation in order for a person to have symptoms of the condition. Therefore, anyone who has these types has a 50%, or one in two, chance of passing CMT on to each of their children. This chance is the same for each pregnancy and does not change based on the number of previous children.

X-linked inheritance

CMTX has X-linked inheritance. Since males only have one X chromosome, they only have one copy of the *Cx32* gene. Thus, when a male has a mutation in his *Cx32* gene, he will have CMT. However, females have two X chromosomes and therefore have two copies of the *Cx32* gene. If they have a mutation in one copy of their *Cx32* genes, they will only have mild to moderate symptoms of CMT that may go unnoticed. This is because their normal copy of the *Cx32* gene produces sufficient amounts of myelin.

Women pass on one or the other of their X chromosomes to their children—sons or daughters. If a woman with a *Cx32* mutation passes her normal X chromosome, she will have an unaffected son or daughter who will not pass CMT on to their children. If the woman passes the chromosome with *Cx32* mutation on she will have an affected son or daughter, although the daughter will be mildly affected or have no symptoms. Therefore, a woman with a *Cx32* mutation has a 50%, or one in two, chance of passing the mutation to her children; a son will be affected, and a daughter may only have mild symptoms.

When males pass on an X chromosome, they have a daughter. When they pass on a Y chromosome, they have a son. Since the *Cx32* mutation is on the X chromosome, a man with CMTX will always pass the *Cx32* mutation on to his daughters. However, when he has a son, he passes on the Y chromosome; the son will not be affected. Therefore, an affected male passes the *Cx32* gene mutation on to all of his daughters, but to none of his sons.

Autosomal recessive inheritance

CMT4 has autosomal recessive inheritance. Boys and girls are equally affected. In order for a person to have CMT4, they must have a mutation in both of their CMT causing genes—one inherited from each parent. The parents of an affected person are called carriers. They have one normal copy of the gene and one copy with a mutation. Carriers do not have symptoms of CMT. Two carrier parents have a 25%, or one in four, chance of passing CMT on to each of their children.

Demographics

As of 2021, Charcot-Marie-Tooth disease was considered the most common inherited disorder involving the peripheral nerves, affecting an estimated 150,000 people in the United States. It is known to occur in all races and ethnic groups. Worldwide, this disorder affects about 1 in 3,300 people.

Signs and symptoms

The onset of symptoms is highly variable, even among members of the same family. Symptoms usually progress very slowly over a person's lifetime. The main problems caused by CMT are weakness and loss of sensation, especially in the feet and hands. The first symptoms are usually problems with the feet such as high arches and problems with walking and running. Tripping while walking and sprained ankles are common. Muscle loss in the feet and calves leads to "foot drop" where the foot does not lift high enough off the ground when walking. Complaints of cold legs are common, as are cramps in the legs, especially after exercise.

In many people, the fingers and hands eventually become affected. Muscle loss in the hands can make fine movements such as working buttons and zippers difficult. Some patients develop tremor in the upper limbs. Loss of sensation can cause problems such as numbness and the inability to feel if something is hot or cold. Most people with CMT remain able to walk throughout their lives.

Diagnosis

Diagnosis of CMT begins with a careful neurological exam to determine the extent and distribution of weakness. A thorough family medical history should be taken at this time to determine if other people in the family are affected. Testing also may be performed to rule out other causes of neuropathy.

A nerve conduction velocity test should be performed to measure how fast impulses travel through the nerves. This test may show characteristic features of CMT, but it is not diagnostic of CMT. Nerve conduction testing may be combined with electromyography (EMG), an electrical test of the muscles.

A nerve biopsy (removal of a small piece of the nerve) may be performed to look for changes characteristic of CMT. However, this testing is not diagnostic of CMT and is usually not necessary for making a diagnosis.

Definitive diagnosis of CMT is made only by genetic testing, usually performed by drawing a small amount of blood. Testing may not be available to detect all mutations that cause CMT. However, research is progressing rapidly and new testing is often made available every

QUESTIONS TO ASK YOUR DOCTOR

- My spouse and I are planning to have children. What are the chances that one of our children will have Charcot-Marie-Tooth disease?
- Will surgery be helpful in treating our child's Charcot-Marie-Tooth disease?
- What type of specialist should we consult about our child's Charcot-Marie-Tooth disease?

few months. All affected members of a family have the same type of CMT. Therefore, once a mutation is found in one affected member, it is possible to test other members who may have symptoms or are at risk of developing CMT.

Prenatal diagnosis

Testing during pregnancy to determine whether an unborn child is affected is possible if genetic testing in a family has identified a specific CMT-causing mutation. This can be done after 10–12 weeks of pregnancy using a procedure called chorionic villus sampling (CVS). CVS involves removing a tiny piece of the placenta and examining the cells. Testing can also be done by amniocentesis after 16 weeks gestation by removing a small amount of the amniotic fluid surrounding the baby and analyzing the cells in the fluid. Each of these procedures has a small risk of miscarriage associated with it. Those who are interested in learning more should check with their doctor or genetic counselor. Couples interested in these options should obtain genetic counseling to carefully explore all of the benefits and limitations of these procedures.

Treatment and management

There is no cure for CMT. However, physical and occupational therapy are an important part of CMT treatment. Physical therapy is used to preserve range of motion and minimize deformity caused by muscle shortening, or contracture. Braces are sometimes used to improve control of the lower extremities and can help tremendously with balance. After wearing braces, people often find that they have more energy because they are using less energy to focus on their walking. Occupational therapy is used to provide devices and techniques that can assist tasks such as dressing, feeding, writing, and other routine activities of daily life. Voice-activated software can also help people who have problems with fine motor control.

Understanding of the molecular basis of CMT continues to increase at a rapid pace. In addition, the neurophysiologic deficits and clinical problems associated with CMT are more clearly understood. The precise genetic cause of many types of CMT has now been determined. Advances in molecular biology and genetic manipulation techniques have allowed doctors to begin to understand how specific genetic mutations result in disease onset, progression, and symptoms for patients.

It is very important that people with CMT avoid injury that causes them to be immobile for long periods of time. It is often difficult for people with CMT to return to their original strength after injury.

There is a long list of medications that should be avoided, if possible, by people diagnosed with CMT, such as hydralazine (Apresoline), vitamin megadoses (A, B₆, and D), paclitaxel (Taxol), and large intravenous doses of penicillin. Complete lists are available from the CMT support groups. People considering taking any of these medications should weigh the risks and benefits with their physician.

Prognosis

The symptoms of CMT usually progress slowly over many years, but do not usually shorten life expectancy. Most people with CMT do not need to use a wheelchair during their lifetime, but are able to lead full and productive lives despite their physical challenges.

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ORGANIZATIONS

Charcot-Marie-Tooth Association, P.O. Box 105, Glenolden, PA 19036, (610) 499-9264 or (800) 606-2682, (610) 499-9267, info@cmtausa.org, <http://www.cmtausa.org>

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CHARGE syndrome

Definition

CHARGE syndrome is a group of major and minor malformations that have been observed to occur together more frequently than expected by chance. The name of the syndrome is an acronym for some of its features:

- C—Coloboma and/or cranial nerves
- H—Heart defects
- A—Atresia choanae
- R—Retarded growth and development
- G—Genital anomalies
- E—Ear anomalies

While these features have classically been used for identification of affected individuals, many other malformations and medical problems have been observed to occur with this syndrome.

Description

CHARGE syndrome was first described in 1979 as an association of multiple congenital anomalies, all of which included choanal atresia, meaning the blocking of the choanae, the passages from the back of the nose to the throat that allow breathing through the nose. Soon after, several other papers were published describing similar patients who all had both choanal atresia and coloboma—that is, a cleft or failure to close off the eyeball. In 1981, the CHARGE acronym was proposed to describe the features of the condition. Due to the large number of patients described since 1979, CHARGE is now regarded as a recognizable syndrome. Additionally, in 2004, loss-of-function mutations in the *CDH7* gene were shown to cause CHARGE syndrome. The majority of patients with a clinical diagnosis of CHARGE syndrome are found to have a mutation in the *CDH7* gene. However, for the remaining 10%, the cause for the condition remains unclear. Crucial development of the choanae, heart, ear, and other organs occurs 35–45 days after

conception and any disruption in development during this time is believed to lead to many of the features of the syndrome.

Infants with CHARGE syndrome generally have difficulty with feeding and most of those affected have intellectual disability. About half die during the first year of life from respiratory insufficiency, central nervous system (CNS) malformations, and bilateral choanal atresia.

Genetic profile

Up to 90% of individuals with a clinical diagnosis of CHARGE syndrome have a mutation in the *CDH7* gene. Additionally, many individuals suspected of having CHARGE syndrome, but not meeting clinical diagnostic criteria, are also found to carry a *CDH7* mutation. When both individuals with a clinical diagnosis of CHARGE syndrome and those that are highly suspicious for the syndrome are analyzed, mutations in *CHD7* account for about 70% of cases.

CHARGE syndrome, when caused by *CDH7* mutations, is inherited in an autosomal dominant fashion. Most cases of CHARGE syndrome are the first in the family and caused by *de novo* mutations. There are few familial cases known and it is believed most are due to germline mosaicism. If a parent has CHARGE syndrome, the risk for children also having CHARGE syndrome is 50%. However, if neither parent has CHARGE syndrome, the chance of the parents having a second child with CHARGE syndrome is around 1%–2%.

In addition, some patients with CHARGE syndrome also have features of another condition called DiGeorge sequence, which involves an immune deficiency, characteristic heart abnormalities, and distinct craniofacial features. Many patients with DiGeorge sequence have a missing chromosome 22q11. Therefore, newly diagnosed cases of CHARGE syndrome without a confirmatory *CHD7* mutation should have molecular studies to rule out 22q11.2 deletions and other cytogenetic abnormalities.

Demographics

The incidence of CHARGE syndrome is approximately 1 in 10,000. However, this is probably an underestimate of the true number of people affected. The incidence is likely to increase as the diagnostic features of the condition are refined and milder cases are diagnosed. CHARGE syndrome affects males more seriously than females, resulting in a higher number of females who survive. The cause of this difference is unclear. The syndrome has not been reported more often in any particular race or geographic area.

KEY TERMS

Cryptorchidism—A condition in which one or both testes fail to descend normally.

Germline mosaicism—A rare event that occurs when one parent carries an altered gene mutation that affects his or her germline cells (either the egg or sperm cells) but is not found in the somatic (body) cells.

Phenotype—The physical expression of an individual's genes.

Variable expressivity—Differences in the symptoms of a disorder between family members with the same genetic disease.

Signs and symptoms

The majority of individuals with CHARGE syndrome have a mutation in the *CHD7* gene. For individuals with a clinical diagnosis but without an identifiable *CHD7* mutation, the disorder is believed to be caused by a disruption of fetal growth during the first three months of pregnancy. A disruption during this period of pregnancy affects many different organ systems undergoing development. There are no teratogens known to increase the risk for CHARGE syndrome.

Choanal atresia

Choanal atresia, the narrowing of passages from the back of the nose to the throat, may occur on one or both sides (bilateral) of the nose. This condition usually leads to breathing difficulties shortly after birth. Bilateral choanal atresia may result in early death, and surgery is often required to open up the nasal passages. Choanal atresia is also often accompanied by hearing loss. Since bilateral choanal atresia is rare, CHARGE syndrome should be considered in all babies with this finding. Fifty to sixty percent of children diagnosed with CHARGE syndrome have choanal atresia.

Heart abnormalities

Seventy-five to eighty-five percent of children with CHARGE syndrome have heart abnormalities. Many are minor defects, but many require treatment or surgery. Some of the heart problems seen in CHARGE syndrome are very serious (e.g., tetralogy of Fallot) and life-threatening. Every child with a diagnosis of CHARGE syndrome should have an echocardiogram, a test that uses sound waves to produce pictures of the heart.

QUESTIONS TO ASK YOUR DOCTOR

- Where does the name “CHARGE syndrome” come from?
- What are the symptoms associated with CHARGE syndrome?
- What do we know about the way in which CHARGE syndrome is transmitted from generation to generation?
- What is the long-term prognosis for a child diagnosed with CHARGE syndrome?

Coloboma and eye abnormalities

A coloboma is a cleft or failure to close off the eyeball properly. This can result in a keyhole-shaped pupil or abnormalities in the retina of the eye or its optic nerve. The condition is visible during an ophthalmology exam. Colobomas may or may not cause visual changes. About 80% of children with CHARGE syndrome have colobomas, and the effect on vision varies from mild to severe. Other eye abnormalities include microphthalmia (small eye slits) or anophthalmia (no eyes). Consistent eye examinations are recommended for children diagnosed with the syndrome.

Ear abnormalities and deafness

At least 90% of patients with CHARGE syndrome have either external ear anomalies or hearing loss. The most common external ear anomalies include low-set ears, asymmetric ears, small ear lobes, or absent ear lobes. The degree of hearing loss varies from mild to severe. It is important for all patients to have regular hearing exams over time so that changes in sound perception can be detected. Hearing aids are used as soon as hearing loss is detected. Some patients require corrective surgery of the outer ear, so that a hearing aid can be worn. Children with CHARGE syndrome often develop ear infections and this can affect hearing over time as well.

Cranial nerve defects

Defects related to the formation of the cranial nerves during fetal development are common in patients with CHARGE syndrome. The defects include anosmia (inability to smell), facial palsy, hearing loss, and swallowing difficulty. Facial palsy is the inability to sense or control movement of part of the face. This usually occurs on one side of the face, which, in affected individuals, results in a characteristic asymmetric and expressionless look. Swallowing problems

can also occur along with several different defects in the formation of the throat.

Facial features

The facial features of CHARGE syndrome are considered minor diagnostic signs because they are not as obvious as the facial features of other genetic syndromes. However, many patients have facial asymmetry, a small and underdeveloped jaw, a broad forehead, a square face, arched eyebrows, and external ear malformations.

Growth and developmental delays

Most babies with CHARGE syndrome have normal length and weight at birth. Difficulty with feeding and the presence of other malformations often leads to weight loss, so that these babies usually weigh less for their age. Teenagers are also often shorter than average due to a delay in the onset of puberty. In a small number of patients, growth delay is due to a lack of growth hormone.

There are serious delays in motor development of children with CHARGE syndrome as well. Many children have low muscle tone and difficulty with balance that leads to delays in walking. Physical therapy is often helpful. Most children with CHARGE syndrome are identified as having an intellectual disability. However, successful treatment of other features of the condition can improve learning potential. Therefore, assessments made before other medical problems are addressed are often more pessimistic than later exams.

Urogenital abnormalities

Underdevelopment of the genitals occurs in at least half of the male patients diagnosed with CHARGE syndrome and in some females as well. Abnormalities of genitalia in males include an underdeveloped penis (micropenis or microphallus) and testicles that fail to descend to the scrotum (cryptorchidism). In females, there may be overgrowth or underdevelopment of the labia or clitoris. Information concerning the fertility of patients is not available. About 25% of children have renal abnormalities that may lead to repeated infections. A renal ultrasound is indicated in children with the syndrome.

Central nervous system anomalies

In one series of tested patients, CNS anomalies were noted in 83% of the patients who underwent brain imaging tests. These tests are used to produce pictures of the brain such as MRI, CT scan, and ultrasound, or after autopsy. The CNS anomalies included diminution of the size of the brain (cerebral atrophy), asymmetry, and midline defects such as partial development (e.g., agenesis of the corpus callosum). In addition, brain stem dysfunction has also

been observed after birth, a disorder that can cause respiratory and swallowing problems. These findings were associated with a poor prognosis.

Associated anomalies

Many other features have been reported in patients with CHARGE syndrome. Some of these include a cleft lip and/or palate, dental anomalies, absence of the thymus and parathyroid glands that lead to immunodeficiency (the inability of the body to produce a normal immune response), seizures, abnormally low levels of calcium (hypocalcaemia) or sugar (hypoglycemia) in the body, obstruction of the anal opening (imperforate anus), groin hernias, curvature of the spine (scoliosis), skeletal anomalies, body temperature regulation problems, and umbilical hernias.

Diagnosis

The clinical presentation of CHARGE syndrome is extremely variable. A diagnosis is made clinically by fulfilling a combination of major and minor diagnostic criteria. A mutation in the *CHD7* gene is useful in guiding the diagnostic process, as not all patients with *CHD7* mutations meet all criteria required for a clinical diagnosis. Clinical diagnostic criteria for CHARGE syndrome were initially established in 1981 and have undergone several revisions. Major diagnostic characteristics of CHARGE syndrome include choanal atresia or stenosis, ocular coloboma, cranial nerve abnormalities, and the characteristic CHARGE syndrome ear. Minor characteristics include genital hypoplasia, developmental delay, cardiovascular malformation, growth deficiency, orofacial cleft, tracheoesophageal fistula, and distinctive facial features. A clinical diagnosis of CHARGE syndrome is made when an individual has all four major criteria, or three major and one minor criterion. A possible diagnosis of CHARGE syndrome is made when an individual has two major criteria and several minor criteria.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) can be performed when the familial *CHD7* mutation is known. The condition may also be suspected when a prenatal ultrasound reveals fetal growth restriction, CNS malformations, heart defects, and urinary tract malformations. In one series, 37.5% of patients diagnosed with CHARGE were noted to have an abnormal feature detected on ultrasound.

There are several other conditions that include signs similar to CHARGE syndrome. These include VACTERL association (for vertebral, anal, cardiac, tracheoesophageal, renal, and limb abnormalities), velocardiofacial (VCF) syndrome (deletion 22q11 syndrome), and prenatal retinoic acid exposure (Accutane embryopathy).

Treatment and management

Treatment for CHARGE syndrome is specific to the features present in each child. Choanal atresia can be treated with dilatations of the choanae or nasal passages. Heart defects may require surgery. Children with CHARGE syndrome should get ophthalmology and hearing screens every six months. Plastic surgery is sometimes needed for corrections of ear malformations or facial asymmetry. Medications are needed when seizures are present. Growth hormone is sometimes prescribed for growth delay or underdeveloped genitalia.

A developmental evaluation and a plan for special-needs education are required. Patients with CHARGE syndrome who have both hearing and vision difficulty should receive care from childhood educators experienced in dual sensory impairment. Once these children establish a system of mobility and communication, the degree of developmental delay may improve. Lengthy hospital stays for children with CHARGE syndrome may limit the ability of specialists to work with the child in the early months. When the major hospitalizations are completed, development may improve as the result of regular care by the appropriate child specialists. Other learning problems have been noted and should also be addressed if present. These include attention deficit disorder, autism, and obsessive-compulsive disorder. Parents are often in the position of coordinating the many components of special-needs education for their children. The national and international support groups for CHARGE syndrome are able to provide information and assistance in this area.

Prognosis

It has been noted in several studies that about half of patients diagnosed with CHARGE syndrome die from complications of the condition. One study suggests that 40% of those die shortly after birth. Factors that appear to undermine survival include the presence of CNS malformations, bilateral choanal atresia, TE fistula, and male sex. Heart abnormalities and brain stem dysfunctions were not found to be related to poor prognosis. Significant hospitalizations are needed for most children with CHARGE syndrome.

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ORGANIZATIONS

CHARGE Family Support Group, 82 Gwendolen Ave., London, UK E13 0RD, 020-8552-6961, <http://www.chargesyndrome.org.uk/>

CHARGE Syndrome Foundation, 318 Half Day Rd. #305, Buffalo Grove, IL 60089, (516) 684-4720, <http://www.chargesyndrome.org>

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Chediak-Higashi syndrome

Definition

Chediak-Higashi syndrome (CHS) is a very rare, often fatal, genetic disorder that disrupts the function of lysosomes—the recycling organelles within cells—and similar subcellular structures. In particular, CHS affects the function of immune-system cells called phagocytes, blood-clotting cells called platelets, and pigment-producing cells called melanocytes, resulting in a wide range of serious symptoms. CHS also affects nerve cells, resulting in neurologic symptoms. CHS is caused by mutations (changes) in the *LYST* gene that produces the lysosomal trafficking regulator protein. Because of its severe immune-system effects, CHS is considered a primary immunodeficiency disorder.

Description

CHS was first described by Beguez Cesar in 1943, but was named for the scientists Chédiak and Higashi, who elaborated on the disorder in 1952 and 1954 respectively. The disease progresses from a stable phase to an accelerated phase in which infections, a lymphoma-type illness, and/or organ failure are frequently fatal.

CHS particularly affects immune-system cells, especially phagocytes, melanin production, and platelets. Beginning in infancy or early childhood, immunodeficiency from CHS results in susceptibility to repeated and persistent serious or life-threatening viral and bacterial infections. Children with CHS who are not successfully treated usually enter the accelerated phase of the disease, in which immune-system white blood cells divide and proliferate out of control, invading organs throughout the body, and causing a potentially fatal illness similar to lymphoma. CHS also results in abnormal melanosomes. These are subcellular structures in cells called melanocytes that are similar to lysosomes and that produce melanin—the pigment that gives skin, hair, and eyes their color. This often results in a condition called oculocutaneous albinism. Affected individuals usually have light-colored skin and hair, sensitivity to sunlight, and various vision problems that result from a lack of pigment in the iris and retina of the eye. Defective platelets lead to blood-clotting problems, easy bruising, and abnormal bleeding.

Rarely, a milder form of CHS develops in adulthood. Although this form of CHS is less likely to cause severe infections or pigmentation changes, affected individuals are at risk for progressive neurological problems. These include tremor, movement difficulties, imbalance, weakness, loss of sensation in the arms and legs, and cognitive decline.

Genetic profile

CHS is an autosomal recessive disorder. "Autosomal" means that the defective *LYST* gene responsible for CHS is located on a chromosome other than the X or Y sex chromosomes, and is therefore equally likely to affect males and females. "Recessive" means that to be affected by CHS, an individual must inherit two defective copies of the gene, one from each parent. Those parents are carriers who have one mutated copy of the gene, one normal copy, and do not have symptoms of the disorder. However, when both parents carry a defective *LYST* gene, each of their offspring has a 25% risk of inheriting two mutated copies and developing CHS. Each child of a carrier has a 50% risk of inheriting the mutant gene from the parent.

The *LYST* gene, also known as *CHS1* or lysosomal trafficking regulator, is located on the long arm (q) of chromosome 1 (positions 1q42.1–q42.2). *LYST* encodes a protein that helps transport toxic substances, digested pathogens such as bacteria, and worn-out cell components to lysosomes inside cells, where digestive enzymes break them down and recycle the molecules. At least 30 different mutations (changes) in the *LYST* gene can cause CHS by affecting the size, structure, and function of lysosomes and related subcellular compartments. Most of the

KEY TERMS

Autosomal recessive—A pattern of inheritance in which two copies of an abnormal gene must be present in order for the disease or trait to develop.

Carrier—Having one abnormal gene for a trait, such as Chediak-Higashi syndrome, and one normal gene for the trait (a heterozygote), without signs or symptoms of the disorder but with the possibility of passing the abnormal gene on to offspring.

Lymphoma—Cancer of the lymphatic tissue.

Lysosomes—Membrane-enclosed compartments within cells, in which digestive enzymes break down and recycle toxins, infectious organisms, and worn-out cellular components.

LYST—The gene that encodes the lysosomal trafficking regulator protein that is required for normal functioning of lysosomes and similar subcellular compartments.

Melanin—A pigment produced by the body that gives color to the skin, hair, and eyes.

Melanocytes—Cells that produce melanin.

Melanosomes—Subcellular structures, similar to lysosomes, that produce melanin in melanocytes.

Oculocutaneous albinism—An absence of pigment in the skin, hair, and eyes resulting in sun sensitivity and vision problems.

Phagocytes—Immune-system white blood cells that engulf and digest bacteria and other foreign material and debris.

Platelets—Small cell-like bodies in the blood that are involved in clot formation.

mutations that result in severe CHS in childhood produce a short, nonfunctional lysosomal trafficking regulator protein. Mutations that result in the milder adult form of the disorder usually change just one amino acid in the protein, so that the *LYST* protein retains some function.

LYST mutations result in lysosomes that are abnormally large and interfere with cellular functions. For example, immune-system cells with enlarged lysosomes are unable to respond appropriately to disease-causing bacteria. Melanosomes are also abnormally large in CHS, and the melanin becomes trapped in them, making them unable to provide pigment to the skin, hair, and eyes. Abnormal lysosome-like structures in platelets are

believed to be responsible for abnormal blood clotting. Abnormal lysosomes in nerve cells are thought to be responsible for the neurologic symptoms of CHS.

Demographics

CHS is extremely rare—only about 500 cases have been described worldwide. It often affects families that have a history of intermarriage among close relatives, which increases the risk that a child will inherit two defective *LYST* genes. In addition to humans, CHS also occurs in cattle, cats, mice, rats, and foxes.

Signs and symptoms

Symptoms of CHS include:

- silver hair, light-colored eyes, light sensitivity, vision problems, and jerky eye movements caused by melanin deficiency (albinism)
- frequent, often severe and persistent infections of the lungs, skin, and mucous membranes
- fevers
- gum disease
- easy bruising and nosebleeds
- nerve problems, such as numbness, tremor, or seizures
- weakness
- poor coordination

In the accelerated phase, CHS-affected children may have an enlarged liver and spleen (hepatosplenomegaly), low blood platelet counts (thrombocytopenia), low counts of immune-system white blood cells called neutrophils (neutropenia), and low red blood cell counts (anemia). Abnormal cells may infiltrate and suppress the bone marrow, further lowering blood cells counts and causing abnormal bleeding, life-threatening infections, organ failure, and lymphoma-like illness.

Diagnosis

Diagnosis of CHS is based on microscopic examination of blood cells, and possibly bone marrow cells, that reveal giant lysosomal granules within certain white blood cells. Genetic testing can reveal mutations in the *LYST* gene, and can also determine if one or both parents are carriers of *LYST* mutations. Prenatal genetic testing for CHS is available if *LYST* mutations have been identified in family members.

A physical exam may reveal a swollen spleen or liver, or yellowing of the skin or eyes (jaundice) from liver dysfunction. Blood counts, nervous system tests, and imaging of internal organs will be performed.

QUESTIONS TO ASK YOUR DOCTOR

- How did my child inherit Chediak-Higashi syndrome?
- Can my partner and I have genetic counseling and/or testing for the gene that causes Chediak-Higashi syndrome?
- What is the risk that we will have another child with Chediak-Higashi syndrome?
- Will my child with Chediak-Higashi syndrome be able to have a bone marrow transplant?
- What is the prognosis for a child who has been diagnosed with Chediak-Higashi syndrome?

Treatment and management

Other than antibiotics and antiviral medications for preventing and treating infections, the only treatment for CHS is a bone marrow transplant, which can cure the immunodeficiency. The earlier the bone marrow transplant is performed, the better the outcome. Once the disease enters the accelerated phase, however, it is very difficult to treat. Surgery may be required to drain abscesses. The lymphoma-like illness may be treated with steroids and anticancer drugs, but is usually fatal within months.

Prognosis

In the past, most children with CHS died within the first decade of life, although there have been reports of people surviving into their 30s. About 80% of children with CHS eventually enter the accelerated phase. Death usually results from chronic infections or lymphoma-like illness in the accelerated phase. However, bone marrow transplants have now enabled a majority of children with CHS to survive and thrive for at least 13 years following treatment.

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ORGANIZATIONS

Eunice Kennedy Shriver National Institute of Child Health and Human Development, NICHD Information Resource Center, PO Box 3006, Rockville, MD 20847, (800) 370-2943, (866) 760-5947, NICHDInformationResourceCenter@mail.nih.gov, <http://www.nichd.nih.gov>

Immune Deficiency Foundation, 110 West Rd., Suite 300, Towson, MD 21204, (800) 296-4433, (410) 321-9165, <https://primaryimmune.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Orphanet/INSERM US14 Rare Disease Platform, 96, rue Didot, Paris, France 75014, +33(0)156.53.81.37, +33(0) 156.53.81.38, contact.orphanet@inserm.fr, <http://www.orpha.net>

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Chiari malformation see **Arnold-Chiari malformation**

Chondrodysplasia punctata

Definition

Chondrodysplasia punctata is a group of inherited disorders affecting the skeletal system, skin, eyes, and mental functioning.

Description

Chondrodysplasia punctata is characterized by shortened bones; punctated or dot-like calcification deposits in the cartilage; and abnormal peroxisomes. Peroxisomes

are structures within cells that help remove toxins from the body.

There are three main variations of chondrodysplasia punctata: rhizomelic chondrodysplasia punctata, non-rhizomelic chondrodysplasia punctata, and Sheffield type. Within these variations, there are different syndromes characterized by distinct anomalies and modes of transmission.

Rhizomelic chondrodysplasia punctata is characterized by shortened long bones in the arms and legs, abnormalities of the spine, stippled or dotted appearance to the cartilage, scaling of the skin, cataracts, and profound intellectual disability. This type of chondrodysplasia punctata is caused by a single-gene mutation. Most fetuses with rhizomelic chondrodysplasia punctata die *in utero* or shortly after birth. Those that survive usually die within the first ten years of life.

Non-rhizomelic chondrodysplasia punctata, sometimes called Conradi-Hünemann disease, encompasses several distinct syndromes with unique characteristics and modes of transmission. Happle's chondrodysplasia is one type of non-rhizomelic chondrodysplasia characterized by asymmetry of the arms and legs, distinctive skin sores or scales, and cataract often affecting only one eye. Intelligence is usually normal. This type predominantly affects women and is usually lethal in males, generally resulting in miscarriage of male fetuses.

Another type of non-rhizomelic chondrodysplasia is brachytelephalangic chondrodysplasia punctata, which is characterized by severe facial abnormalities, abnormalities of the cartilage in the trachea and larynx, calcifications in the feet and legs, and hypoplastic, or small little fingers and little toes. The abnormal facial features of this syndrome are called Binder's maxillonasal dysostosis and include abnormalities of the upper jaw, flat nose, cleft palate, smooth or absent philtrum, and small teeth. These facial malformations and anomalies of the trachea and larynx can cause serious breathing difficulties for newborns. Infants with brachytelephalangic chondrodysplasia punctata often require respiratory therapy. This syndrome primarily affects boys and may cause intellectual disability.

The Sheffield type of chondrodysplasia punctata is a mild form of the disorder affecting males and females equally. It is characterized by the abnormal dotted cartilage formations, flattened facial features, and intellectual disability. This is considered a milder form of the disorder. The inheritance has not been determined, and the genetic mutation responsible has not been identified.

Genetic profile

The genetic cause of rhizomelic chondrodysplasia punctata is well documented. Many of the anomalies result from abnormalities of the perisomes and the

resulting inability of the body to process and remove toxic enzymes and proteins. Perisomes are structures found within cells that remove toxins from cells and therefore from the body. Researchers have identified a genetic mutation of the peroxisome biogenesis factor 7 (*PEX7*) as causing these perisomal abnormalities. This mutation is transmitted as an autosomal recessive trait. Autosomal recessive conditions are carried on a chromosome that is not involved in determining sex and must be present in both parents to be transmitted to a child. In the case of rhizomelic chondrodysplasia, the *PEX7* gene is found on chromosome 4 in the 4p16 locus.

Non-rhizomelic chondrodysplasia is an X-linked disorder, which means the mutations responsible for causing it are located on the X chromosome. There are two types of X-linked transmission: dominant and recessive. In X-linked dominant traits, the condition will manifest if only one copy of the genetic mutation is present. Many X-linked dominant conditions are milder in females than in males, because genetic material on the second X chromosome can reduce the effects of the mutation. X-linked dominant mutations can have severe effects in females and may be lethal in males. Happle's chondrodysplasia is an X-linked dominant condition resulting from mutations in the emopamil binding protein (*EBP*) gene.

In X-linked recessive traits, the genetic mutation is recessive, meaning the characteristics of the mutation will be seen only when another normal copy of the gene is not present. For this reason, X-linked recessive mutations most frequently affect males. Females must have two mutated copies of the same gene to demonstrate the abnormalities the mutation causes. It is rare for females to be affected by X-linked recessive genetic mutations, but they may be carriers, passing the gene on to their offspring. Brachytelephalangic chondrodysplasia punctata is an X-linked recessive condition caused by a mutation of the arylsulfatase E (*ARSE*) gene and a deletion of the short arm of the X chromosome.

Demographics

Chondrodysplasia punctata is a very rare condition. It affects fewer than 1 in every 100,000 individuals.

The rhizomelic type of chondrodysplasia punctata is an autosomal recessive condition affecting males and females equally. In the non-rhizomelic types of the disorder, Happle's chondrodysplasia punctata affects females almost exclusively and is generally lethal to males. Brachytelephalangic chondrodysplasia punctata is seen more frequently in males; however, it may be seen in females. The milder form of the disorder, Sheffield type, affects females and males equally.

KEY TERMS

Asymmetry—Lack of similar size, length, and shape on both sides of the body.

Autosomal—Describes a genetic trait found on a chromosome that is not involved in determining sex.

Calcification—The process by which tissue becomes hardened by the deposition of calcium.

Cataract—Clouding of the lens in the eye.

Cleft palate—An abnormal opening or cleft between roof of the mouth and the nasal cavity.

Dermatologic—Pertaining to the field of dermatology, the science of the skin and diseases that affect the skin.

Dominant—Describes a genetic trait that is expressed when only one copy of the gene is present.

Hypoplastic—Small.

Ichthyosis—A skin condition characterized by a fish-scale appearance.

In vitro fertilization (IVF)—Sometimes referred to as producing a “test tube baby,” IVF is the fertilization of a human egg outside the body.

Larynx—The voice box.

Microcephaly—A birth defect in which the brain and head are too small.

Mutation—A permanent change in genetic material that is transmittable.

Orthopedic—Pertaining to the field of orthopedics, the science of the bones and diseases of the bones.

Peroxisomes—Structures within the cell that remove toxins from the cell.

Philtrum—The grooved space between the nose and the upper lip.

Prenatal ultrasound—An imaging test using high-frequency sound waves to create images of internal organs. “Prenatal” indicates the test is performed on a fetus while still in the womb.

Prevalence—The number of individuals in a population that have a specific condition.

Punctated—Having a dotted pattern.

Recessive—A genetic trait that is only expressed when another identical recessive gene is present.

Trachea—The windpipe.

Vertebrae—Bony structures of the spine.

X-linked—A genetic trait that is carried on the X chromosome.

X-ray—An imaging test that uses beams of energy to create images of structures within the body.

Signs and symptoms

The symptoms of chondrodysplasia punctata may involve the skeletal system, cartilage, face, eyes, and intellectual functioning. The specific signs and symptoms of this disorder depend on which type is present.

The symptoms of rhizomelic chondrodysplasia punctata can include:

- abnormal hair loss
- cataracts
- cartilage abnormalities
- curvature of the spine
- facial abnormalities
- ichthyosis (scaly skin)
- intellectual disability
- microcephaly
- short stature or dwarfism

The symptoms of non-rhizomelic chondrodysplasia punctata can include:

- abnormalities of the eye

- abnormalities of the cartilage in the larynx and trachea
- asymmetry of the body
- cartilage abnormalities
- dwarfism
- hearing impairment
- heart defects
- intellectual disability
- mid-face abnormalities
- kidney malformations
- prematurity
- punctate vertebrae (dotted appearance in x-rays)
- short and in-curving fingers
- shortened limbs

Diagnosis

For parents who know that they are carriers of the X-linked type of chondrodysplasia punctata, there is a prenatal procedure and test called preimplantation genetic diagnosis (PGD). After in vitro fertilization (IVF), PGD

can test for genetic abnormalities as well as sex before an embryo is implanted.

Prenatal ultrasound may be helpful in diagnosing chondrodysplasia punctata in the fetus. A second trimester ultrasound may detect the characteristic punctated calcifications of the spine and feet. Combined with evidence of shortened limbs, a diagnosis may be made. However, in milder cases of the disorder, the defects may be too subtle for detection by a routine prenatal ultrasound.

A physical examination may diagnose the external features of this disorder, including the facial abnormalities, shortened limbs, curvature of the spine, and ichthyosis.

A definitive diagnosis may be made by x-ray of the limbs and spine. In children one year or younger, punctated calcifications may be seen in the long bones and the feet in the areas of cartilage at the ends of growing bones. This cartilage disappears after the first year of age and is replaced with growth plates. These plates appear normal on x-ray. In adults and older children, the diagnosis is based on shortened bones in the arms and legs, and the presence of other physical characteristics of the disorder.

Treatment and management

The treatment and management of chondrodysplasia punctata is primarily orthopedic and dermatologic. The characteristic stippling or dotted cartilage will disappear as the child ages; however, shortened arms and legs and curvature of the spine require orthopedic treatment. In some cases, surgery may be necessary to help patients whose legs are different lengths.

In some individuals, bone growth may be induced by a surgical bone-lengthening procedure. This procedure involves several surgeries and an extensive recovery period. The bone to be lengthened is cut. Leaving a narrow gap between the two pieces of bone, metal pins are inserted into the bone, and the skin is closed. An external frame is attached to the pins. Gradually, the bone is pulled apart just enough to provide a small gap for the bone to grow into. As the bone grows, the space is widened, and more bone grows. After the bone has healed, the pins are surgically removed.

Spinal abnormalities, such as spinal cord compression and scoliosis, may be treated surgically. A spinal column fusion can relieve the stress on the spinal cord caused by malformations of the spinal column. In a spinal fusion, two or more vertebrae are fused together using bone grafts or metal rods.

Ichthyosis is often most severe at birth and can resolve completely as the child ages. However, in some individuals, the skin lesions may be extensive and long

lasting, leading to recurrent skin infections. Management of ichthyosis involves topical treatment and, in severe cases, bandaging to help prevent infection.

Prognosis

Prognosis of chondrodysplasia punctata depends on the type. The rhizomelic form of this disorder has a very poor prognosis. Most individuals with this type of chondrodysplasia punctata do not survive the fetal period or die shortly after birth. Of those that do survive, life expectancy is ten years or less. Along with the skeletal anomalies, profound intellectual disability is common as well.

The non-rhizomelic type, also known as Conradi-Hünemann disease, can have a better prognosis. Though the condition is extremely rare, a range of outcomes has been reported from death to mildly affected adults. The X-linked dominant type, or Happel's type, is usually lethal to males, and they generally do not survive past the second trimester of pregnancy. However, females with this type usually survive and may have normal intelligence.

The X-linked recessive type called brachytelephalangic chondrodysplasia punctata can have a range of possible prognoses. Because a component of this type is a flat mid-face, small nose, and cartilage abnormalities of the larynx and trachea, these children may have breathing difficulties and may die shortly after birth. If these anomalies are not present or are mild, the prognosis is much better. Individuals with this type of the disorder usually have normal intelligence.

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ORGANIZATIONS

- Human Growth Foundation, 997 Glen Cove Ave., Suite 5, Glen Head, NY 11545, (800) 451-6434, hgf1@hgfound.org, <http://www.hgfound.org>
- Little People of America, 617 Broadway #518, Sonoma, CA 95476, (888) LPA-2001, <http://www.lpaonline.org/index.html>
- March of Dimes, 1550 Crystal Drive, Suite 1300, Arlington, VA 22202, (888) 663-4637, <http://www.marchofdimes.org>

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Chondroectodermal dysplasia see **Ellis-Van Creveld syndrome**

Chondrosarcoma

Definition

Chondrosarcoma is a malignant tumor that produces a special type of connective tissue called cartilage. Malignant tumors have cells that have the ability to invade and are characterized by uncontrolled growth.

Description

Cartilage is a type of connective tissue that acts as a resistant surface. Cells called chondrocytes produce cartilage. Chondrosarcoma is a malignant growth arising in chondrocytes. There are two types of chondrosarcomas, either primary or secondary. Primary chondrosarcomas arise in areas of previously normal bone that are derived from cartilage. Secondary chondrosarcomas are lesions produced from pre-existing cartilage lesions. The chondrosarcoma tumors either produce enlargement or erosion of the area involved. The lesion is classified further as to where the lesion occurs and the grade of the lesion. It is graded from 1 (low-grade) to 3 (high-grade). This classification states that the higher the grade of the tumor, the higher the increased atypia, or abnormal cell growth.

Two noncancerous diseases, Maffucci syndrome and Ollier disease, are similar to chondrosarcoma. Ollier disease, also known as enchondromatosis or dyschondroplasia, is a disorder affecting the growth plates of bone where new bone is deposited. The cartilage laid down is not reabsorbed, and masses form near the ends of the long

KEY TERMS

Atypia—A term for a structural abnormality in a cell.

Cartilage—Supportive connective tissue that cushions bone at the joints or connects muscle to bone.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Curettage—A surgical scraping or cleaning.

Enchondromas—Benign cartilaginous tumors arising in the cavity of bone. They have the possibility of causing lytic destruction within the bone.

Excision—Surgical removal.

Lysis—Area of destruction.

Maffucci syndrome—A manifestation of Ollier disease (multiple enchondromatosis) with hemangiomas, which present as soft tissue masses.

Myxoid—Resembling mucus.

Ollier disease—Also termed multiple enchondromatosis. Excessive cartilage growth within the bone extremities that results in benign cartilaginous tumors arising in the bone cavity.

Radiolucent—Transparent to x-ray or radiation. The black area on x-ray film.

Urinary urgency—An exaggerated or increased sense of needing to urinate.

bones such as the thigh bone (femur) and upper arm bone (humerus). Maffucci syndrome has the same abnormalities as Ollier disease as well as soft tissue destruction including the skin. Patients with Maffucci or Ollier disease should have bone scans every three to five years to monitor potential malignant transformations.

Genetic profile

Anomalies of chromosomes 5, 7, 8, and 18 and structural alterations of chromosomes 1, 12, and 15 are commonly found in patients diagnosed with chondrosarcoma. Interestingly, the gene for the area of normal cartilage production, type II collagen, has been found in the same regions as chondrosarcoma. Studies of the tumor suppressor gene, *EXT1*, have shown that changes (mutations) of this gene may also be important in the growth of chondrosarcoma.

Demographics

As of 2021, an estimated 3,610 new cases of bone and joint cancer will be diagnosed per year in the United States.

Primary cancer of bones accounts for less than 0.2% of all cancers. Chondrosarcoma is the second most common primary malignant bone tumor, meaning it did not originate at another site in the body. Osteosarcoma is the most common.

There are conflicting reports as to how much more frequently men are diagnosed with chondrosarcoma than females. Findings range from twice as many males to only slightly more males than females. Chondrosarcoma occurs in people from the age of 30–70 years old, but it most commonly affects people over the age of 40. No ethnic group is affected more frequently than another.

Signs and symptoms

The signs and symptoms vary due to the type of tumor, but pain is typically the first symptom. If it is a fast-growing, high-grade form of chondrosarcoma, then the individual may have very severe pain. A low-grade slow-growing tumor usually produces pain and swelling in the area of the tumor. If the tumor is located in the pelvis or hip area, the individual may have difficulty with urination or urinary urgency. The patient may also have the sensation of a groin pull if the tumor is in the pelvic area.

Diagnosis

Usually, chondrosarcoma is diagnosed with x-ray radiography. X-rays can show soft tissue calcification, where the muscles appear to be forming bone. The appearance of a soft tissue mass that has not yet calcified may also be visible. If the chondrosarcoma is secondary to another type of tumor, the chondrosarcoma may start to erode the edges of the other tumor. This is common when an enchondroma, a type of tumor within the bone shaft, is present. In this case, the chondrosarcoma produces areas of lysis, or destruction of the surrounding tissue.

Biopsy is used to determine the grade of the tumor. Grade 1 chondrosarcomas, or low-grade, slow-growing lesions, have a mild increase of new cell growth. Grade 3 chondrosarcomas are the opposite; they are high-grade and fast-growing, and have a dramatic increase in cellular growth. The more radiolucent or transparent to x-rays the tumor appears, the greater the chance it is a higher grade.

Other imaging tests may also be used. Computed tomography scanning, CT, is an advanced form of x-ray that can also produce bone pictures and help determine how much calcification the tumor is producing. Magnetic resonance imaging, MRI, will aid diagnosis since it can differentiate soft tissues such as muscle and fat. MRI will help determine the amount of malignant degeneration of the chondrosarcoma.

QUESTIONS TO ASK YOUR DOCTOR

- To what stage has my chondrosarcoma progressed?
- What treatments do you recommend for the disease at this point in my life?
- Given my current health status, what prognosis can you make for my recovery from this disorder?
- Are there clinical trials currently underway for treatment of this disease?

Treatment and management

The main course of therapy for chondrosarcoma is surgical removal of the tumor. The amount of surgery depends on the location and the stage of the tumor. Very low-grade tumors may be surgically removed. High-grade chondrosarcomas necessitate more radical operations in which normal tissue is also removed due to the possibility of spread. If the tumor is located in an extremity such as an arm or leg, then amputation, or surgical removal of the extremity, may be necessary in order to prevent metastasis, or spread of the cancer. Chemotherapy and radiotherapy may also be used depending on the type of tumor and the area of the body affected, but are usually not effective.

Prognosis

The higher the grade of a chondrosarcoma, the more likely the tumor will spread and thus worsen the prognosis. One study found the five-year survival rate of patients with grades 1, 2, and 3 to be 90%, 83%, and 43% respectively. This means that five years after the diagnosis of the tumor, 90 out of 100 people with grade 1 were still alive. On the opposite spectrum, 43 out of 100 patients with grade 3 chondrosarcoma survived five years. Therefore the survival rate is very much dependent on the stage of the tumor and also on its location. Size of the tumor is also an important factor. Tumors greater than 4 in. (10 cm) are more likely to become aggressive and spread. When they do spread, or metastasize, they often migrate to the lungs and skeleton.

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 Cancernet. National Cancer Institute, National Institutes of Health, NCI Public Inquiries Office, Building 31, Room 10A03, 31 Center Dr., MSC 2580, Bethesda, MD 20892-2580,

Jason S. Schliesser, DC

CHOPS syndrome

Definition

First identified in 2015, CHOPS syndrome is a very rare genetic disorder caused by a mutation in the *AFF4* gene. It is characterized by intellectual impairment, facial abnormalities, heart defects, obesity, pulmonary disorders, and skeletal dysplasia (abnormal development).

Description

On March 2, 2015, geneticists at Children's Hospital of Philadelphia announced the discovery of a unique genetic syndrome involving multiple congenital anomalies. The syndrome was named using the acronym CHOPS to describe its clinical characteristics: C—cognitive impairment and coarse facies (abnormal facial features), H—heart defects, O—obesity, P—pulmonary involvement, and S—short stature and skeletal dysplasia.

Genetic profile

CHOPS syndrome is extremely rare. It is caused by a mutation in the protein-coding portion of the *AFF4* gene.

Mutations in the *AFF4* gene interrupt the work of an important group of proteins called the super elongation complex (SEC). The SEC is an extremely important regulator in the process of transcription. In order for the genetic code within the DNA to be activated, it must first be transcribed or copied to RNA. During the process of transcription, DNA is copied to a type of RNA called messenger RNA (mRNA). The mRNA then goes through a process called translation in which it creates the proteins necessary to pass on the coded information from the DNA.

In humans, DNA is found almost exclusively within the nucleus of a cell. In order to express the traits contained in the DNA, the coded information must pass outside the cell's nucleus. RNA makes this possible because it can travel outside a cell's nucleus. Once the genetic material is copied to mRNA, it moves outside the nucleus of the cell, and it uses the copied information to produce proteins. mRNA passes on all information necessary for every part of an embryo to develop. It instructs cells to differentiate or become different cell types such as muscle, skin, or bone.

The SEC acts as the director of this process, signaling the mRNA when it is time to produce specific proteins. At each stage of fetal development, the SEC activates the mRNA. During the development of an embryo, this process is very sensitive and must be timed precisely in order for an embryo to develop into a fully formed typical fetus. If anything interrupts or delays this process at any point, it may disrupt normal fetal development.

When the SEC within the *AFF4* gene becomes abnormal through mutation, it causes abnormal proteins to be produced in every cell of the embryo. These abnormal proteins accumulate throughout the developing embryo, causing a cascade of abnormalities in other genes that are controlled by the *AFF4* gene.

This mutation is a random, or *de novo*, mutation. It is a germline mutation, meaning that it occurs in one of the individual egg or sperm cells that join to create the affected child. The mutation that causes CHOPS syndrome is a new mutation, not present in either parent but found in a single egg or sperm. Because of this, it is unlikely that subsequent children born to these parents will have the same mutation or develop CHOPS syndrome.

Demographics

In 2015, when CHOPS syndrome was first identified, there were three known cases. Researchers expected that more individuals with this syndrome would be identified as information about CHOPS syndrome became more widely known. A fourth case was reported in Korea in November 2020.

Signs and symptoms

The signs and symptoms of CHOPS syndrome include cognitive impairment, facial abnormalities, heart defects, obesity, pulmonary disorders, skeletal dysplasia, and short stature. These symptoms are similar to the features of Cornelia de Lange syndrome, a genetic disorder characterized by slow growth, intellectual disability, autistic-like behaviors, skeletal abnormalities of the arms and hands, unique facial features, heart defects, and short stature. However, the disorders are not identical. Differences between children with Cornelia de Lange syndrome and those diagnosed with CHOPS syndrome led researchers to investigate their genetic profiles. Over the course of ten years, researchers were able to identify three children with the previously unnamed disorder.

Cornelia de Lange syndrome is caused by a mutation in three genes. The children with CHOPS syndrome did not have any of these mutations. After years of investigating, scientists discovered the *AFF4* mutation. This groundbreaking discovery is the first example of a human developmental disorder caused by a mutation in the SEC.

Diagnosis

Diagnosis is made by clinical observation and identification of the features of CHOPS, which include developmental and intellectual delays, facial abnormalities, heart defects, obesity, pulmonary disorders, and skeletal dysplasia. In the presence of these clinical features, gene sequencing may be performed to determine whether there is a mutation in the *AFF4* gene.

In gene sequencing, a sample of blood or tissue is used to analyze the sequence or order of DNA in a person and to identify any specific abnormalities. In order to diagnose CHOPS syndrome, researchers studied the exomes, or regions in a gene that produce proteins. By studying these areas, they were able to identify the mutations responsible for CHOPS syndrome.

Treatment and management

CHOPS syndrome is a genetic disorder, and as of 2021, there was no cure. Management of the features, or symptoms, of the disorder is standard care.

Treatment of cognitive impairment and intellectual disability begins in early childhood and continues throughout adolescence and early adulthood. Early intervention educational programs may be especially helpful. Ongoing educational services and treatment involve a multidisciplinary team of professionals such as special educators, speech and language therapists, behavioral therapists, occupational therapists, and healthcare providers.

KEY TERMS

Congenital—A disorder or condition present at birth.

DNA (deoxyribonucleic acid)—A molecule within each cell that carries the genetic code for that organism.

Dysplasia—Abnormal development producing atypical shape or size.

Exome—The portion of a gene responsible for coding the instructions for protein production in the cell.

Gene sequencing—The process of mapping the order of DNA or genetic material in a cell or group of cells.

Germline mutation—A mutation or change in the DNA of a cell that will become either an egg or sperm.

Orthotics—A field of science that deals with the use of external mechanical devices to support or assist weak or abnormal joints, limbs, or muscles.

RNA (ribonucleic acid)—A molecule that assists in protein synthesis and gene expression.

Transcription—The process of making an RNA copy of genetic material.

Translation—The process of converting the sequence of messenger RNA into a series of amino acids in order to implement the genetic code of an organism.

Treatment of the medical conditions characteristic of CHOPS syndrome requires ongoing care from a team of healthcare providers. Complications from the associated heart defects and pulmonary disorders may lead to frequent hospitalizations.

The treatment of skeletal dysplasia and short stature is supportive. Medical care for these conditions involves preventing orthopedic and neurologic complications. Depending on the extent of the skeletal dysplasia, orthotics, assistive devices, and surgery may be necessary to improve mobility and decrease discomfort.

Because obesity can contribute to complications in individuals with skeletal dysplasia, it is important to address the accompanying obesity of CHOPS syndrome. Registered dietitians and physical therapists may help ensure that those with CHOPS syndrome have the proper nutrition and exercise they need to help reduce the impact of increased body weight.

QUESTIONS TO ASK YOUR DOCTOR

- What additional medical tests does a person with CHOPS syndrome need?
- What are the long-term effects of CHOPS syndrome?
- What special care does a person with CHOPS syndrome require?
- What other healthcare professionals should be consulted?
- Are there organizations or support groups to talk to other people whose children have this condition?
- Is there any information to take home?

Prognosis

Since there are so few known cases of CHOPS syndrome, the prognosis is not yet well determined. Each characteristic of CHOPS syndrome has a varying degree of risk associated with it; when combined, these risks may contribute to a shortened lifespan.

The prognosis for those with intellectual disability or cognitive impairment varies depending on the severity of the delays experienced by the individual. With successful early intervention and educational services, those with this condition alone may live long and productive lives.

Individuals with heart defects will require ongoing medical care and monitoring, and their prognosis will depend on the severity of the specific cardiac anomaly they have. However, early diagnosis of heart anomalies tends to lead to more effective treatment and a more positive prognosis.

The prognosis of those with the associated pulmonary disorders of CHOPS syndrome depends on the severity of the pulmonary conditions affecting the individual. Pulmonary disease can lead to frequent illness and hospitalizations, and it may shorten lifespan.

The prognosis of those with skeletal dysplasia depends on the severity of the skeletal abnormalities. Many people with skeletal dysplasia go on to live a normal lifespan. The associated obesity of CHOPS syndrome may negatively impact the health and comfort of individuals with more significant skeletal disorders.

As more children with CHOPS syndrome are identified, the long-term prognosis for this unique combination

of conditions and symptoms will be better understood and will become more predictable.

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- Genetic Disease Foundation, Mount Sinai School of Medicine, One Gustavo L. Levy Place, Box 1497, New York, NY 10029, <http://www.geneticdiseasefoundation.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>
- Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

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Chorionic villus sampling

Definition

Chorionic villus sampling (CVS) is a diagnostic test for genetic disorders in a fetus. It is performed between 10 and 12 weeks of gestation and involves sampling cells of the placental chorionic villi.

Purpose

CVS is a procedure that is commonly performed on pregnant women who are considered to be at risk for

having a baby with a genetic disorder. In particular, CVS may be offered to women aged 35 and older who are considered to be at greater risk for certain fetal genetic abnormalities, especially Down syndrome (trisomy 21)—an extra entire or partial chromosome 21. Down syndrome is by far the most common chromosomal abnormality. It occurs in approximately 1 in 700 births in the United States and causes physical and intellectual disabilities ranging from mild to severe. The risk of Down syndrome and certain other chromosomal abnormalities increases dramatically with increasing maternal age. Other candidates for CVS include the following:

- Women who have had a previous child or pregnancy affected by a birth defect
- Women who have had abnormal results on a maternal blood screening test for fetal abnormalities
- Women or women who have partners who have a genetic disorder or a family history of a genetic disorder, such as cystic fibrosis or sickle-cell disease
- Women or women who have partners who belong to an ethnic group with a high risk for certain genetic disorders

As of 2021, CVS could test for more than 200 genetic disorders. In addition to chromosome abnormalities, CVS can detect mutations (changes) in specific genes. In addition to Down syndrome, CVS is commonly used to test for inherited hemoglobinopathies, such as sickle-cell disease and Tay-Sachs disease, a serious genetic disorder of lipid (fat) metabolism that typically affects people of Eastern European Jewish ancestry. CVS also reveals whether the fetus is male (one X chromosome and one Y chromosome) or female (two X chromosomes). In addition to chromosome and DNA analyses for genetic defects, CVS may be able to detect the presence of bacteria and the concentration of metabolites.

Many pregnant women have diagnostic testing by amniocentesis, a procedure that withdraws from the womb a small amount of amniotic fluid containing fetal cells. The primary advantage of CVS over amniocentesis is that CVS is performed early in pregnancy—between 10 and 12 weeks (first trimester)—whereas amniocentesis is not performed until about 16 weeks of gestation (second trimester). This means that, in the unlikely case that an abnormality is discovered, the parents have more time to make decisions about whether to terminate the pregnancy, plan for caring for a child with a genetic disorder, or, in some cases, undergo fetal surgery or other treatment to alleviate the disorder.

Precautions

CVS is not offered to all pregnant women because it is an invasive procedure and there is a very small risk of miscarriage. Furthermore, the procedure itself—as well



A doctor holds an ultrasound emitter on a woman's pregnant abdomen while drawing a chorionic villus sample into a syringe. (Saturn Stills/Science Source)

as waiting for the results—can be stressful for some women, and CVS is more expensive than standard screening tests or amniocentesis. Therefore, CVS is only offered to women who are at increased risk of giving birth to a child with genetic abnormalities because of maternal age or other risk factors. Furthermore, CVS is not appropriate for all at-risk pregnant women. For example, many couples would not consider terminating a pregnancy even in the presence of serious or life-threatening fetal defects; others prefer not to know in advance that their child may have a genetic disorder.

CVS testing is not 100% accurate. For Down syndrome, the false-positive error rate is about 1% and the false-negative error rate is about 2%. In addition, CVS cannot test for all fetal abnormalities. For example, it does not detect neural tube defects (abnormalities in the formation of the brain and/or spinal column, such as spina bifida). Neural tube defects are detected by the presence of excess amounts of a protein called alpha-fetoprotein (AFP) in maternal blood serum or in amniotic fluid obtained via amniocentesis. CVS cannot detect Rh incompatibility, in which a mother who is negative for the Rh blood type may produce antibodies that attack an Rh-positive fetus, nor can CVS detect birth defects that occur during fetal development that are not due to genetic abnormalities or are caused by genetic abnormalities that cannot be—or were not—tested for.

As of 2021, new noninvasive and highly accurate screening tests were becoming available for conditions

such as Down syndrome. These tests can spare women invasive procedures such as CVS. They examine cell-free fetal DNA present in the mother's blood. At about ten weeks of gestation, approximately 10%–20% of the cell-free DNA in the mother's blood is fetal DNA from the placenta. These screening tests are performed late in the first trimester, but they can be performed as early as nine weeks. They are much more accurate and have far fewer false positives than the standard blood screening tests.

Ultrasound and the noninvasive screening tests that were typically offered to all pregnant women in 2015 are significantly less accurate than these newer tests, missing about 8% of Down syndrome cases, as well as yielding false-positive results that require women to subsequently undergo CVS or amniocentesis. The new tests are extremely accurate for Down syndrome, missing few if any affected fetuses and with false-positive results of less than 1%. The tests can also detect other genetic abnormalities, such as extra copies (trisomy) of chromosomes 13 and 18 or the absence of an X or Y sex chromosome. One new test is much better at predicting trisomy 18 than standard screening tests.

As of 2021, none of the new noninvasive tests had been approved by the U.S. Food and Drug Administration (FDA), and most had not yet undergone rigorous evaluation for effectiveness in clinical trials. Furthermore, the tests are quite expensive and not generally covered by insurance for women at low risk. Nevertheless, they may be recommended for women at high risk of having a baby with a chromosomal abnormality. These newer fetal DNA tests do miss some chromosomal abnormalities that can be detected with standard screening. They are also valid only for single-fetus pregnancies and are not diagnostic, so positive results for a chromosome abnormality still necessitates CVS or amniocentesis. However, studies of one new fetal DNA test suggest that it would reduce the number of women referred for CVS or amniocentesis by 90%. The American College of Obstetricians and Gynecologists and other professional societies have recommended these new-generation tests for women at higher risk for having a child with Down syndrome or another trisomy, but had not endorsed the tests for women at low risk.

Description

The chorion is the outermost fetal membrane that helps form the placenta, the organ formed by fetal and maternal tissues that provides nutrients and oxygen to the developing fetus and removes fetal waste products. The chorionic villi are finger-like folds in the chorion that contain capillaries where the fetal blood supply contacts

KEY TERMS

Amniocentesis—Prenatal testing performed at 16–20 weeks gestation by inserting a needle through the mother's abdomen and obtaining a small sample of amniotic fluid containing fetal cells for biochemical and/or DNA testing; an alternative to chorionic villus sampling.

Chorionic villi (singular, villus)—Finger-like folds in the early fetal membrane that partially forms the placenta; a source of fetal cells for genetic testing.

Cystic fibrosis—An inherited genetic disorder that affects many body systems, especially the lungs and digestive system.

Down syndrome—Trisomy 21, a genetic disorder caused by all or part of an extra chromosome 21; characterized by intellectual disability, characteristic facial features, and various other developmental defects.

Placenta—The organ that develops in the uterus during pregnancy and connects the mother's blood supply with that of the fetus.

Rh factor—Rhesus factor, a protein on the surfaces of red blood cells of many people; if the fetus is Rh-positive but the mother is Rh-negative, the mother must be treated with immune globulin to prevent the production of antibodies that will cross the placenta and attack the fetal blood cells.

Sickle-cell disease—An inherited disorder in which red blood cells contain an abnormal form of hemoglobin (the protein that carries oxygen), causing the cells to become sickle-shaped. The misshapen cells can clog blood vessels, preventing oxygen from reaching tissues.

Transabdominal CVS—Chorionic villus sampling performed using a needle inserted through the abdomen.

Transcervical CVS—Chorionic villus sampling performed using a catheter inserted through the vagina and cervix.

the maternal blood supply for the exchange of oxygen, nutrients, and waste. CVS removes a tiny amount of tissue from a chorionic villus. The tissue sample will contain fetal cells for testing. After about 12 weeks of gestation, the chorionic villi have formed the placenta, and CVS can no longer be performed. CVS was developed in the early 1980s and quickly became a widely performed procedure.

CVS is usually performed by a trained and experienced obstetrician or obstetrical surgeon. The doctor will be assisted by a nurse. A trained genetic counselor will be involved both before and after the procedure.

There are two types of CVS. Transabdominal CVS is performed by inserting a thin needle through the mother's abdomen into the uterus and chorionic villi. A small tissue sample is removed, and the needle is withdrawn. This procedure is very similar to amniocentesis. Transcervical CVS is performed by widening the vagina with a speculum and inserting a thin plastic tube (a catheter) through the mother's vagina and cervix (the opening to the uterus at the upper end of the vagina) to reach the chorionic villi. A tiny sample of tissue is then gently sucked through the tube, and the tube is removed from the uterus and vagina. Transabdominal or transcervical CVS is chosen according to the position of the fetus in the uterus.

The healthcare provider may also apply pressure to the mother's abdomen to determine the position of her uterus. With both types of CVS, ultrasound is used to guide the needle or tube to an appropriate area, and for removal of the tissue without harming the fetus. Ultrasound bounces harmless sound waves off fetal structures through a handheld device called a transducer, and the images formed are projected on a screen. A clear water-based gel is applied to the skin to facilitate the transmission of the sound waves as the transducer is moved over the area. Transcervical CVS may cause a feeling of pressure and some discomfort or cramping, similar to monthly periods or having a Pap test. Many women, however, find the procedure to be entirely painless. Once removed from the uterus, the tissue sample is placed in a dish and sent to a laboratory, where the chromosomes and DNA samples are removed from the fetal cells. The methods for handling the sample, examining the chromosomes, and testing for variants or mutations in specific genes depend on the type of technology used by the laboratory and the specific genetic tests to be performed. An entire CVS appointment, including preparation, may take 30–45 minutes, but the actual procedure takes only about 5 minutes.

Preparation

Women and their partners typically meet with a genetic counselor prior to deciding to have CVS. The counselor will inquire about any history of genetic disorders in the families of both parents to assess the need for CVS and any specific genetic tests that should be performed. Choosing to undergo CVS is a personal decision for each woman, and genetic counselors, as well as other healthcare providers and religious or spiritual counselors, can help a woman and her partner decide whether to

QUESTIONS TO ASK YOUR DOCTOR

- Should I have chorionic villus sampling because I am over age 35?
- What risk factors would indicate the need for chorionic villus sampling?
- Do you recommend that my partner and I meet with a genetic counselor?
- What are the advantages and risks of chorionic villus sampling compared with amniocentesis?
- Are there blood screening tests available that could be used instead of chorionic villus sampling?

proceed. The woman's healthcare provider will explain the CVS procedure, risks, and alternatives.

Women undergoing CVS are told to drink fluids and not urinate on the morning of the procedure so that the bladder is full during the procedure. This helps the physician determine where to place the needle. The woman will be asked about allergies to iodine, shellfish, or other substances. She signs a consent form for CVS and changes into a hospital gown. Women who are Rh-negative and unsensitized are given Rh immune globulin (RHIG or RhoGAM) at the time of the CVS to prevent complications of Rh incompatibility.

Aftercare

Women should relax for the remainder of the day after CVS. They may have spotting (a small amount of vaginal bleeding) or cramping for a few hours. Women should call their healthcare provider immediately if they experience heavy bleeding, fever, or contractions following CVS. A follow-up ultrasound will be performed two to four days after CVS to ensure that the pregnancy is proceeding normally.

Risks

The risks of CVS are only slightly higher than the risks of amniocentesis. There is a 1% risk of miscarriage following CVS. Miscarriage rates with transcervical CVS are slightly higher than with transabdominal CVS. Other possible complications include bleeding, infection, rupture of the membranes surrounding the fetus, or Rh incompatibility in the mother if this was not detected previously. There is a very slight risk of causing the loss of fingers or toes of the fetus, other limb abnormalities, or

defects in the jaw or tongue, but only if CVS is performed too early—before nine weeks of gestation.

Results

Results of the tests on cells obtained by CVS are typically available in one to two weeks. The test results are usually normal, indicating that the baby is healthy and without genetic abnormalities, even when results were positive with a maternal blood screening test. However, testing may not detect some genetic abnormalities. In the rare instances in which a genetic abnormality is detected, the healthcare provider will explain the results and discuss options with the parents. Some genetic abnormalities can be treated with medications or surgery before or after birth. Early knowledge of a birth defect can help the parents and healthcare providers plan for the baby's birth. Early knowledge can also help emotionally prepare parents to care for a newborn with special needs and ensure that the baby receives medical care immediately upon birth. In cases of severe birth defects, women may decide to terminate the pregnancy.

Although the laboratory results will indicate the baby's sex, it is up to the parents whether they want to know whether their child is male or female. Many people prefer to wait until the baby is born.

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- American College of Obstetricians and Gynecologists, 409 12th Street SW, Washington, DC 20024-2188, (202) 638-5577 or (800) 673-8444, resources@acog.org, <http://www.acog.org>
- March of Dimes, 1550 Crystal Drive, Suite 1300, Arlington, VA 22202, (888) 663-4637, <http://www.marchofdimes.org>

Margaret Alic, PhD

Choroideremia

Definition

Choroideremia is a rare genetic disorder causing progressive eyesight loss due to the wasting away of retinal layers. It first affects the choroid and the retinal pigmented epithelium (RPE) layers and finally the photoreceptor cell layer. Atrophy (wasting) of the optic nerve is also observed in choroideremia.

Description

Formerly called tapetochoroidal dystrophy, choroideremia is a chronic form of retinal disease characterized by degeneration of the layers of the retina, which is the light-sensitive part of the eye. There are four main retinal layers: the outer neural retina, consisting of nerve cells and blood vessels; the retinal pigment epithelium (RPE); the choroid layer that contains connective eye tissue and a capillary layer (chorio capillaris); and the photoreceptor (light-sensitive) layer that contains the rods and cones, which function as detectors to process light, color, and shape signals to the brain. Choroideremia is a progressive disease, meaning that the layers become affected one after the other over time.

The pigmentary changes in the RPE begin with fine spotting and continue with areas of depigmentation and increasing loss of the chorio capillaris. Chorio capillaris loss and degeneration of the larger choroidal blood vessels cause areas of bare sclera. The sclera is the tough white fibrous tissue that covers the "white" of the eye. The disease begins in mid-periphery of the choroid, but then progresses to include the entire choroid.

Choroidal vessels provide oxygen and nutrients to both the RPE and the retina's photoreceptor cells. The RPE, which lies directly beneath the retina, supports the function of photoreceptor cells. Photoreceptor cells (rods and cones) convert light into the electrical impulses that transfer messages to the brain where seeing actually occurs. In the early stages of choroideremia, the choroid and the RPE begin to deteriorate. Eventually,

photoreceptor cells also degenerate, resulting in a loss of central vision.

The age at which choroideremia first appears varies; initial symptoms (usually night blindness) may occur as early as three years of age and as late as forty years. However, occurrence peaks between the ages of ten and forty. The visual field becomes progressively constricted, and patients usually reach legal blindness by twenty-five years of age. Loss of central vision usually occurs after the age of thirty-five. However, in most patients with choroideremia, visual acuity (acuteness or sharpness of vision) is well maintained until the late stages of the disease.

Genetic profile

Choroideremia is an X-linked disorder, or a condition that is transmitted on the X chromosome. Females have two X chromosomes; males have an X and a Y chromosome. Thus in females, the altered gene on one X chromosome can be masked by the normal gene on the other X chromosome. Female carriers—who may or may not be symptomatic—have a 50% chance of passing the X-linked abnormal gene to their daughters, who become carriers; and a 50% chance of passing the gene to their sons, who are then affected by the disease.

In most individuals, choroideremia is caused by mutations (pathogenic variations) in the *CHM* gene and affected individuals display only disease-related ocular symptoms. However, in very rare cases, a small number of males have a chromosome deletion on their X-chromosome (at Xq21) involving the *CHM* gene. Depending on the size of this deletion, affected males can have associated hearing loss, birth defects, and varying degrees of intellectual disabilities. In these individuals, the mothers are the carriers, showing the same deletions but not the severe clinical manifestations.

Demographics

Choroideremia is believed to affect approximately 1 in 50,000 individuals—primarily men—although women who are carriers may exhibit mild symptoms as well. In an area of northern Finland (the Sala region) about 1 in 40 people have the disorder, due to inheritance of a single mutation from common ancestors (founder effect).

Signs and symptoms

Choroideremia is characterized by extensive abnormalities in the RPE layer. The initial symptoms include wasting of the retinal layers and choroid of

KEY TERMS

Choriocapillaris—Capillary layer of the choroid.

Choroid—A vascular membrane that covers the back of the eye between the retina and the sclera and serves to nourish the retina and absorb scattered light.

Electroretinogram (ERG)—A measurement of electrical activity in the retina.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Retinal pigment epithelium (RPE)—The pigmented cell layer that nourishes the retinal cells; located just outside the retina and attached to the choroid.

Retinitis pigmentosa—Progressive deterioration of the retina, often leading to vision loss and blindness.

the eye. The choroid (the vascular membrane located between the retina inside the eye and the sclera) contains large branched pigmented cells and prevents light rays from passing through areas of the eye outside of the pupils. Night blindness is usually the first noticeable symptom of choroideremia, usually occurring during childhood.

Because the diffuse, progressive atrophy of the chorio capillaris and RPE layers begins peripherally and spreads centrally, central macular function (central vision) is preserved until late in the course of the disease. Myopia occurs more frequently in men diagnosed with choroideremia. Although symptoms vary widely among affected individuals, men usually retain little or no useful vision beyond the age of 60.

Degeneration of the vessels of the choroid and functional damage to the retina occur later in life and usually lead to progressive central vision field loss and eventual blindness. Small bony-like formations and scattered pigment clumps tend to accumulate in the middle portion and on the edges of the choroid. In addition, color vision is initially normal but may later evolve into tritanopia (color blindness in which there is an abnormality in the perception of blue).

Female carriers usually have no symptoms and have normal visual fields, normal visual acuity, and normal electroretinograms (a measurement of electrical activity of the retina). However, female carriers sometimes show abnormalities of the interior lining of the eye in the form of pigment spotting with tiny patches of RPE depigmentation. Brownish granular pigmentation and changes in

QUESTIONS TO ASK YOUR DOCTOR

- A cousin was recently diagnosed with choroideremia. Does the disorder run in families?
- What are the chances that my future children might inherit the disorder?
- What are the primary features of the disorder?
- At what age do the symptoms of choroideremia first manifest themselves?
- What kinds of treatment are available for this disorder?

the RPE and choroid may occur later. There is also some evidence to suggest that mild progression of symptoms—and even the full disease—may occur in a small number of female carriers.

A variety of other degenerations of the choroid may look like choroideremia. Some abnormalities seen in the early stages of the disorder are symptoms also seen in other genetic vision disorders causing retinal degeneration, such as X-linked retinitis pigmentosa. However, unlike retinitis pigmentosa, which starts in early childhood, the onset of choroideremia is variable and is rarely seen in childhood. The distinguishing feature of choroideremia is the diffuse choroidal atrophy that is uncommon in early retinitis pigmentosa.

Diagnosis

Individuals with other disorders (hearing loss, intellectual disabilities) in addition to choroideremia should be tested for DNA deletions. Chromosome microarray, a DNA testing technique that detects deletions, should be the first test performed.

For individuals of Finnish ancestry with choroideremia, targeted mutation analysis for the mutations found in this population is done first.

If the DNA mutation in a family is known, prenatal diagnosis for choroideremia can be done. All family members with a history of choroideremia are encouraged to consult an ophthalmologist and to seek genetic counseling. These professionals can explain the disease and the inheritance risk for all family members and for future offspring.

Treatment and management

Although there is currently no treatment, choroideremia is a disease that has been shown to be a prime

candidate for the development of an effective gene therapy. As of 2021, numerous research studies were evaluating various methods of gene therapy and stem cell therapies. The goal of these therapies is to repair the gene mutation in the eyes and generate working REP-1 protein.

Assistance for individuals with choroideremia is available through low-vision aids, including optical, electronic, and computer-based devices. Personal, educational, and vocational counseling, as well as adaptive training skills, are also available through community resources. Additionally, some physicians recommend nutritional therapy including fresh fruits and vegetables, an antioxidant supplement, and omega-3 fatty acids from fish or supplements. Protecting the eyes from UV light (sunlight) by use of sunglasses or other means is also advised.

Prognosis

Progression of the disease continues throughout the individual's life, although both the rate and degree of visual loss are variable among those affected, even within the same family.

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"What Is Choroideremia?" Choroideremia Research Foundation. April 22, 2021. <https://www.curechm.org/> (accessed May 26, 2021).

ORGANIZATIONS

American Foundation for the Blind, 1401 South Clark Street, Suite 730, Arlington, VA 22202, (212) 502-7600, <https://www.afb.org/>

Choroideremia Research Foundation, 23 E. Brundreth St., Springfield, MA 01109, (800) 210-0233, info@curechm.org, <http://curechm.org>

National Eye Institute, 31 Center Dr., MSC 2510, Bethesda, MD 20892-2510, (301) 496-5248 (English and Spanish), 2020@nei.nih.gov, <http://www.nei.nih.gov>

National Federation of the Blind, 200 E. Wells St. at Jernigan Place, Baltimore, MD 21230, (410) 659-9314, 410-685-5653, <http://www.nfb.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 746-0100, (203) 798-2291, <http://www.rarediseases.org>

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Chromosomal abnormalities

Definition

Chromosomal abnormalities describe changes in the normal number of chromosomes or structural problems within the chromosomes themselves. They are also called chromosomal aberrations or anomalies. There are two basic categories: numerical, in which there are an abnormal number of chromosomes; and structural, in which a portion of the chromosome's structure is missing, duplicated, translocated, or otherwise changed.

Chromosomal abnormalities occur when a gamete (sex cell; egg or sperm) with an incorrect number of chromosomes or a structurally faulty chromosome unites with a normal egg or sperm during conception. Some chromosomal abnormalities occur shortly after conception. In this case, the zygote, the cell formed during conception that eventually develops into an embryo, divides incorrectly.

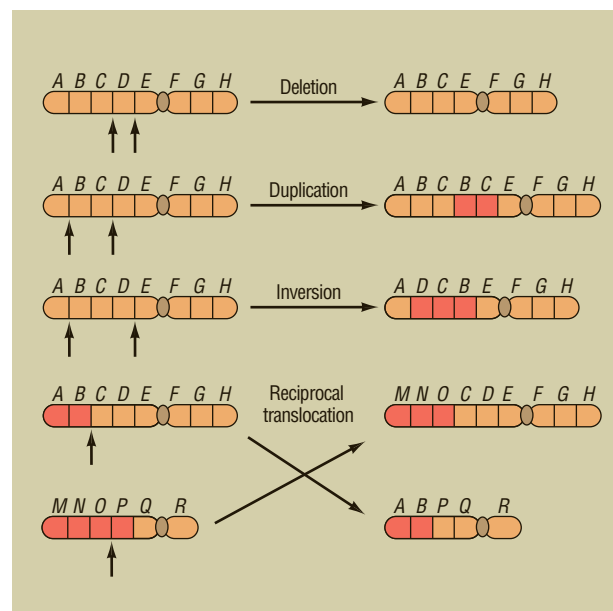
Chromosomal abnormalities can cause serious mental or physical disabilities. Down syndrome, for instance, is caused by an extra chromosome 21. People with Down syndrome have some degree of intellectual disability and may have a host of physical problems, including heart disorders. Other individuals with Down syndrome *mosaics* have a mixture of normal cells and cells with three copies of chromosome 21, resulting in a milder form of the disorder. Most abnormalities in chromosome number lead to the death of the embryo. Zygotes that receive a full extra set of chromosomes, a condition called polyploidy, usually do not survive inside the uterus and are spontaneously aborted (a process sometimes called a miscarriage).

Normal number and structure of human chromosomes

A chromosome consists of the body's genetic material, the deoxyribonucleic acid, or DNA, along with many

kinds of proteins. Within the chromosomes, the DNA is tightly coiled around these proteins (called histones) allowing approximately 6-foot-long (2 m) strands of DNA to occupy a microscopic space within the nucleus of the cell. When a cell is not dividing, the chromosomes are invisible within the cell's nucleus. Just prior to cell division, the chromosomes begin to replicate and condense. As the replicated DNA condenses, each chromosome looks somewhat like a fuzzy "X" under the microscope. Chromosomes contain the genes (segments of DNA that code for proteins) of an individual. When a chromosome is structurally faulty, or when a cell contains an abnormal number of chromosomes, the types and amounts of the proteins encoded by the genes are changed. When proteins are altered in the human body, the result can be serious mental and physical disorders or disease.

Humans have 46 chromosomes—22 pairs of autosomal chromosomes (also called autosomes) and one pair of sex chromosomes. These chromosomes may be examined by constructing a karyotype, or organized depiction, of the chromosomes. To construct a karyotype, a technician stops cell division just after the chromosomes have replicated using a chemical like colchicine. The chromosomes are visible within the nucleus at this point. The image of the chromosomes seen through the microscope is photographed. Each chromosome is cut out of the picture and arranged on another sheet in the correct sequence and orientation. The resultant image is called a karyogram. The chromosome pairs are identified according to size, shape, and characteristic stripe patterns (called banding).



Chromosomal abnormalities chart (Gale)

Normal cell division

In most animals, two types of cell division take place: mitosis and meiosis. In mitosis, each cell division produces two cells that are identical to the parent cell; i.e., one parent cell produces two daughter cells. Compared to its parent chromosome, each daughter cell has exactly the same number of chromosomes and identical genes. This preservation of chromosome number and structure is accomplished through the replication of the entire set of chromosomes just before mitosis.

Sex cells (eggs and sperm) undergo a different type of cell division called meiosis. Because sex cells each contribute half of a zygote's genetic material, sex cells must carry only half the full number of chromosomes. This reduction in the number of chromosomes within sex cells is accomplished during two rounds of cell division, called meiosis I and meiosis II. Before meiosis I, the chromosomes replicate. During meiosis I, a cell with 46 replicated chromosomes divides to form two cells that each contain 23 replicated chromosomes. Normally, the meiosis I division separates the 23 pairs of chromosomes evenly, so that each daughter cell contains one chromosome from each chromosome pair. No replication occurs between meiosis I and meiosis II. During meiosis II, the two daughter cells containing 23 replicated chromosomes divide to form four daughter cells, each containing 23 non-replicated chromosomes. Mistakes can occur during either meiosis I or meiosis II. Chromosome pairs may fail to separate during meiosis I, or a replicated chromosome may fail to separate during meiosis II.

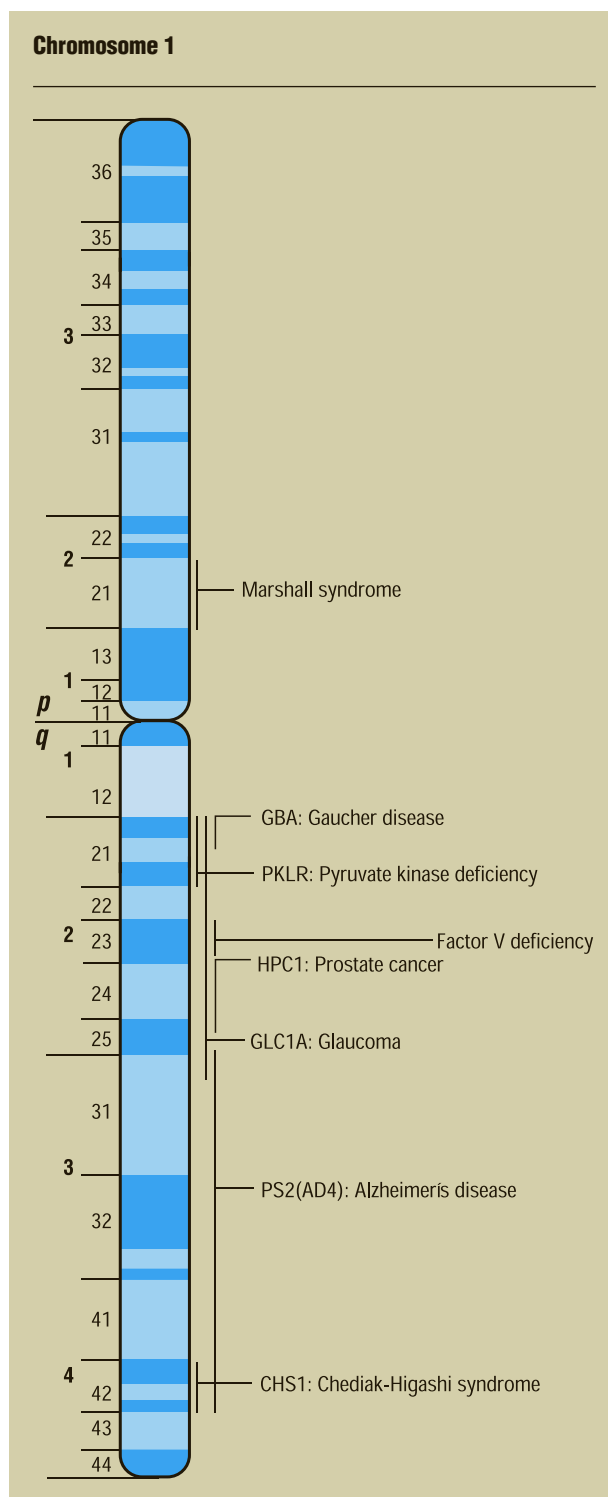
Meiosis produces four daughter cells, each with half the normal number of chromosomes. These sex cells are called haploid cells (haploid means "half the number"). Non-sex cells in humans are called diploid (meaning "double the number") since they contain the full number of normal chromosomes. Human diploid cells normally each have 46 chromosomes, and haploid cells normally each have 23 chromosomes.

Alterations in chromosome number

Two kinds of chromosome number alterations can occur in humans: aneuploidy, an abnormal number of chromosomes; and polyploidy, more than two complete sets of chromosomes.

Aneuploidy

Most alterations in chromosome number occur during meiosis. During normal meiosis, chromosomes are distributed evenly among the four daughter cells. Sometimes, however, an uneven number of chromosomes is distributed to the daughter cells. As noted in the previous section, chromosome pairs may not move apart in meiosis I, or the chromosomes may not separate in



Chromosome 1 (Gale)

meiosis II. The result of both kinds of mistakes (called nondisjunction of the chromosomes) is that one daughter cell receives an extra chromosome and another daughter cell does not receive any chromosome.

When an egg or sperm that has undergone faulty meiosis and has an abnormal number of chromosomes unites with a normal egg or sperm during conception, the zygote formed will have an abnormal number of chromosomes. This condition is called *aneuploidy*. There are several types of aneuploidy. If the zygote has an extra chromosome, the condition is called *trisomy*. If the zygote is missing a chromosome, the condition is called *monosomy*.

If the zygote survives and develops into a fetus, the chromosomal abnormality is transmitted to all of its cells. The child that is born will have symptoms related to the presence of an extra chromosome or absence of a chromosome.

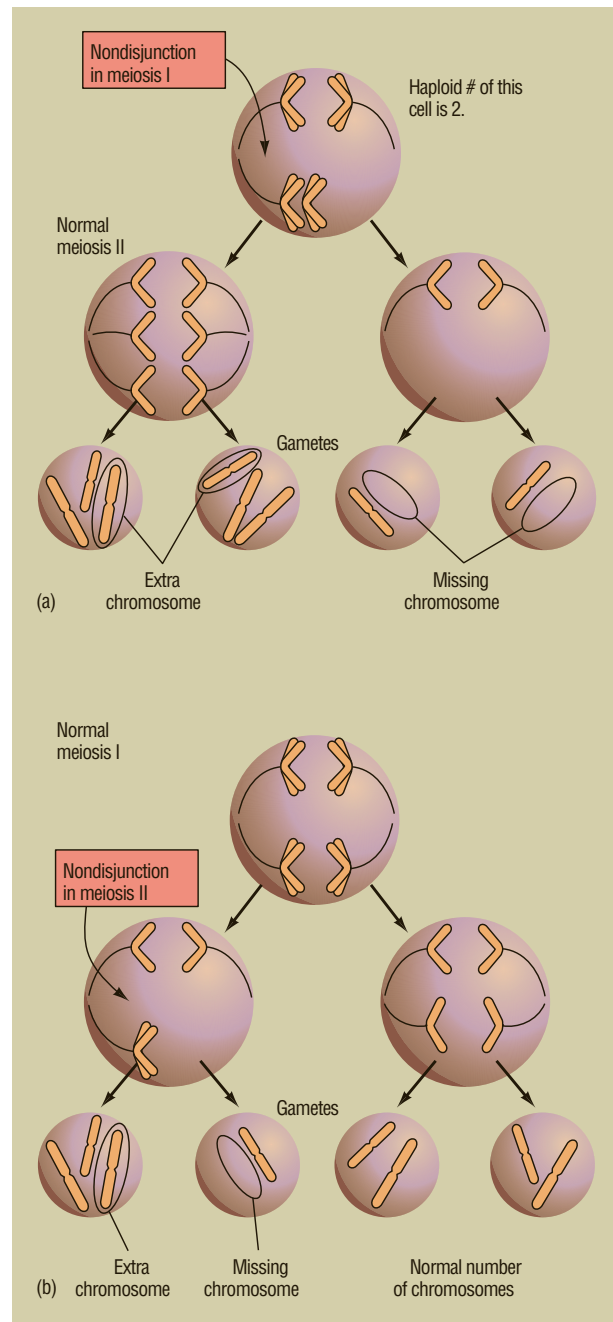
Examples of aneuploidy include trisomy 21, also known as Down syndrome, and trisomy 13, also called Patau syndrome. Trisomy 13 occurs in 1 out of every 5,000 births. Its symptoms are more severe than those of Down syndrome. Children with trisomy 13 always have severe physical and brain malformations and often have cleft palate and eye defects. Trisomy 18, known as Edwards syndrome, results in severe multiple defects. Children with trisomy 13 and trisomy 18 usually survive less than a year after birth.

Aneuploidy of sex chromosomes

Sometimes nondisjunction occurs in the sex chromosomes. Humans have one set of sex chromosomes. These sex chromosomes are called “X” and “Y” after their approximate shapes in a karyotype. Males have both an X and a Y chromosome, while females have two X chromosomes. Disorders associated with abnormal numbers of sex chromosomes are less severe than those associated with abnormal numbers of autosomes. This is thought to be because the Y chromosome carries few genes and the extra X chromosomes are inactivated shortly after conception. Nevertheless, aneuploidy in sex chromosomes causes changes in physical appearance and in fertility.

Individuals with Klinefelter syndrome, for instance, are men with two X chromosomes (XXY). This condition occurs in 1 out of every 600 male births. Men with Klinefelter syndrome have small testes and are usually sterile. Some men with Klinefelter develop enlarged breasts (gynecomastia). Males who are XXY are of normal intelligence. However, intellectual disabilities are not unusual in males with more than two X chromosomes, such as XXXY, XXXXY, or XXXXXY.

Males with an extra Y chromosome (XYY) have no physical defects, although they may be taller than average. XYY males occur in 1 out of every 1,000 male births.



Chromosomal abnormalities chart (Gale)

Females with an extra X chromosome (XXX) are sometimes said to have triple X syndrome and were sometimes called metafemales. This defect occurs in 1 out of every 1,000 female births. Females with XXX do not usually have any intellectual disability; their pubertal development and fertility are normal.

Females with only one X chromosome (XO) have Turner syndrome. Turner syndrome is also called monosomy X and occurs in 1 out of every 2,000–5,000 female

Klinefelter's syndrome	XXY
Extra Y	XYY
Metafemale	XXX
Turner's syndrome	XO

Chromosomal abnormalities in various syndromes (Gale)

births. The sex organs of females with Turner syndrome do not mature at puberty. Therefore, these women are usually sterile. They are of short stature and have no mental deficiencies. Heart defects are more common in girls with Turner syndrome.

Polyploidy

Polyploidy is lethal in humans. Normally, humans have two complete sets of chromosomes. Normal human cells other than sex cells are thus described as diploid. In polyploidy, a zygote receives more than two complete chromosome sets. Examples of polyploidy include triploidy, in which a zygote has three sets of chromosomes, and tetraploidy, in which a zygote has four sets of chromosomes. Triploidy may result from the fertilization of an abnormal diploid sex cell with a normal sex cell or from the fertilization of one egg by two sperm. Tetraploidy could result from the failure of the zygote to divide after it replicates its chromosomes. Human zygotes with either of these conditions usually die before birth or soon after. Interestingly, polyploidy is common in plants and is essential for the proper development of certain stages of the plant life cycle. Also, some kinds of cancerous cells have been shown to exhibit polyploidy.

Alterations in chromosome structure

Another kind of chromosomal abnormality is any change of chromosome structure. Structural defects arise during replication of the chromosomes just before a meiotic cell division. Meiosis is a complex process that often

involves the chromosomes exchanging segments with each other in a process called crossing-over. If the process is faulty, the structure of the chromosome changes. Sometimes these structural changes are harmless to the zygote. Other structural changes, however, can be lethal.

Six types of general structural alterations occur during replication of chromosomes. All six types begin with the breakage of a chromosome during replication. In a deletion, the broken segment of the chromosome is lost. Thus, all the genes that are present on this segment are also lost. In an insertion, the segment deleted from one chromosome is implanted into a different chromosome instead of being lost altogether. In duplication, the segment is inserted into the homologous chromosome as extra (duplicated) DNA. In an inversion, the broken segment reattaches to the original chromosome but is reversed end to end. In a translocation, the segment attaches to an entirely different chromosome. In a ring, a portion of the chromosome breaks off and the ends join to form a circle or ring. The ring type of structural alteration may occur with or without the loss of genetic material.

Because chromosomal structural changes cause the loss or misplacement of genes, the results can be quite severe. Deletions and duplications lead to missing or extra chromosomal material, meaning that there are too many or too few genes in that region. Translocations may or may not be harmful. If the translocation is balanced, meaning that all DNA is present and none is missing, the only effect may be a higher risk of abnormal sperm or eggs. If the translocation is not balanced, the chance of associated physical and cognitive abnormalities increases. Inversions of DNA may also be harmless except for a risk of abnormal sperm or eggs. However, both inversions and balanced translocations may have clinical consequences, depending on where the breakage and rejoining of DNA occurred.

A structural abnormality in chromosome 21 occurs in about 4% of people with Down syndrome. In this abnormality—a translocation—a piece of chromosome 21 breaks off during meiosis of the egg or sperm cell and attaches to chromosomes 13, 14, or 22. The parents of a child with Down syndrome due to this type of translocation could be balanced carriers for the translocation, and if so, are at increased risk of having another child with Down syndrome.

Some structural chromosomal abnormalities have been implicated in certain cancers. For instance, myelogenous leukemia is a cancer of the white blood cells. Researchers have found that the cancerous cells contain a translocation of chromosome 22, in which a broken segment switches places with the tip of chromosome 9.

Syndromes associated with chromosomal deletions

Many syndromes are associated with chromosomal deletions. These include cri du chat syndrome, velocardiofacial syndrome, Prader-Willi syndrome, Angelman syndrome, Wolf-Hirschhorn syndrome, Smith-Magenis syndrome, Miller-Dieker syndrome, Langer-Giedion syndrome, and the trichorhinophalangeal syndromes.

Cri du chat means “cat’s cry” in French. Children with this syndrome have an abnormally developed larynx that makes their cry sound like the meowing of a cat in distress. They also have a small head, misshapen ears, and a rounded face, as well as other systemic abnormalities and intellectual disability. Cri du chat syndrome is caused by a deletion of a segment of DNA in chromosome 5.

Velocardiofacial syndrome is also called DiGeorge syndrome or Shprintzen syndrome. More recently, it has been called deletion 22q11 syndrome because it is caused by a deletion of part of chromosome 22. Individuals with velocardiofacial syndrome may have congenital heart disease, cleft palate, learning difficulties, and subtle characteristic facial features.

Two syndromes caused by a chromosome abnormality illustrate an interesting concept: The severity or type of symptoms associated with a chromosomal defect may depend upon whether the child receives the changed gene from the mother or the father. Both Prader-Willi syndrome and Angelman syndrome are usually caused by a deletion in chromosome 15. Prader-Willi syndrome is characterized by intellectual disability, obesity, short stature, and small hands and feet. Angelman syndrome is characterized by jerky movements and neurological symptoms. People with this syndrome also have an inability to control laughter; they may laugh inappropriately at odd moments. If a child inherits the changed chromosome from its father, the result is Prader-Willi syndrome. However, if the child inherits the changed chromosome from its mother, the child will have Angelman syndrome.

A person may have Prader-Willi or Angelman syndrome without the chromosomal deletion usually associated with these conditions, due to a chromosomal error called uniparental disomy. Usually, one of each chromosome pair is inherited from each parent. Usually, every section of DNA has two copies—one maternally inherited and the other paternally inherited. Uniparental disomy refers to the mistake of both copies of a section of DNA being inherited from one parent. Two copies of a maternally inherited chromosome 15 (no paternal gene present) causes Prader-Willi syndrome, and two copies of a paternally inherited chromosome 15 causes Angelman syndrome.

The sequence of events leading to Prader-Willi and Angelman syndrome is unknown. Researchers have determined that the genes in this region on chromosome 15 may be “turned off,” depending on which parent contributed the chromosome. This process of gene inactivation is called imprinting. Some people have both Prader-Willi and Angelman syndrome because the mechanism controlling the imprinting malfunctions.

Expansion of chromosomal material

Not only can the sex of the parent from whom a gene is inherited determine whether it is “turned on” or “turned off,” but the sex of the parent may also influence whether certain abnormal sections of chromosomes become more abnormal. For example, the sex of the parent contributing the X chromosome may increase or decrease the chance that a child will be affected with fragile X syndrome.

Fragile X syndrome occurs in 1 out of 1,000 male births and 1 out of 2,000 female births. Males are affected more severely than females and the syndrome may be more pronounced if the child inherits the disorder from his/her mother. This difference is explained by the fact that fragile X syndrome is caused by an abnormality of the X chromosome. Remember that a male is XY and a female is XX. A male child receives a Y chromosome from the father and an X chromosome from the mother. A female child, however, can receive an X from either the mother or the father. Girls with fragile X syndrome are less severely affected than boys because they have a normal X chromosome that helps to protect them from the abnormal X chromosome. However, it was somewhat perplexing to researchers that girls are affected at all.

This mystery was solved when researchers learned that there is a range of abnormality in the fragile X chromosome. If the abnormality of the fragile X region of the chromosome is severe, the influence can be strong enough to affect females. If the abnormality is mild, females will not have symptoms of fragile X syndrome. Furthermore, the fragile X region of the X chromosome may become more severe when it is maternally inherited. The sex of the parent that the region is inherited from affects whether the chromosome abnormality remains stable or becomes greater.

Many other conditions are associated with similar chromosomal abnormalities and may remain stable or become more severe depending upon whether the chromosome region is inherited from the mother or the father. In some of these conditions, the region becomes more abnormal when it is paternally inherited. Huntington’s disease, an adult-onset neurological disease, is one such condition.

KEY TERMS

Aneuploidy—A condition in which the number of chromosomes in the nucleus of a cell is abnormal.

Autosomal chromosome—Any chromosome that is not a sex chromosome. Autosomal chromosomes are also called autosomes.

Chromosome—A packaged and organized structure containing most of the DNA of a living organism.

Chromosome microarray analysis (CMA)—A computerized technique that compares a patient's DNA with control DNA to identify clinically significant chromosomal abnormalities below the resolution level of conventional chromosome analysis.

Deletion—A mutation in which part of a chromosome or a sequence of DNA is missing.

Duplication—A mutation in which part of the chromosome is repeated, adding extra genetic material.

Gamete—A cell that fuses with another cell during fertilization in organisms that reproduce sexually. Gametes carry half of an individual's genetic information. They are formed through the process of meiosis.

Histones—Alkaline proteins found in cell nuclei that act as spools for winding strands of DNA, allowing the DNA to be stored compactly within the cell nucleus.

Insertion—A mutation in which part of a chromosome is deleted from its normal location and implanted into another chromosome.

Inversion—A rearrangement of genetic material within a chromosome that occurs when a portion of the chromosome breaks off, is reversed end to end, and is reattached.

Karyotype—The complete set of chromosomes in a species, or in a specific individual of that species. The chromosomes are depicted in a standard format known as a karyogram.

Meiosis—A specialized form of cell division in which DNA replication is followed by two rounds of cell division to produce four daughter cells with half the number of chromosomes as the parent cell. The two rounds of cell division are known as meiosis I and meiosis II.

Mitosis—The division of a cell into two identical daughter cells that are genetically identical to each other and to the parent cell.

Monosomy—A type of aneuploidy in which a cell contains only one copy of a chromosome rather than the normal two.

Mosaicism—A condition resulting from abnormal chromosome division, such that the organism contains different types of cells with different numbers of chromosomes.

Ploidy—The number of sets of chromosomes in the nucleus of a cell.

Point mutation—A mutation within a DNA or RNA molecule that involves a change in only one nucleotide base. It is also known as a single base substitution.

Polyploidy—A condition in which the nucleus of a cell contains more than two paired sets of chromosomes.

Ring—A structural chromosomal abnormality in which a portion of a chromosome breaks off and its ends join to form a circle or ring. There may or may not be loss of genetic material in a ring chromosome.

Translocation—A mutation in which a portion of a chromosome is transferred to another chromosome.

Trisomy—A type of aneuploidy in which there are three copies of a given chromosome instead of the normal two.

Zygote—The cell formed when sperm and egg are joined during the process of sexual reproduction.

Maternal and paternal age-related abnormalities

Currently, no cures exist for any of the syndromes caused by chromosomal abnormalities. For most of the conditions caused by aneuploidy, the risk of giving birth to a child with a chromosomal abnormality increases with the mother's age. The risk of Down syndrome, for instance, jumps from 1 in 1,000 when the mother is age

15–30 to 1 in 350 at age 35. This risk is most likely because the risk for nondisjunction as the eggs finish forming increases as maternal age increases. A man's age increases the nondisjunction risk slightly because of differences in the way eggs and sperm develop. Sperm mature and reproduce throughout a man's adult life. However, older men are more likely than younger men to have mutations occur during spermatogenesis. Women, on the other hand, are born with all the eggs they

will ever have. At birth these eggs are part way through meiosis I, and each month as a woman ovulates one egg finishes meiosis I and begins meiosis II.

Genetic testing and diagnosis

People at high risk of chromosomal abnormalities may opt to know whether the fetus they have conceived has one of these abnormalities. There are several methods of prenatal screening and testing as of 2021, as well as testing infants and children after birth for chromosomal abnormalities.

Amniocentesis and chorionic villus sampling

Amniocentesis is a procedure in which some of the amniotic fluid that surrounds and cushions the fetus in the uterus is sampled with a needle placed in the uterus. Real-time ultrasound is used to guide the procedure. The amniotic fluid contains fetal cells that can be tested for chromosomal, DNA, and biochemical abnormalities. Another test, chorionic villus sampling (CVS), involves taking a piece of tissue from the developing placenta. Undergoing either amniocentesis or CVS increases the risk of miscarriage slightly. Women and couples considering the procedure should be fully informed of the risks, benefits, and limitations of each procedure. If an abnormality is detected, the prenatal care provider discusses the options available with the woman or couple. Chromosomal abnormalities cannot be corrected. Some parents may choose to terminate the pregnancy. Other parents choose to continue the pregnancy and use the time to prepare for the birth of a child with special needs.

Chromosome microarray analysis

Chromosome microarray analysis (CMA) is a newer technique that has been in use since the early 21st century. It allows screening to identify gains and losses of DNA across the entire human genome. CMA can detect chromosomal abnormalities below the level of conventional karyotyping. To perform CMA, a laboratory technician extracts DNA from a sample of fetal tissue obtained by amniocentesis or chorionic villus sampling, and then hybridizes it onto a glass slide containing a large number (as many as two million) of molecular probes. The probes represent control DNA derived from a person without any chromosomal abnormalities. The prepared slide is then scanned by a computer to identify copy number variants (CNVs). CNVs include microduplications or microdeletions too small to be seen under a microscope; most abnormalities of chromosome number (trisomies and monosomies); most unbalanced rearrangements of chromosome structure; and some forms of mosaicism. The advantage of CMA is that it can detect unexpected chromosomal abnormalities as well as suspected CNVs.

CMA has some limitations as well as advantages. First, it can detect abnormalities of unknown clinical significance, thus adding to parental anxiety. Second, CMA cannot detect all genetic disorders. It does not, for example, detect point mutations (small changes within the sequence of a single gene) or balanced chromosomal rearrangements (balanced translocations or inversions).

CMA can be used for either prenatal or postnatal analysis. Prenatal CMA is usually undertaken after an ultrasound examination indicates the presence of fetal abnormalities. As of 2021, however, CMA is more often used to evaluate infants or children who display any abnormal characteristics but do not fit a known genetic syndrome. Some of the characteristics that would suggest CMA testing include developmental delays, multiple congenital abnormalities, intellectual impairment, or autism spectrum disorders. Parents should plan for a consultation with a geneticist before and after CMA testing in order to understand the results of the test and to determine whether further genetic testing (of the child or of other family members) may be advisable.

Many resources are available to parents learning of abnormalities before or after birth. In the case of a sex chromosome abnormality, it is common for people to learn of the abnormality as a teenager or even as an adult. A primary care physician, obstetrician, or support group can recommend a specialist offering more information. This specialist is often a medical geneticist, perinatologist, or genetic counselor. Many organizations also provide resources and information to individuals and families.

In conclusion, the division of chromosomes during development and during sperm and egg formation is a complex process. Most of the time, however, the process occurs normally. Mistakes that are made can result in changes in chromosome number as well as abnormal chromosomes. Extra or missing chromosomal material usually leads to physical and cognitive defects. Changes in sex chromosome complement are often associated with milder problems. Some problems with chromosomes are relatively common and are associated with well-defined syndromes. Other problems with chromosomes occur rarely and problems associated with the change are seen in only a few individuals.

Resources

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ORGANIZATIONS

Chromosome Disorder Outreach (CDO), PO Box 724, Boca Raton, FL 33429-0724, (561) 395-4252, info@chromodisorder.org, <http://www.chromodisorder.org>

March of Dimes, 1550 Crystal Drive, Suite 1300, Arlington, VA 22202, (888) 663-4637, <http://www.marchofdimes.org/contact-us.aspx>, <http://www.marchofdimes.org>

National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, (301) 402-2218, <http://www.genome.gov/10005049>, <http://www.genome.gov>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

National Society of Genetic Counselors (NSGC), 330 N. Wabash Ave., Suite 2000, Chicago, IL 60611, (312) 321-6834, (312) 673-6972, nsgc@nsgc.org, <http://www.nsgc.org>

Society for Maternal-Fetal Medicine (SMFM), 409 12th St., SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

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Chromosome

Definition

Chromosomes are microscopic units containing organized genetic information that are located in the nuclei of diploid and haploid cells (for example, human somatic and sex cells), and are also present in one-cell nonnucleated organisms (unicellular microorganisms),

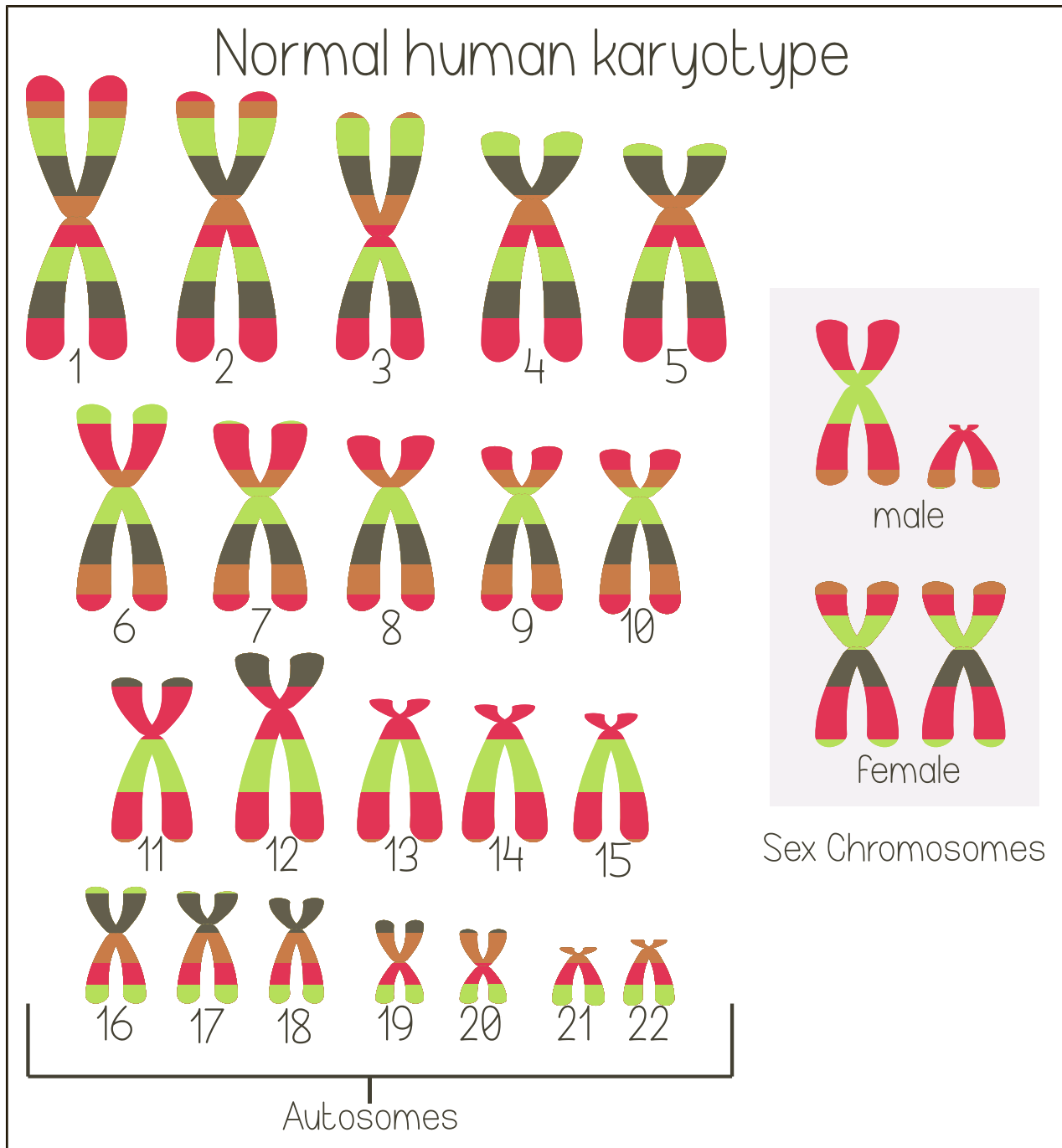
like bacteria, which do not have an organized nucleus. The sum total of genetic information contained in different chromosomes of a given individual or species is generically referred to as the genome.

Description

In humans, chromosomes are structurally made of roughly equal amounts of proteins and DNA. Each chromosome contains a double-strand DNA molecule arranged as a helix and tightly coiled and neatly packed by a family of proteins called histones. DNA strands are composed of linked nucleotides. Each nucleotide has a sugar (deoxyribose), a nitrogenous base, and one to three phosphate groups. Each nucleotide is linked to adjacent nucleotides in the same DNA strand by phosphodiester bonds. Nucleotides of one DNA strand link to their complementary nucleotide on the opposite DNA strand by hydrogen bonds, thus forming a pair of nucleotides, known as a base pair or nucleotide base. Genes contain up to thousands of sequences of these base pairs. What distinguishes one gene from another is the sequence of nucleotides that code for the synthesis of a specific protein or portion of a protein. Some proteins are necessary for the structure of cells and tissues. Others, like enzymes—a class of active (catalyst) proteins—promote essential biochemical reactions, such as digestion, energy generation for cellular activity, or metabolism of toxic compounds. Some genes produce several slightly different versions of a given protein through a process of alternate transcription of base pair segments known as codons.

Numbers of autosomal chromosomes differ in cells of different species but are usually the same in every cell of a given species. Sex determination cells (mature ovum and sperm) are an exception, where the number of chromosomes is halved. Chromosomes also differ in size. For instance, the smallest human chromosome, the sex chromosome Y, contains 57 million base pairs (bp), whereas the largest one, chromosome 1, contains 249 million base pairs. All three billion base pairs in the human genome are stored in 46 chromosomes. Human genetic information is therefore stored in 23 pairs of chromosomes (totaling 46); 23 inherited from the mother, and 23 from the father. Two of these chromosomes are sex chromosomes (chromosomes X and Y). The remaining 44 are autosomes, meaning that they are not sex chromosomes and are present in all somatic cells (i.e., any other body cell that is not a germinal cell for spermatozoa in males or ova in females). Sex chromosomes specify the offspring's sex: normal females have two X chromosomes, and normal males have one X and one Y chromosome.

Each set of 23 chromosomes constitutes one set of alleles, containing gene copies inherited from one of the progenitors. The other allele is complementary, or homologous, meaning that it contains copies of the same genes



Normal human karyotype. (Capreola/Shutterstock.)

and on the same positions, but originated from the other parent. As an example, every normal child inherits one copy of gene *BRCA1*, located on chromosome 17, from the mother, and another copy of *BRCA1* from the father, located on the other allelic chromosome 17. “Allele” is a Greek-derived word that means “one of a pair,” or any one of a series of genes having the same locus (position) on homologous chromosomes.

The first chromosome observations were made under light microscopes, revealing rod-shaped structures in varied sizes and conformations commonly J- or V-shaped in eukaryotic cells and ring-shaped chromosomes in bacteria. Staining reveals a pattern of light and dark bands. Today those bands are known to correspond to regional variations in the amounts of the two nucleotide base pairs: adenine-thymine (A-T) or

T-A) in contrast with amounts of guanine-cytosine (G-C or C-G).

Genetic abnormalities and diseases occur when one of the following events happens: a) one chromosome copy is missing, b) extra copies of a chromosome are present, c) a chromosome breaks and its fragment is fused into another chromosome (insertion), d) a fragment is deleted, e) a gene is transferred from one chromosome to another (translocation), f) duplication of a chromosomal segment occurs, or g) inversion of a chromosomal segment occurs. Down syndrome, for instance, is caused by the presence of a third copy of chromosome 21.

In nondividing cells, it is not possible to distinguish morphological details of individual chromosomes, because they remain elongated and entangled to each other. However, when a cell is dividing, i.e., undergoing mitosis, chromosomes become highly condensed and each individual chromosome occupies a well-defined spatial location.

Mitotic chromosomes present a constricted region, to which the spindle fibers attach during cellular division. Such a constricted region, known as the centromere or primary constriction, may be located in three different positions in chromosomes. Centromeric position allows the classification of chromosomes in three groups: a) acrocentric: centromere lies very near one end; b) metacentric: centromere at the middle, dividing the chromosome in two equal parts or arms; and c) submetacentric: centromere near the middle, but dividing the chromosome in two unequal arms.

When a chromosome loses its centromere, it is known as acentric. As the centromere is essential for both division and retention of chromosome copies in the new cells, acentric chromosomes will not pass to the daughter cells during the parental cell division. Therefore, daughter cells will lack one chromosome in their karyotype. A karyotype map shows mitotic chromosomes in the mitotic phase, known as metaphase. In metaphase, chromosomes align in pairs. In a normal human karyotype, there are 22 pairs of autosomal chromosomes and two sex chromosomes (X and Y). Each pair of autosomal chromosomes contains two complementary or homologous chromosomes, a maternal and a paternal copy.

Some chromosomes also present a secondary constriction that always appears at the same site. They are also useful, along with centromere position and chromosome size, for identifying and characterizing individual chromosomes in a karyotype.

Karyotype analysis was the first genetic screening utilized by geneticists to assess inherited abnormalities, like additional copies of a chromosome or a missing copy, as well as DNA content and gender of the

individual. With the development of new molecular screening techniques and the growing number of identified individual genes, detection of other more subtle chromosomal mutations is now possible (e.g., determinations of gene mutations, levels of gene expression, etc.). Such data allow scientists to better understand disease causation and to develop new therapies and medicines for those diseases.

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Sandra Galeotti, MS

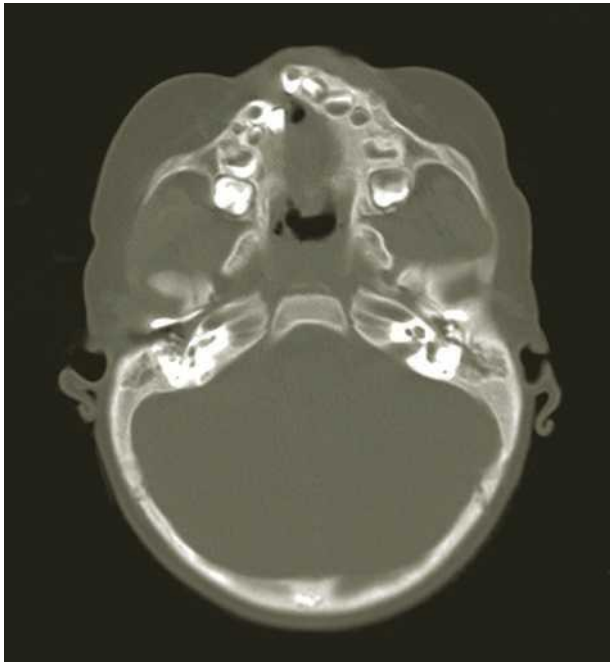
Cleft lip and palate

Definition

A cleft is a birth defect that occurs when the tissues of the lip and/or palate of the fetus do not fuse very early in pregnancy. A cleft lip, sometimes referred to as a hare-lip, is an opening in the upper lip that can extend into the base of the nostril. A cleft palate is an opening in the roof of the mouth.

Description

“Cleft” means “split or separated.” During the first months of pregnancy, separate areas of the face, such as bony and muscular parts, the mouth, and the throat, develop individually and then join together. If some parts do not join properly, the result is a cleft, the type and severity of which can vary. During the fifth through ninth weeks of pregnancy, genetic and environmental factors are most likely to affect lip and palate development. Cleft palate occurs when the right and left segments of the palate fail to join properly. The back of the palate (toward the throat) is called the soft palate, and the front section (toward the mouth opening) is known as the hard palate. A cleft palate can range from just an opening at the back of the soft palate, to a nearly complete separation of the roof of the mouth (soft and hard palate). In some cases, an infant with a cleft palate may also have a small lower



This axial (cross-sectional) CT image of a child shows a bony cleft along the anterior maxilla (left). Cleft lip and palate can be easily demonstrated using CT imaging and is a good technique to determine the extent of the malformation prior to surgery. (Living Art Enterprises/Science Source)

jaw and have difficulty breathing. This condition is called Pierre Robin sequence.

Infants born with cleft lips will have an opening involving the upper lip. The length of the opening ranges from a small notch to a cleft that extends into the base of the nostril. Cleft lips may involve one or both sides of the lip. They occur when the lip elements fail to come together during fetal development, thus creating an opening in the upper lip between the mouth and nose. The lip looks split. The incomplete cleft lip results in less facial distortion because the connected parts of muscle and tissue have a stabilizing effect. In a complete cleft lip, the muscles pull away from the center of the face, resulting in distortion of the nose and mouth. A cleft on one side is called a unilateral cleft. If a cleft occurs on both sides, it is called a bilateral cleft.

Cleft lips can develop with or without cleft palates, which may also occur without cleft lips.

Genetic profile

The causes of clefts are still poorly understood. Although it is not completely clear what causes cleft deformities, there is a definite genetic (inheritable) component. Most scientists believe that clefting occurs as a result of a combination of genetic and environmental

factors. In the United States and western Europe, researchers report that a family history of facial clefts is present in approximately 40% of all cases. The likelihood of a baby being born with a facial cleft increases if a first-degree relative (mother, father, or sibling) has a cleft. Mothers who abuse alcohol and drugs, lack vitamins (especially folic acid) during the first weeks of pregnancy, or have diabetes are more likely to have a child with facial clefts. Clefts may occur alone or with other abnormalities that may be hidden or obvious. Up to 13% of infants with a cleft lip or palate have other birth defects. Some cases involve genetic syndromes that may result in specific problems for the infant and may have a high risk of affecting others in the family. For that reason, newborns with clefts should be thoroughly examined by a specialized physician soon after birth.

Demographics

In the United States, about one in every 1,600 babies is born with cleft lip with cleft palate, about one in every 2,800 babies is born with cleft lip without cleft palate, and about one in every 1,700 babies is born with cleft palate. Boys are twice as likely as girls to have cleft lip with or without cleft palate. Girls are more likely than boys to have cleft palate without cleft lip. In cleft lip with cleft palate, the sex ratio correlates with the severity and laterality of the cleft. Clefts may affect the left or right side of the mouth only (unilateral) or both sides (bilateral). The prevalence of clefts varies considerably in different racial groups. In whites, cleft lip and cleft lip with cleft palate occur significantly more often in males, and cleft palate occurs significantly more often in females. The lowest prevalence rate is for blacks. Cleft lip and cleft palate are more common in families who are Asian, Hispanic, or Native American. A high prevalence of cleft lip is seen in the Japanese population, however, and the highest prevalence is noted in the North American Indian populations. In contrast, no remarkable variation among races was found in isolated cleft palate.

Risk factors

Several factors may increase the risk of cleft lip and cleft palate. Parents with a family history of cleft lip or cleft palate have a higher risk of having a baby with a cleft lip or cleft palate. Women who binge-drink during the first weeks of pregnancy are more likely than other women to have a baby with a cleft lip or cleft palate. Not getting enough nutrients, like folic acid, before and during pregnancy is also a risk factor. Other risk factors include having diabetes before pregnancy, being obese during pregnancy, having certain infections, and taking certain medicines during pregnancy.

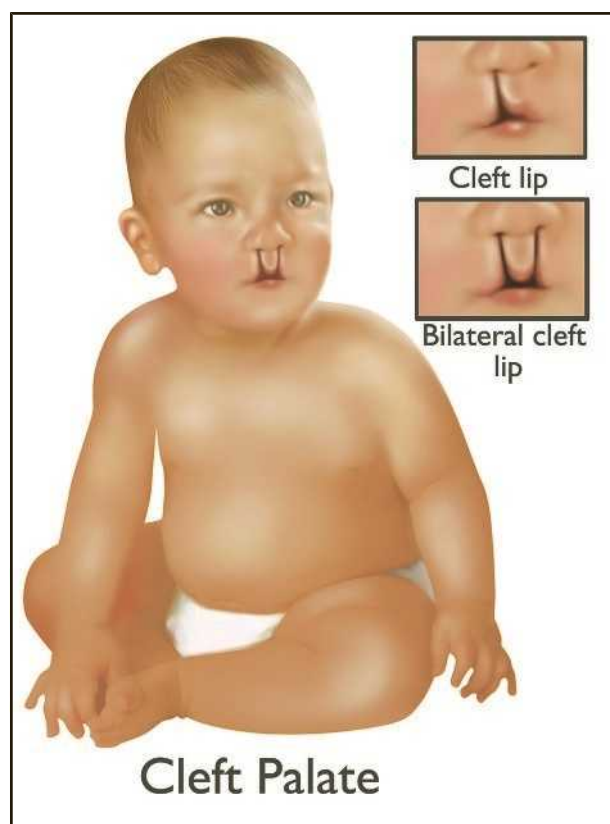


Illustration of a baby with a cleft palate. A cleft palate is a deformity resulting in an opening in the upper lip when the facial structures do not fuse properly. (Gwen Shockey/ Science Source)

Signs and symptoms

Babies born with a cleft lip will have an elongated opening in the upper lip. The size of this opening may range from a small notch to an opening that extends into the base of the nostril. The cleft lip may be below the right or left nostril or below both nostrils.

Babies born with a cleft palate will have an opening in the roof of the mouth. The size and position of the cleft varies, and it may involve only the hard palate or only the soft palate and may occur on both sides of the center of the palate.

In some cases, the cleft palate will be covered with the normal lining of the mouth and can only be felt by the examiner.

Infants with cleft lips and palates have feeding difficulties, which are more severe in those with cleft palates. The difficulty in feeding is due to the baby's being unable to achieve complete suction. In the case of a cleft in the hard palate, liquids enter the nose from the mouth through the opening in the hard palate.

A cleft palate also affects a child's speech, since the palate is necessary for speech formation. The child's speech pattern may still be affected despite surgical repair.

Ear infections are more common in babies born with cleft palates. The infections occur because the muscles of the palate do not open the Eustachian tubes, which drain the middle ear. This allows fluid to collect and increases the risk of infection and hearing loss.

Teeth may also erupt misaligned.

Diagnosis

Cleft lip and palate can be diagnosed before birth by ultrasound. After birth, they are diagnosed by physical exam.

Treatment and management

Traditional

If cleft lip and/or palate are diagnosed by ultrasound before birth, further testing may be necessary to diagnose associated abnormalities if present. Referral to a cleft team is essential. A cleft team consists of specialists in the management of patients with clefts and includes surgeons as well as nurses and speech therapists. Members of the team inform the parents of all aspects of management. Feeding methods are also discussed, since feeding is the first problem that must be addressed. It may be possible to breast-feed a baby born with only a cleft lip, but babies born with cleft palates usually have more problems with feeding and frequently require special bottles and teats. A palatal obturator is a device that fits into the roof of the mouth, thus blocking the cleft opening and allowing easier suckling.

Surgery to repair cleft lips is sometimes performed after orthodontic treatment to narrow the gap in the upper lip. Orthodontic treatment can involve acrylic splints with or without screws, or the use of adhesive tape placed across the gap in the lip. The orthodontic treatment for cleft lip should begin within the first three weeks of life and continue until the cleft lip is repaired.

The timing of surgical cleft lip repair depends on the judgment of the surgeon who will perform the operation. The procedure is usually performed between one and three months of age. The goals of the operation are to close the gap in the upper lip, place scars in the natural skin curves, and repair muscle so that the lip appears normal during movement. The closure is done in the three layers (skin, muscle, and mucosa) that line the inside of the lip. At the time of the procedure, if the nose is shaped abnormally because of the cleft lip, it is also corrected.

Sometimes further surgery may be needed on the lip and/or nose to refine the result.

The goals of the surgeon repairing a cleft palate are normal speech, normal facial growth, and hearing for the affected infant. The repair of the cleft palate is usually performed between three and 18 months of age. The timing may extend beyond this and varies with the type of cleft plate and the center where the procedure is being performed. Depending on the type of cleft palate, more than one operation may be needed to close the cleft and improve speech.

Babies born with cleft palates are vulnerable to ear infections. Their Eustachian tubes do not effectively drain fluid from the middle ear, so fluid accumulates and infection sets in, which may lead to hearing loss. These children require drainage tubes to be inserted in order to prevent fluid accumulation.

Babies born with clefts usually require orthodontic treatment between ages 13 and 18. They also require speech therapy.

Alternative

Nonsurgical treatment of a cleft palate is available for patients who are at high risk for surgery and consists of a prosthetic appliance worn to block the opening in the palate.

Nutritional concerns

Infants with cleft lip or cleft soft palate generally have few feeding problems. However, when the cleft involves the hard palate, the infant is usually not able to suck efficiently. For those infants, caregivers must experiment with various feeding techniques, such as special nipples or alternate feeding positions. The infant with a cleft should be held in a nearly sitting position during feeding to prevent the breast or formula milk from flowing back into the nose. They should be burped frequently, approximately every three or four minutes. The sucking reflex is strong in all infants and should be encouraged in infants with facial clefts even if the sucking is inefficient, since the reflex seems to help the later development of speech. It is important to keep the cleft clean and not to allow formula, mucus, or other matter to collect in it.

Prevention

While little is known about how to prevent clefts, researchers from the California Birth Defects Monitoring Program found that women who are considering pregnancy may be able to reduce the risk of facial clefts (and possibly other birth defects) in their offspring by taking a multivitamin containing folic acid for one month prior to becoming pregnant. Other studies have shown that fetuses

QUESTIONS TO ASK YOUR DOCTOR

- Can the cleft be surgically corrected?
- What are the treatment options?
- Is child development affected by clefting?
- At what age should surgery be performed?

with certain predisposing genes may be at increased risk for cleft palate if their mothers smoke. Because some types of medications (for example, some drugs used to treat epilepsy) have been linked to increased risk of clefts, women who take medications for chronic illnesses should check with their doctors before they become pregnant.

Prognosis

Individuals born with cleft lip and palate have a good prognosis, and approximately 80% will develop normal speech. There is no known means of preventing clefting. Good prenatal care is essential, and avoiding harmful substances appears to reduce the risk.

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ORGANIZATIONS

American Cleft Palate Craniofacial Association, 1504 East Franklin Street, Suite 102, Chapel Hill, NC 27514-2820, (919) 933-9044 or (800) 242-5338, (919) 933-9604, info@acpa-cpf.org, <https://acpa-cpf.org/>.

National Institute on Deafness and Other Communication Disorders, 31 Center Drive, MSC 2320, Bethesda, MD 20892-2320, (301) 827-8183, (301) 402-0018, nidcdinfo@nidcd.nih.gov, <http://www.nidcd.nih.gov/Pages/default.aspx>

National Institute of Dental and Craniofacial Research, Bethesda, MD 20892-2190, (866) 232-4528, (301) 480-4098, nidcrinfo@mail.nih.gov, <http://www.nidcr.nih.gov>

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Revised by Bharati K. Hegde, BE, MS, PhD

Cleft palate see **Cleft lip and palate**

Cleidocranial dysostosis see **Cleidocranial dysplasia**

Cleidocranial dysplasia

Definition

Cleidocranial dysplasia (CCD), also known as cleidocranial dysostosis, is a hereditary condition that causes abnormal formation of the collarbone, delayed fusion of the bones in the skull, extra teeth to appear, short stature, and other changes in the skeleton.

Description

Cleidocranial dysplasia is one of the skeletal dysplasia conditions, a large family of disorders involving abnormal growth and development of the skeleton.

CCD involves a characteristic group of abnormalities that affect mostly the skull, teeth, and clavicles. Other bones, such as the ribs, pelvis, and bones of the hands

KEY TERMS

Autosomal dominant—Requiring only one copy of the mutated gene to cause the disorder.

Clavicle—Also called the collarbone. Bone that connects the shoulder and the breast bone.

Complete penetrance—Condition in which all who carry the gene display some symptoms.

Deciduous teeth—The first set of teeth or “baby teeth.”

Fontanelle—One of several soft spots on the skull where the developing bones of the skull have yet to fuse.

Hypoplasia—Incomplete or underdeveloped tissue or organ.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual and can be transmitted to offspring. The change may manifest as disease.

and feet may also be affected. Older children and adults with CCD are typically shorter than average. Most individuals with this condition do not have significant physical or mental disability.

Genetic profile

CCD is an autosomal dominant condition. This means that it only takes one copy of the mutated gene to cause the disorder. The symptoms can vary, but the disorder has complete penetrance, which means that all individuals who carry the gene for CCD have some symptoms. It is estimated that one-third of cases represent *de novo*, or new, mutations. The gene responsible for CCD has been mapped to the short arm of chromosome 6 and is called *RUNX2*. There are other names for the gene, including *CBFA1*. This gene provides instructions for making a protein that is involved in making and maintaining bone and cartilage. More than 70 mutations in the *RUNX2* gene have been identified in people with CCD, and the *RUNX2* gene causes most cases of the condition.

Demographics

CCD is rare, and occurs in only about one per million people around the world. More than 500 cases of CCD among individuals of various ethnic backgrounds have been described in the medical literature. The incidence of CCD is reported to be highest around Cape Town, South Africa. Research on this population helped localize the gene responsible for the condition.

Signs and symptoms

Infants with CCD typically show a delay or failure of the fusion of the openings between the bones of the skull. In some cases, the anterior fontanelle (the soft spot on an infant's head) or other areas of the skull may remain unfused through life. A typical facial appearance in people who have CCD includes a broad forehead and widely spaced eyes. The overall head size is usually at the upper limit of normal.

Almost every person with CCD has some degree of hypoplasia, which means underdevelopment, of the collarbones. In severe cases, both clavicles may be absent. Most often, the child has hypoplasia of the outside ends of the collarbones. Depending on how severely underdeveloped the collarbones are, the child's shoulders may appear abnormal. Some people with CCD appear to have narrow, sloping shoulders. Some have the unusual ability to bring their shoulders together beneath their chin. This hypoplasia of the collarbones usually does not result in physical disability for the individual.

Dental abnormalities are common among people with CCD and are considered characteristic of the disorder. Almost all individuals are slow to lose their deciduous teeth (baby teeth), and have delayed eruption of the permanent teeth. Some people with CCD describe "living without teeth" until their permanent teeth started growing. Additionally, the person may have a large number of extra teeth. These extra teeth can be so numerous that they constitute nearly a third complete set of teeth. Additionally, the enamel of the teeth may be abnormal and prone to decay.

Other signs of CCD include a small rib cage with short or abnormal ribs. The vertebrae of the spine may be malformed. The pelvis may be underdeveloped with an increased space between the pubic bones. The growth of the bones in the hands and feet is often abnormal; most are shorter but others are longer than normal. Final height in adults with CCD is usually shorter than expected given the family background.

More unusual complications associated with CCD include scoliosis (curvature of the spine), bone fragility, deafness, cleft palate, and a small jaw.

Diagnosis

The diagnosis of CCD is typically made by the doctor following review of the information obtained from physical exams, case history, or x-rays. The underdeveloped collarbone may only be seen through x-rays.

The combination of hypoplastic clavicles, open fontanelles, and extra teeth is considered typical of CCD. The multiple dental problems in CCD are also quite

QUESTIONS TO ASK YOUR DOCTOR

- What are the primary signs and symptoms of cleidocranial dysplasia?
- How is this disorder transmitted from one generation to the next?
- What types of treatment should be considered first for a child diagnosed with cleidocranial dysplasia?
- Will a child born with cleidocranial dysplasia develop physical and mental problems other than its primary symptoms?

specific and the diagnosis is evident in any individual with normal deciduous teeth, delayed eruption of permanent teeth, and multiple extra teeth.

Testing for *RUNX2* gene mutations may also be performed. Identification of a mutation may confirm the initial diagnosis or allow diagnosis before birth.

In a few cases, recognition of the features of CCD by ultrasound imaging, a technique that produces pictures of the fetus, has led to diagnosis of the condition before birth.

Treatment and management

There is no specific treatment for cleidocranial dysplasia. Typically, a course of treatment is designed to manage the specific symptoms.

Children with CCD may be screened for deafness.

Long-term dental treatment is often required. Surgery may be performed to remove the baby teeth and open the bony coverings surrounding the permanent teeth, with the goal of promoting their eruption. Orthodontic procedures may be required to align the teeth.

A pregnant woman with CCD may have to deliver her child by caesarean section because of her pelvic abnormality.

Prognosis

CCD is not expected to affect life expectancy in most cases, and most people with the disorder enjoy good overall health.

In some newborns, the small rib cage and reduced lung capacity may lead to respiratory distress. Height is often lower compared to that of other family members. The clavicular hypoplasia does not appear to significantly

impair function. Some individuals with hypoplastic or absent collarbones have worked in physically demanding jobs without difficulty. Dental problems are expected and are sometimes severe enough to cause dental disability. Intelligence is usually normal.

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ORGANIZATIONS

FACES: The National Craniofacial Association, PO Box 11082, Chattanooga, TN 37401, (800) 332-2373, faces@faces-cranio.org, <http://www.faces-cranio.org>

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Clubfoot

Definition

Clubfoot is a condition in which one or both feet are twisted into an abnormal position at birth. The condition is also known as talipes.

Description

True clubfoot is characterized by abnormal bone formation in the foot. There are four variations of clubfoot, including talipes varus, talipes valgus, talipes equinus,



An untreated clubbed foot. (Mike Devlin/Science Source)

and talipes calcaneus. In talipes varus, the most common form of clubfoot, the foot generally turns inward so that the leg and foot look somewhat like the letter J. In talipes valgus, the foot rotates outward like the letter L. In talipes equinus, the foot points downward, similar to that of a toe dancer. In talipes calcaneus, the foot points upward, with the heel pointing down.

Clubfoot can affect one foot or both. Sometimes an infant's feet appear abnormal at birth because of the intra-uterine position of the fetus birth. If there is no anatomic abnormality of the bone, this is not true clubfoot, and the problem can usually be corrected by applying special braces or casts to straighten the foot.

True clubfoot is usually obvious at birth because a clubfoot has a typical appearance of pointing downward and being twisted inward. Since the condition starts in the first trimester of pregnancy, the abnormality is quite well established at birth, and the foot is often very rigid. Uncorrected clubfoot in an adult causes only part of the foot, usually the outer edge or the heel or the toes, to touch the ground. For a person with clubfoot, walking becomes difficult or impossible.

Risk factors

Risk factors for clubfoot include smoking and a family history of clubfoot or neuromuscular disorders, such as cerebral palsy or spina bifida.

Genetic profile

Experts do not agree on the precise cause of clubfoot. Genetic patterns of inheritance have been extensively investigated using family studies and other epidemiological methods. No definitive conclusions have been reached, although a Mendelian pattern of inheritance is suspected. This may be due to the interaction of several different inheritance patterns, different patterns of

development appearing as the same condition, or a complex interaction between genetic and environmental factors. A 2009 study reported that two biologically plausible candidate genes are present on chromosomes 3 and 13, a result that supports the continued search for responsible genes. Clubfoot can also be present in people with such syndromes as Ehlers-Danlos or Loeys-Dietz.

A family history of clubfoot has been reported in 24.4% of families in a single study. These findings suggest the potential role of one or more genes being responsible for clubfoot.

Several environmental causes have been proposed for clubfoot. Obstetricians think that intrauterine crowding causes clubfoot. This theory is supported by a significantly higher incidence of clubfoot among twins compared to singleton births. Intrauterine exposure to the drug misoprostol has been linked with clubfoot. Misoprostol is commonly used when trying, usually unsuccessfully, to induce abortion in Brazil and in other countries in South and Central America. Researchers in Norway have reported that males who are in the printing trades have significantly more offspring with clubfoot than men in other occupations. For unknown reasons, amniocentesis, a prenatal test, has also been associated with clubfoot. The infants of mothers who smoke during pregnancy have a greater chance of being born with clubfoot than offspring of women who do not smoke.

Demographics

The ratio of males to females with clubfoot is 2.5 to 1. The incidence of clubfoot varies only slightly. In the United States, the incidence is approximately 1 to 4 in every 1,000 live births. A 1980 Danish study reported an overall incidence of 1.2 in every 1,000 children; by 1994, that number had doubled to 2.41 in every 1,000 live births. A reason for the increase has yet to be identified.

Signs and symptoms

The physical appearance of a clubfoot may vary. However, at birth, an affected foot usually turns inward and points downward. It resists realignment. The calf muscle may be smaller and less well developed than normal. One or both feet may be affected.

Diagnosis

Examination

True clubfoot is usually recognizable and obvious on physical examination. Clubfoot is diagnosed by physician inspection. This is most often completed immediately after birth.

QUESTIONS TO ASK YOUR DOCTOR

- How does clubfoot affect a child?
- Can it be corrected by nonsurgical treatment?
- What are the outcomes?
- What are the surgical options?
- How do various types of clubfoot differ from each other?
- What kinds of treatment are available for a child born with a clubfoot?
- At what age should those treatments begin, and what side effects may be associated with the treatments?
- To what extent will a child born with clubfoot be able to live a normal life after treatment?

Tests

A routine x-ray of the foot that shows the bones to be malformed or misaligned supplies a confirmed diagnosis of clubfoot. Ultrasonography is not always useful in diagnosing the presence of clubfoot prior to the birth of a child.

Treatment and management

Traditional

Most orthopedic surgeons agree that the initial treatment of congenital (present at birth) clubfoot should be nonoperative. Nonsurgical treatment should begin in the first days of life to take advantage of the favorable fibro-elastic properties of the foot's connective tissues, those forming the ligaments, joint capsules, and tendons. The Ponseti method of stretching and casting has been used with increasing success since the 1990s. The Ponseti method requires that a doctor stretch the child's affected foot toward its anatomically correct position and hold it in place with a cast. The foot is realigned and a new cast applied weekly for several weeks. Once the correct position has been achieved, a brace must be worn during periods of sleep to maintain the correction. To be successful, the method requires active parental involvement. Because the cause of clubfoot is unknown, there are no measures to specifically prevent it. However, pregnant women can take steps to limit the risk of birth defects such as clubfoot by avoiding smoking, alcohol consumption, or the intake of medications not approved by a physician.

Surgical

When clubfoot is severe enough to require surgery, the condition is usually not completely correctable, although significant improvement is possible. In the most severe cases, surgery may be required, especially when the Achilles tendon, which joins the muscles in the calf to the bone of the heel, needs to be lengthened. Because an early operation induces fibrosis, a scarring and stiffness of the tissue, surgery should be delayed until an affected child is at least three months old.

Much of a clubfoot abnormality can be corrected by the use of manipulation and casting during the first three months of life. Proper manipulative techniques must be followed by applications of appropriately molded plaster casts to provide effective and safe correction of most varieties of clubfoot. Long-term care by an orthopedist is required after initial treatment to ensure that the correction of the abnormality is maintained. Exercises, corrective shoes, or nighttime splints may be needed until the child stops growing.

Prognosis

With prompt, expert treatment, clubfoot is usually correctable. Most individuals are able to wear regular shoes and lead active lives. If clubfoot is not appropriately treated, the abnormality becomes fixed. This has an effect on the growth of the leg and foot, and some degree of permanent disability usually results.

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ORGANIZATIONS

- Birth Defect Research for Children, 976 Lake Baldwin Lane, Suite 104, Orlando, FL 32814, (407) 895-0802, staff@birthdefects.org, <http://www.birthdefects.org>
- March of Dimes Foundation, 1550 Crystal Drive, Suite 1300, Arlington, VA 22202, (888) 663-4637, <http://www.marchofdimes.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06813, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>
- Ponseti International Association, University of Iowa Healthcare, International Office, 118 CMAB, Iowa City, IA 52242, (319) 467-5107, ponseti@healthcare.uiowa.edu, <http://www.ponseti.info>

L. Fleming Fallon, Jr., MD, PhD, DrPH

Cobblestone dysplasia see **Lissencephaly syndrome**

Cockayne syndrome

Definition

Cockayne syndrome (CS) is a rare inherited disorder that results in an extreme sensitivity to ultraviolet (UV) irradiation, dwarfism, intellectual deficits, and premature aging.

Description

Since first reported in 1936 by Dr. Edward A. Cockayne, fewer than 200 cases of this disorder have been documented in medical literature. At birth, newborns with CS may have microcephaly (small-sized head) and low birth weight. During the first year of life, they do not feed well, and as a result they suffer from growth failure and delayed development. The disease usually results in death during the teenage years.

Cockayne syndrome can be divided into subtypes, which are distinguished by the severity and age of onset of symptoms. Classical or Type I CS is characterized by symptoms that appear in early childhood. Type II CS has severe symptoms that are apparent at birth. It is also called cerebro-oculo-facio-skeletal (COFS) syndrome or Pena-Shokeir syndrome Type II. A few cases of Type III CS have been diagnosed with the onset of symptoms in late childhood. There are also cases that combine features of CS and another photosensitivity disorder called xeroderma pigmentosum.

Risk factors

People with a family history of CS are at risk, since defective genes are associated with the disease.

Demographics

CS occurs in fewer than one in 250,000 births and does not affect any single ethnic group more than any other. Males and females are equally affected.

Signs and symptoms

CS results from mutations in the *ERCC6* and *ERCC8* genes (also known as the *CS* genes) located on chromosomes 10 and 5, respectively. An affected person has inherited one abnormal or nonworking gene from each parent, a pattern that is consistent with autosomal recessive inheritance. When functioning normally, the *CS* genes help cells remove and destroy deoxyribonucleic acid (DNA) errors from strands undergoing active transcription. The *CS* genes also allow cells to synthesize ribonucleic acid (RNA) after exposure to UV light. Although the parents of an affected child may be normal, each of them carries an abnormal gene for CS. Therefore, they have a 25% risk with each pregnancy of having another affected child.

As Cockayne syndrome is divided into four subtypes, symptoms vary but can be very striking. The symptoms associated with each subtype overlap. The most severe end of the spectrum is Type II CS in which individuals show a prenatal onset of symptoms. Classical or Type I CS is characterized by symptoms that appear in early childhood and are more severe than those seen in Type III. Individuals with XP-CS have mutations in *ERCC6* and, similar to XP, have facial freckling and early skin cancers. These individuals also have some of the less threatening features of CS.

The spectrum of symptoms associated with CS includes developmental delay, failure to grow during the first year of life, a small head size, dental anomalies, and progressive hearing loss. Intellectual impairment in the mild-to-moderate range is found in all patients with CS. A small number of patients will have severe-to-profound intellectual deficits, with some having only a few words of speech. Skin rashes appear with exposure to sunlight, and patients develop dry, scaly skin and thin hair. As part of the disease process, the skin develops an aged, leathery appearance. Although the eyes appear normal early in life, the retina later loses its pigment or color and develops a “salt-and-pepper” appearance. If cataracts appear within the first three years of life, the patient usually has the more severe form of CS that leads to death before adolescence. More than half of patients with CS have sensorineural hearing loss. The range of loss is from mild to severe.

Another finding of CS is an unusual gait (pattern of walking), caused by a combination of leg spasticity and contractures of the hips, knees, and ankles. The stooped posture, often seen in CS, results from kyphosis and joint

contractures. Some of the first signs of neurological changes are increased or decreased muscle tone and reflexes.

The most notable sign of CS is precocious senility (premature memory loss and confusion). Patients experiencing precocious senility undergo neurological changes that resemble normal aging. The central and peripheral nervous systems lose myelin, and neurons disappear from the central cortex and cerebellum. However, unlike in normal aging, these changes occur at an extremely accelerated pace, leading to death during early adolescence.

Diagnosis

The diagnosis of Cockayne Syndrome is often difficult to establish, depending on the type of CS, since many of the symptoms develop gradually. A diagnosis is generally made based on the observation of any combination of the characteristic symptoms during a medical examination. Genetic testing for mutations in the *ERCC6* and *ERCC8* genes or a DNA repair assay on fibroblasts can confirm the diagnosis. The fibroblasts of a person with CS present notably decreased development.

Treatment and management

There is no cure for CS at present. Patients are treated according to the symptoms they have. Physical therapy helps to prevent joint contractures that limit walking. Poor feeders may require a gastrostomy tube to prevent malnutrition. Patients are also advised to use sunscreen liberally and to limit their exposure to sunlight. Special-needs education helps to maximize the child’s learning potential.

Since carriers of the gene that causes CS appear normal, and routine testing before pregnancy is not yet available, couples will not be aware of their risk until they have an affected child. For future pregnancies, prenatal diagnosis can determine whether the baby has CS.

Prognosis

Scientists have determined that some of the symptoms of CS are caused by defects in the chemical pathway that repairs DNA. One of these defects leads to damage in mitochondria, which are organelles in the cell involved in respiration and energy production. The damage allows the buildup of a protein called HTRA3 that appears to interfere with mitochondrial function. By using an antioxidant, scientists have been able to decrease HTRA3 to normal levels and prevent mitochondrial damage in cells of some types of CS in the laboratory. This work is still in the experimental stage, and as of 2021 it does not have therapeutic applications for individuals, but it is a step toward understanding the chemical pathway that causes CS symptoms. At present, the prognosis for CS is grim. Most patients die during the early adolescent years. Some survive until

QUESTIONS TO ASK YOUR DOCTOR

- What symptoms suggest a diagnosis of Cockayne syndrome in a newborn child or infant?
- What kind of genetic testing is currently available?
- What is the risk of CS for future pregnancies?
- What are the major health issues associated with CS?
- What confirmatory tests are available for such a diagnosis?
- What are the treatment options for Cockayne syndrome?
- Are there treatments available that will slow the progress of this disorder?
- What is the long-term prognosis for a child born with Cockayne syndrome?

early adulthood. However, some patients have a more severe form and may die during early childhood.

Clinical trials for Cockayne syndrome are underway; there are 7 as of 2021. Participation in a U.S. clinical trial is voluntary and at no cost to the participant. All clinical trials receiving U.S. government funding, and some supported by private industry, are posted at <https://www.clinicaltrials.gov>. Foreign trials are listed at <https://www.orpha.net>.

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MAGIC Foundation for Children's Growth, 4200 Cantera Drive, #106, Warrenville, IL 60555, (630) 836-8200, (800) 362-4423, (630) 836-8181, contactus@magicfoundation.org, <https://www.magicfoundation.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <https://rarediseases.org>

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Revised by Tish Davidson, AM

CODAS syndrome

Definition

CODAS syndrome is a very rare genetic disorder that affects five major body organs or systems: the brain, eyes, ears, teeth, and skeleton. The acronym CODAS stands for cerebral, ocular, dental, auricular, and skeletal. CODAS syndrome was named by the team of Canadian researchers who identified it in 1991 in a single patient from Manitoba.

Description

Children with CODAS syndrome have a distinctive set of abnormalities that include developmental delays, cataracts in both eyes, deformities of the facial features, misshapen ears combined with mild to moderate hearing loss, abnormally shaped teeth combined with delayed eruption of baby teeth, delayed maturation of the skeleton together with hip displacement and scoliosis, and overall short stature.

Genetic profile

The gene whose mutations are responsible for CODAS syndrome was not identified until early 2015. Two groups of geneticists, one in southeastern Pennsylvania and the other in Switzerland, identified the specific gene as the

KEY TERMS

Auricular—Pertaining to the ear.

Autosomal recessive—A pattern of inheritance in which two copies of a defective gene on a nonsex chromosome must be present for a disease or inherited trait to develop in an individual.

Autosome—Any human chromosome other than a sex chromosome.

Corpus callosum—A wide, flat bundle of nerve fibers that connects the two cerebral hemispheres and allows communication of nerve impulses between the two hemispheres.

Cryptorchidism—The absence of one or both testes in the male scrotum at the time of birth.

Epicanthal fold—A skinfold in the upper eyelid that covers the inner angle of the eye. Epicanthal folds are common in persons of Asian, Native American, Alaska Native, or Berber heritage, but they may also occur as a symptom of some genetic syndromes.

Fistula (plural, fistulae)—An abnormal connection between two hollow body organs or spaces.

Hypotonia—A state of low muscle tone that often involves loss of muscle strength as well.

Mitochondria (singular, mitochondrion)—An organelle found in most human cells that generates most of the cell's supply of adenosine triphosphate (ATP), a critical source of chemical energy. Mitochondria are sometimes described as the powerhouses of the cell.

Omphalocele—A birth defect in which the infant's intestines, liver, and occasionally other organs remain outside the abdomen in a sac. Omphaloceles result from the failure of the abdominal muscles to develop properly.

Organelle—A specialized subunit within a cell.

Peptidase—Any enzyme that breaks down proteins. The gene whose mutations cause CODAS syndrome codes for a peptidase enzyme. Peptidases are also called proteases.

Ptois—Drooping or falling of the upper or lower eyelid.

Scoliosis—Abnormal curvature of the spine, usually defined as greater than 10 degrees to the right or left as the doctor faces the patient.

LONPI gene on chromosome 19 at 19p13.2. This gene encodes an enzyme called lon peptidase 1, which helps to remove damaged proteins from the mitochondria of cells and thus maintain quality control of the proteins produced in the cell. Lon peptidase 1 is also thought to play a role in regulating gene expression. Although mutations in the *LONPI* gene have been identified as the cause of CODAS syndrome, it is not yet clear how these mutations cause the specific signs and symptoms of the syndrome.

CODAS syndrome is inherited in an autosomal recessive pattern, which means that two copies of the mutated *LONPI* gene, one from each parent, are required for the symptoms of the syndrome to appear.

Demographics

CODAS syndrome affects fewer than one person per million. As of 2010, only four cases had been reported worldwide, one each in France, Brazil, and western Canada, in addition to the original patient in Canada. The geneticists in Pennsylvania discussed their findings of four different *LONPI* mutations in ten patients, who included the two Canadian children identified by 2010, as well as eight Amish children from six different Old Order Amish families in southeastern Pennsylvania. The total number

of children identified as having the syndrome between 1991 and 2015 was only 12, which suggests that CODAS syndrome is extremely rare. In 2019, two Korean siblings were diagnosed with CODAS syndrome, bringing the total number of cases to 14 as of 2021.

Although 9 of these 14 patients are of Amish/Swiss or German/Mennonite heritage, the Korean siblings are of full Korean heritage, the Brazilian patient is of Portuguese ancestry, the French patient's parents immigrated from Morocco, and the remaining Canadian patient is of mixed European ancestry. Therefore, it is difficult to determine whether the syndrome may occur in people of other racial or ethnic groups. It is known, however, that males and females are equally affected.

Signs and symptoms

The signs and symptoms of CODAS syndrome are as follows, grouped according to the organ or body system involved:

- **Cerebral:** Delayed motor development, cognitive impairments, and underdevelopment of the corpus callosum, a band of nerve fibers in the brain that connects the two cerebral hemispheres.

- Ocular: Congenital cataracts, epicanthal folds, drooping eyelids (ptosis), and cross-eyes.
- Facial: Abnormal facial features include a grooved or abnormally short nose, an overly broad forehead, and a flattened midface.
- Dental/oral: Delayed eruption of baby teeth, abnormally shaped teeth with protrusions from the enamel, excessive salivation, and difficulty swallowing. Some patients also lack vocal cords.
- Auricular: Ears that are folded, crumpled, or flattened against the skull, and hearing loss that appears after the first few months of life.
- Skeletal: Short stature, abnormally shaped spinal vertebrae, scoliosis, hip displacement, delayed ossification of the long bones in the legs, hypotonia, excessive mobility in the joints, abnormally short finger bones, and development of knock knees or feet turned too far outward in later childhood.

Other symptoms found in some (though not all) children with CODAS syndrome include cryptorchidism (undescended testicles) in male infants, an abnormal passage (fistula) between the rectum and vagina in female infants, seizures, heart defects, structural abnormalities in the urinary tract, an abnormal opening in the abdominal wall that allows the liver and intestines to protrude (omphalocele), and an imperforate (closed) anus.

Diagnosis

In the early cases, the diagnosis of CODAS syndrome was made after the child's birth on the basis of the child's clinical features. Single-gene testing for mutations in the *LONP1* gene has been available since 2018.

Treatment and management

Treatment of patients with CODAS syndrome is essentially supportive, as many patients do not survive early infancy. Some of the skeletal abnormalities may be corrected by surgery in selected patients.

Families of Old Order Amish or Mennonite heritage who are concerned about the possibility of CODAS syndrome occurring in their children can consult the Windows of Hope Project in Ohio or the Clinic for Special Children in Pennsylvania. These organizations specialize in genetic counseling and testing for families from these faith communities. In fact, two of the geneticists who contributed to the study that was published in January 2015 were staff members of the Clinic for Special Children.

Prognosis

The prognosis of patients with CODAS syndrome is poor. Generalizations are difficult, however, because so few patients with the syndrome have been identified. Some

QUESTIONS TO ASK YOUR DOCTOR

- Have you ever referred a family to the Clinic for Special Children or another genetic counseling service?
- Do you think that the discovery of the association of a specific gene with CODAS syndrome will lead to identification of more cases of the syndrome?
- Do you think that researchers may eventually develop a cure for CODAS and other very rare genetic syndromes?

infants with the syndrome die shortly after birth due to obstruction of the airway, while others are stillborn. Some of the Pennsylvania patients required tube feeding in order to survive the first few days of life. One patient lived to the age of 14 but was killed in an accident. The Korean siblings have benefited from five years of intensive rehabilitation.

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American Academy of Ophthalmology (AAO), PO Box 7424, San Francisco, CA 94120-7424, (415) 561-8500, (415) 561-8533, <http://www.aao.org>

Clinic for Special Children, 535 Bunker Hill Rd., Strasburg, PA 17579, (717) 687-9407, (717) 687-9237, queries@clinicforspecialchildren.org, <https://clinicforspecialchildren.org>

National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Dr., MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, (301) 402-2218, <http://www.genome.gov>

New Leaf Center Clinic for Special Children, PO Box 336,
16014 E. Chestnut Street, Mt. Eaton, OH 44659, (330)
359-9888, <http://newleafclinic.org/>

Office of Rare Diseases Research (ORDR), National Center for
Advancing Translational Sciences (NCATS), 6701
Democracy Blvd., Suite 1001, MSC 4874, Bethesda, MD
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Rebecca J. Frey, PhD

Coffin-Lowry syndrome

Definition

Coffin-Lowry syndrome (CLS) is an inherited syndrome characterized by intellectual disability, slow growth, distinctive facial appearance, large soft hands, loose joints, skeletal changes, and low muscle tone (hypotonia). Full expression of the disorder is seen only in males, although females may have some of the physical features and learning disability.

Description

Coffin-Lowry syndrome is one of a large number of intellectual disability syndromes caused by abnormalities (mutations) of genes on the X chromosome. The pattern of physical findings, combined with mental disability,

KEY TERMS

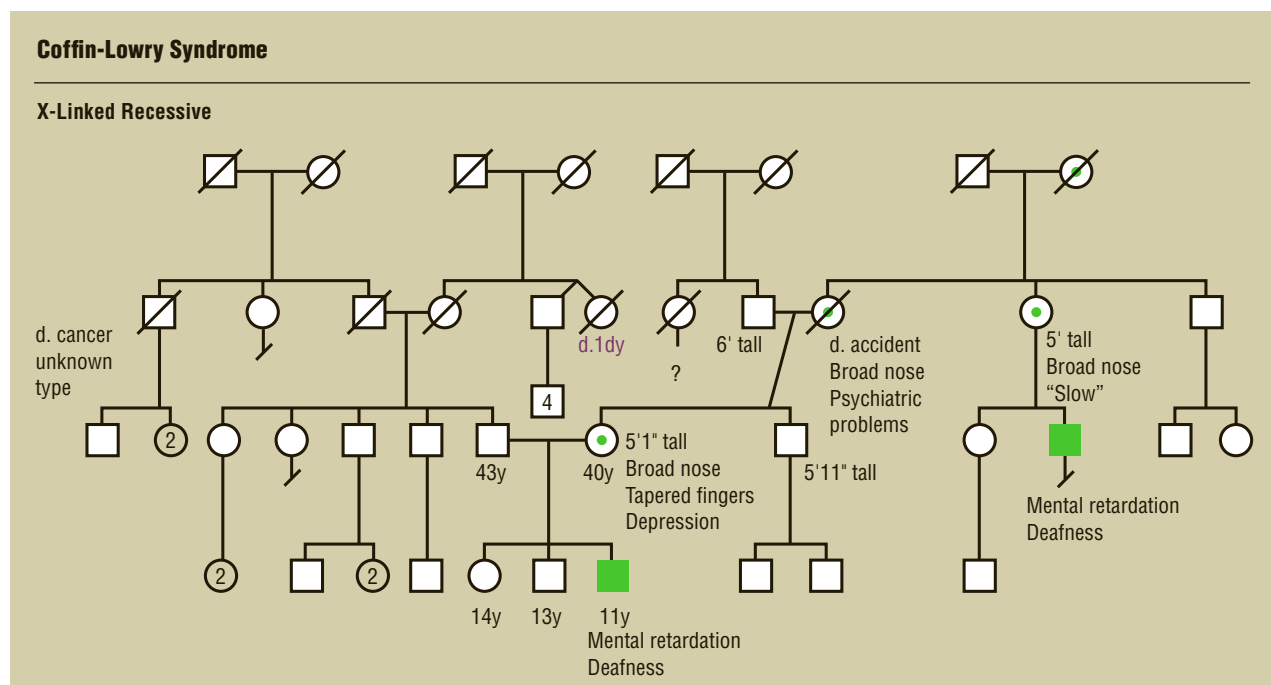
Intellectual disability—Significant impairment in intellectual function and adaptation in society. Usually associated with an intelligence quotient (IQ) below 70.

X-linked—Located on the X chromosome, one of the sex chromosomes. X-linked genes follow a characteristic pattern of inheritance from one generation to the next.

makes the condition readily recognizable, and its frequency makes it one of the most well-known X-linked intellectual disability syndromes. Although CLS was initially considered to be two separate syndromes, Coffin syndrome and Lowry syndrome, the two entities were recognized as the same disease in 1975. Coffin-Lowry syndrome may also be called intellectual disability with osteocartilaginous abnormalities.

Genetic profile

Coffin-Lowry syndrome is caused by mutations in the *RPS6KA3* gene. Located on the short arm of the X chromosome, the *RPS6KA3* gene provides instructions for making a protein that plays an important role in the development and function of the brain and the signal



Coffin-Lowry syndrome: pedigree analysis chart. (Gale)

pathways required for learning, long-term memory, and nerve cell maintenance.

Demographics

Coffin-Lowry syndrome appears to occur in all populations. The full syndrome is seen in males with lesser expression in carrier females. Coffin-Lowry syndrome is estimated to have a prevalence range of 1 in 40,000–50,000.

Signs and symptoms

Although the characteristics of Coffin-Lowry change with age, some manifestations are present from birth. Low muscle tone (hypotonia) and distinctive facial features that include prominent forehead, increased space between the eyes, forward direction of the nostrils, arching of the upper lip, and simple ear structure may be present in infancy. With the passing years, the face elongates, the ears become notably large, the lips and nasal structures thicken, and the mouth is usually open and agape. The hands are large and soft with thick fingers that narrow at their ends. The central part of the chest may bow outward, the spine may curve abnormally (kyphoscoliosis), the knees become flexed, and the feet become flat.

Microcephaly is common, and cardiac abnormalities may be present. Approximately 20% of individuals with Coffin-Lowry syndrome may suffer from episodes of brief collapse with no loss of consciousness called stimulus-induced drop attacks (SIDAs). Triggered by unexpected tactile stimulation, sounds, or excitement, SIDAs typically begin between mid-childhood and the teens.

Growth is slow, as manifest by low birth weight, a small head, and short stature during childhood and adult life. All developmental milestones in infancy and childhood are delayed, and intellectual function is severely impaired.

Female carriers consistently manifest milder characteristics such as short stature, increased space between the eyes, thick nasal tissues, prominent lips, and soft fleshy hands with thick fingers. Intellectual function may be normal or mildly impaired.

Diagnosis

The diagnosis is usually based on the presence of the distinctive facial appearance and intellectual disability. In many cases there will be a family history of other affected males or carrier females. X-rays may show a number of minor features including delayed maturation of the bones, expansion at the ends of the bones of the digits, notching of the bones of the spine, and narrowing of the space between the bones of the spine.

QUESTIONS TO ASK YOUR DOCTOR

- One of my cousins had a child with Coffin-Lowry syndrome. How likely is it that one of my children will be born with the disorder?
- How early is a child with Coffin-Lowry diagnosed with the disease, and what features lead to this diagnosis?
- What kinds of problems will parents of a Coffin-Lowry child have to deal with during his or her lifetime?
- Is a child with Coffin-Lowry syndrome expected to live a normal lifespan? If not, at what age is he or she likely to die?

Molecular genetic testing of *RPS6KA3*, the only gene with mutations known to cause Coffin-Lowry syndrome, can be used to confirm the diagnosis of typical Coffin-Lowry syndrome. This genetic testing cannot, however, be used to rule out the diagnosis because only 25%–40% of individuals with Coffin-Lowry syndrome will have an observable mutation in the *RPS6KA3* gene. Some people with the features of Coffin-Lowry syndrome do not have identified mutations in the *RPS6KA3* gene. In these cases, the cause of the condition is unknown, and diagnosis will be made based on clinical symptoms.

Treatment and management

There is no cure for Coffin-Lowry syndrome, but associated conditions may require treatment. Orthopedic intervention may be required to remediate complications from kyphoscoliosis. Antiepileptic medications may be needed to treat stimulus-induced drop attacks. Because of severe intellectual disability, lifelong supervision is generally required. Developmental progress can be promoted by early intervention, speech therapy, and physical therapy.

Prognosis

Long-term survival is the expectation; however, complications from cardiac anomalies, progressive kyphoscoliosis, and severe intellectual disability may shorten the person's lifespan.

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ORGANIZATIONS

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Coffin-Siris syndrome

Definition

Coffin-Siris syndrome is a rare congenital disorder that affects more females than males. Individuals with this syndrome have some degree of intellectual disability or developmental delay, a coarse facial appearance, incompletely formed or absent fifth fingernails, and absent fifth fingers (distal phalanges). Coffin-Siris syndrome is caused by mutations in any of several genes; therefore, the specific symptoms and their severity vary greatly.

Description

Coffin-Siris syndrome was first described in 1970 by Dr. Grange S. Coffin and Dr. Evelyn Siris. It is sometimes known as fifth digit syndrome. All affected children have some degree of intellectual disability or developmental delay and incompletely formed (hypoplastic) or absent fifth fingernails and tips of the fifth fingers (distal phalanges).

KEY TERMS

Consanguinity—A mating between two people who are related to one another by blood.

Hirsutism—The presence of coarse hair on the face, chest, upper back, or abdomen in a female as a result of excessive androgen production.

Hypoplasia—Incomplete or underdevelopment of a tissue or organ.

Hypotonia—Reduced or diminished muscle tone.

Karyotype—A standard arrangement of photographic or computer-generated images of chromosome pairs from a cell in ascending numerical order, from largest to smallest.

Phalanges—Long bones of the fingers and toes, divided by cartilage around the knuckles.

There are some reports of fingers other than the fifth being affected, as well as affected toes and toenails. The face of a child with Coffin-Siris syndrome is usually described as coarse. This includes a flat nasal bridge, broad nose, wide mouth, thick lips, and, in some cases, thick eyebrows, long eyelashes, palate malformations, a large tongue (macroglossia), and a small head (microcephaly). While some infants have an abnormal facial appearance, most of the facial features become more prominent as the child grows. Typically, there is sparse scalp hair in the infant and excessive growth of body hair (hirsutism). Reduced muscle tone (hypotonia), lax joints, delay in bone maturation, and short stature are commonly found. There are reports of frequent upper respiratory and ear infections. Occasionally, children with this disorder have cardiac or spinal abnormalities, hernias, vision or hearing problems, or delayed tooth development (dentition).

Infants with Coffin-Siris syndrome typically have sucking problems and feeding difficulties that may continue as they age. The extent of growth and intellectual disability varies by individual. Intellectual disability is usually reported as moderate. There are delays in motor activities such as rolling over, sitting up, and walking. Speech is usually delayed. Most children are more capable of responding to speech than verbally expressing themselves.

Genetic profile

Coffin-Siris syndrome is caused by mutations in *ARID1A*, *ARID1B*, *SMARCA4*, *SMARCB1*, or *SMARCE1* genes. Each of these genes produces a different portion or subunit of SWI/SNF protein complexes. These protein complexes regulate gene activity by affecting the way DNA and

protein are packaged into chromosomes, a process known as chromatid remodeling. Therefore, SWI/SNF protein complexes affect many different activities, including repairing and copying DNA and controlling the growth, differentiation, and maturation of cells. Thus, defects in any of the proteins in the complexes can have many and varied effects on human growth and development.

Most cases of Coffin-Siris syndrome are sporadic, or random, rather than inherited from a parent. The gene mutations most likely occur during early embryonic development. However, there are some apparently inherited cases of affected siblings and parental relatedness (consanguinity). Coffin-Siris syndrome appears to be an autosomal dominant trait, meaning that one copy of the mutated gene is sufficient to cause the disorder, even in the presence of a second normal gene copy.

Demographics

Coffin-Siris syndrome is very rare, although, as of 2021, 148 cases had been reported in the medical literature. It is more common in females than in males.

Signs and symptoms

At birth, infants with Coffin-Siris syndrome have an absence or incomplete formation of the fifth fingernail and tip of the fifth finger (distal phalanx). Other fingers or toes may also be absent. Infants may have an abnormal facial appearance at birth. As the child grows, the facial abnormalities characteristic of Coffin-Siris syndrome become more apparent. Sparse scalp hair in an infant usually becomes denser with age and excessive hair growth (hirsutism) develops. Infants typically have sucking problems and feeding difficulties that may continue with age.

There is a delay in both gross and fine motor skills. Developments such as sitting up and walking may be delayed or not possible, depending upon the severity of the disorder. Speech is usually delayed, and most children are better able to respond to language than express it. Some older children are able to form short sentences and answer simple questions. Intellectual disability is usually moderate. Social adaptation is usually delayed.

Diagnosis

Diagnosis of Coffin-Siris syndrome may be based upon clinical findings; however, these may overlap with a number of other syndromes. The combination of symptoms such as coarse facial appearance, fifth finger appearance, and developmental delay suggest Coffin-Siris syndrome. X-ray of the hands to reveal the absence of

QUESTIONS TO ASK YOUR DOCTOR

- What characteristic physical and mental features are associated with Coffin-Siris syndrome?
- Is genetic testing available for this disorder, and what information will testing provide?
- What kinds of medications, surgery, and other procedures are available for the treatment of Coffin-Siris syndrome?
- To what extent can a child with Coffin-Siris syndrome be expected to live a normal life during childhood, adolescence, and adulthood?

the fifth finger bone may be the best indicator of this syndrome. Genetic testing can reveal mutations in genes responsible for Coffin-Siris syndrome. Neonatal ultrasounds for cardiac, kidney (renal), and other malformations that may be present with this disorder can also be informative.

Prenatal ultrasound may show intrauterine (occurring within the uterus) growth retardation and reveal the condition of the fifth finger. These symptoms alone cannot conclusively lead to a prenatal diagnosis of Coffin-Siris syndrome, but prenatal genetic testing is possible if the disorder is suspected.

With the identification of gene mutations resulting in Coffin-Siris syndrome, it is expected that diagnostic criteria will become much more precise.

Treatment and management

The treatment or therapy required for children with Coffin-Siris syndrome is based on the particular symptoms of each individual. Some children may require surgery to repair malformations, ranging from cleft palate repair to cardiac, renal, or other surgery. Speech therapy and special education may be required, depending upon the degree of intellectual disability, developmental delay, and motor impairment.

Prognosis

Infants born with Coffin-Siris syndrome may experience a delay or absence of motor and mental abilities, but with appropriate support they can live into adulthood. The prognosis for an individual with Coffin-Siris syndrome depends largely on the degree of intellectual disability and developmental delay.

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- Office of Rare Diseases Research, National Center for Advancing Translational Sciences, National Institutes of Health, 6701 Democracy Blvd., Suite 1001, MSC 4874, Bethesda, MD 29892, (301) 402-4336, (301) 480-4655, idr@nih.gov, <https://rarediseases.info.nih.gov>

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Cohen syndrome

Definition

Cohen syndrome is a very rare genetic disorder characterized by infantile hypotonia (a weakening of the skeletal muscles), childhood obesity, and several malformations. It is caused by mutations in the *VPS13B* gene, often called the *COH1* gene.

Description

Cohen syndrome was first described in 1973 by Dr. M. M. Cohen, Jr., in three children with distinct physical and developmental characteristics. Since then, several hundred cases have been reported throughout the world, offering a picture of an extremely rare disease with a wide range of clinical characteristics. The initial description given by Cohen included obesity, intellectual disability, poor muscle tone, narrow hands and feet, and distinctive facial features with prominent upper central teeth. Mutations in the *VPS13B* gene are the only known cause of Cohen syndrome. The exact function of this gene is unknown, but it is active (turned on) in most cells of the

body and so is assumed to have an important role in cellular functioning. It may be involved in sorting, transporting, and/or processing proteins within the cell.

Cohen syndrome has also been referred to as Pepper syndrome, Cervenka syndrome, hypotonia-obesity-prominent incisors syndrome, obesity-hypotonia syndrome, and Mirhosseini-Holmes-Walton syndrome.

Genetic profile

The *VPS13B* gene is located on the long arm (q) of chromosome 8 at position 22.2.

Chromosomes are the genetic material passed down from generation to generation. Each chromosome is composed of genes that code for proteins and other regions of DNA that have important functions in the body. A person inherits one copy of each of the 23 chromosomes from the mother's egg, and one copy of each from the father's sperm, so that each cell in the body has two nonidentical copies of each gene.

Cohen syndrome is an autosomal recessive disorder. Recessive means that both copies of the *VPS13B* gene must have a change or mutation for a person to develop Cohen syndrome. An individual with only one mutated *VPS13B* gene will not be affected by the disorder, but each of that person's offspring has a 50% chance of inheriting the mutated gene. These individuals are called carriers. If two carriers have a child together, there is a 25% chance with each pregnancy of having a child affected by the syndrome. At least 73 different mutations in *VPS13B* are known to result in Cohen syndrome. Most of these mutations result in a shortened nonfunctional protein.

Demographics

Fewer than 1,000 cases of Cohen syndrome have been reported worldwide. Due to the extreme rarity of the disease, the exact incidence of Cohen syndrome is not known.

Although Cohen syndrome affects both males and females of all races and genders, different *VPS13B* gene mutations commonly occur in some populations, with different signs and symptoms. Thus, certain clinical findings are family- or ethnicity-specific. For example, Cohen syndrome has been studied extensively in Finland. In the populations studied, individuals diagnosed with the syndrome typically have fewer white blood cells than normal (granulocytopenia), a specific eye abnormality called mottled retina, and intellectual disability. As a rule, they do not have truncal obesity, a common characteristic of Cohen syndrome in other populations. Although the symptoms of Cohen syndrome are known to vary widely between affected individuals within the same family,

affected people within the Finnish populations are very similar to each other in their presentation.

Signs and symptoms

Four main areas are affected by Cohen syndrome: physical appearance, mental function, vision, and hematology (blood function). The list of possible abnormalities and conditions is extensive, however, and each case is different. Even common characteristics of Cohen syndrome are not always present.

Physical appearance

At birth, babies with Cohen syndrome usually appear normal, although they typically have low birth weight. As the babies grow, the various physical signs associated with the syndrome become increasingly obvious.

Narrow hands and feet with long, slender fingers are a hallmark feature, found in approximately 89% of diagnosed individuals. Truncal obesity, or the abnormal deposition of fat around the mid-section of the body, has been observed in roughly 70% of patients. Most individuals with Cohen syndrome have large and rather noticeable front teeth, referred to as prominent upper central incisors. In general, the teeth are abnormal in shape and position. A majority of individuals with Cohen syndrome are also short, with many experiencing growth deficiencies at all stages of life. Microcephaly (a small head) is another common feature of the syndrome.

In addition, there are many other associated physical characteristics that occur less often. The palate (roof of the mouth) may be overly high, arched, and narrow. The mid-face can have an underdeveloped appearance, and the area between the nose and the upper lip (the philtrum) may be very short. The eyes can be down-slanting, and thick hair and eyebrows may be observed.

Mental dysfunction

It is thought that every individual with Cohen syndrome experiences some level of developmental delay. Intellectual disability can range from mild to severe. From infancy, many children are obviously behind in developmental milestones and are not able to sit up or roll over within the same time frame as their peers.

Most children with Cohen syndrome do learn to walk, although there have been a few reported cases of individuals who were wheelchair-bound. There is usually a noticeable delay, with affected children not learning to walk independently until much later than their peers (the normal average age for walking independently is 12 months).

Language deficiencies are also a common occurrence. Many affected individuals never learn to talk or have a vocabulary limited to a few single words and

KEY TERMS

Astigmatism—A cause of poor eyesight, usually due to a refractive error caused by an irregularly shaped cornea.

Autism—A syndrome characterized by a lack of responsiveness to other people or outside stimulus, often in conjunction with a severe impairment of verbal and nonverbal communication skills.

Autosomal—Referring to a chromosome other than the X or Y sex chromosomes.

Coloboma of the iris—A birth defect leading to missing structures within the eye.

Granulocytopenia—A reduced number of white blood cells in the circulation.

Hypotonia—Reduced or diminished muscle tone.

Leucopenia—A decrease in white blood cells.

Microphthalmia—Small or underdeveloped eyes.

Mottled retina—Changes in the retina of the eye causing a loss of visual acuity.

Myopia—Nearsightedness; difficulty seeing objects that are far away.

Neutropenia—A condition in which the number of leukocytes (a type of white or colorless blood cell), especially neutrophils, is abnormally low.

Philtrum—The center part of the face between the nose and lips that is usually depressed.

Retinal dystrophy—Degeneration of the retina, causing a decline in visual clarity.

VPS13B—A gene that is active in most cells of the body; mutations in *VPS13B* are responsible for Cohen syndrome.

two-word phrases. In general, an IQ of less than 50 is considered average for Cohen syndrome.

Visual deficiencies

Vision is affected to varying degrees. Severe limitation in eyesight due to myopia is often observed. Several other dysfunctions and defects of the eyes causing low visual clarity have been reported, including retinal dystrophy, strabismus, astigmatism, microphthalmia, and coloboma of the iris.

Hematologic abnormalities

Cohen syndrome can have a profound effect on the composition of the blood. Abnormally low counts of

white blood cells, referred to as granulocytopenia, were once thought to be a standard symptom. It was hoped that this would assist in early diagnosis because it can be tested for at birth. However, further studies have shown that not all affected individuals suffer from granulocytopenia. Some individuals have no blood disorders associated with their disease at all, while others have various forms of white blood cell problems, such as a reduction in the number of white blood cells (leucopenia) or specialized white blood cells called neutrophils (neutropenia).

Other deficiencies

Hypotonia, or low muscle tone, is found in 90%–100% of persons diagnosed with Cohen syndrome. Babies with hypotonia are described as “floppy” due to their lack of muscle strength. Although the observed hypotonia is not thought to be associated with any nervous system disorder, it does delay the overall development of the child, most notably slowing the development of motor skills.

Social skills

Many studies have described Cohen syndrome patients as being outgoing and friendly with mild hyperactivity and severe attention deficits. There are a few reports of diagnosed individuals showing signs of autism, an extreme form of centering attention and interest on one’s self alone.

Diagnosis

In 1972, Dr. Mirhosseini and others described two patients with symptoms similar to those observed in Cohen syndrome. These patients and a few subsequent cases were given a diagnosis of Mirhosseini-Holmes-Walton syndrome. Over the years, scientific opinion has come to consider Mirhosseini-Holmes-Walton syndrome and Cohen syndrome as different manifestations of the same disease.

Diagnosis of Cohen syndrome is difficult due to the varied nature of the symptoms and a lack of consensus about diagnostic criteria. Most features of Cohen syndrome are not evident in the newborn, and many symptoms, such as truncal obesity and visual deficits, are not easily observed until early childhood. In the past, the average age of diagnosis was approximately 6–8 years. However, as physicians become more aware of the disorder, it is hoped that diagnosis will occur at earlier ages, offering affected individuals the opportunity for early intervention and treatment.

Incorrect diagnosis is not uncommon in patients with Cohen syndrome. Affected individuals may be

QUESTIONS TO ASK YOUR DOCTOR

- How is Cohen syndrome inherited?
- Should family members be screened for *VPS13B* gene mutations?
- Is prenatal screening available for Cohen syndrome?
- How early can Cohen syndrome be diagnosed, and how is the diagnosis made?
- What treatments are available for a child born with Cohen syndrome?

misdiagnosed with Marfan syndrome, Sotos syndrome, hypothyroidism, Prader-Willi syndrome, or intellectual disability of an unknown nature.

A correct and early diagnosis is important to ensure a favorable prognosis for the patient, as well as for genetic screening of the child and family members, and genetic counseling concerning the risks involved in future pregnancies.

Treatment and management

There is no cure for Cohen syndrome. Treatment is focused on improving or alleviating symptoms as they arise.

Early correction of vision problems, usually with glasses, often leads to general improvement in cognitive skills, an area of marked deficit in affected individuals.

As is the case for many disorders involving hypotonia and slowed development, physical and occupational therapies are invaluable tools. These treatment strategies are important at any age, but they should be started as early as possible. There is no need to wait for a definitive diagnosis of Cohen syndrome, since any child with hypotonia can benefit from physical and occupational therapy.

Prognosis

Varying symptoms lead to varying prognoses. Intellectual disability can range from mild to severe. However, there is no way to predict the level of developmental delay a specific child will experience. Language deficiencies also vary a great deal, with some children never learning to speak at all and others speaking in complete sentences. The hypotonia observed in infancy may persist, and moderate obesity usually develops in mid-childhood.

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Cole-Carpenter syndrome

Definition

Cole-Carpenter syndrome is a very rare subtype of osteogenesis imperfecta (OI), a group of congenital bone disorders characterized by abnormal bone development (bone dysplasia) resulting from a defective protein in the body's connective tissue. OI is also known as brittle bone disease and fragile bone disease because patients with the disorder are susceptible to frequent bone fractures, as well as various deformities of the skeletal and facial bones. Cole-Carpenter syndrome is distinguished from the more common forms of OI by its genetic profile and by several additional signs and symptoms. It is named for the two American pediatricians who first described it in 1987.

Description

In general, patients with OI suffer from deformities of the long bones; bones that are fragile and easily broken; bluish discoloration of the sclerae (whites of

the eyes); loose joints and poor muscle tone (hypotonia); abnormal curvature of the spine (scoliosis); and a tendency to bruise easily. The severity of these symptoms varies among individuals with the same subtype, as well as between the various recognized subtypes. Some subtypes of OI are characterized by hearing loss in early childhood and failure of the teeth to develop normally.

All forms of OI result from a deficiency of type I collagen. Type I collagen is a protein that forms the long fibers needed for creation of connective tissue in tendons, ligaments, the dermis (the layer of tissue that underlies the skin), and the organic part of bone. Some subtypes of OI are caused by genetic mutations that reduce the quantity of type I collagen produced in the child's body. Other subtypes are caused by mutations that affect the quality of the collagen produced. In Cole-Carpenter syndrome, the child's type I collagen is normal in terms of quality but insufficient in terms of quantity.

The alternate name of Cole-Carpenter syndrome—bone fragility with craniosynostosis, ocular proptosis, hydrocephalus, and distinctive facial features—is derived from the physical characteristics that distinguish the syndrome from other types of OI.

- **Craniosynostosis:** This term refers to an abnormal development of the infant's skull as a result of premature ossification (bone formation) of the fibrous joints between the bones of the skull known as sutures. If these sutures turn to bone shortly after birth, the child's skull may swell on one side of the head or develop another abnormal shape, and the facial features may also be pulled out of their normal alignment by the abnormal growth of the skull.
- **Ocular proptosis:** This term refers to the outward protrusion (bulging) of the patient's eyes.
- **Hydrocephalus:** Hydrocephalus is sometimes referred to as "water on the brain." It results from the accumulation of excess cerebrospinal fluid within the brain. It can cause progressive enlargement of the head in young children, as well as various neurological symptoms.
- **Distinctive facial features:** Children with Cole-Carpenter syndrome have facial deformities that are not found in other types of OI. These deformities include an abnormally small or underdeveloped jaw (micrognathia), an unusually prominent forehead (frontal bossing), and underdevelopment (hypoplasia) of the midface (the area of the face surrounding the nose and cheekbones).

KEY TERMS

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a nonsex chromosome is required for a disease or inherited trait to develop in an individual.

Autosomal recessive—A pattern of inheritance in which two copies of a defective gene on a nonsex chromosome must be present for a disease or inherited trait to develop in an individual.

Autosome—Any human chromosome other than a sex chromosome.

Collagen—The primary structural protein in the connective tissue in the human body.

Cranial suture—Any of the fibrous joints in the skull that hold the bones of the skull together.

Craniosynostosis—A condition in which one or more of the fibrous joints in an infant's skull turns to bone prematurely. As the child's head continues to grow, the growth pattern of the skull is affected, resulting in a misshapen head and often deformed facial features.

De novo mutation—A genetic mutation that is not inherited from either parent.

Dysplasia—A general medical term for an abnormality of development.

Frontal bossing—The medical term for an unusually prominent forehead, often associated with an abnormally heavy brow ridge.

Hydrocephalus—A condition in which there is an abnormally large amount of cerebrospinal fluid in the brain. In young children, the increased pressure resulting from the fluid accumulation may lead to enlargement of the child's head.

Kyphosis—Abnormal outward curvature of the spine resulting in a hunchback.

Micrognathia—The medical term for an undersized or underdeveloped jaw.

Ossification—The process of bone formation.

Proptosis—Bulging of the eye outward from the orbit of the eye. It is also known as exophthalmos.

Sclera (plural, sclerae)—The medical term for the white of the eye.

Scoliosis—Abnormal curvature of the spine, usually defined as greater than 10 degrees to the right or left as the doctor faces the patient.

Wormian bones—Extra pieces of bone that sometimes occur within one or more of the cranial sutures.

Genetic profile

As of 2021, Cole-Carpenter syndrome had been divided into three subtypes. The first two, CLCRP1 and CLCRP2, were identified on the basis of two different genes whose mutations had been identified as causing the syndrome. CLCRP1 is caused by mutations in the *PH4B* gene on chromosome 17 at 17q25.3. This mutation was identified in February 2015. In one of the two original cases described by Cole and Carpenter in 1987, the mutation was inherited from the patient's father; in the other patient, the mutation was *de novo* (new).

CLCRP2 is caused by mutations in a different gene, the *SEC24D* gene on chromosome 4 at 4q26. All three known cases of CLCRP2 involve inherited mutations. The third subtype is caused by a mutation in the cartilage associated protein (CRTAP) [set gene name in italics] gene on the short arm of chromosome 3 at 3p22.3.

The first two subtypes of Cole-Carpenter syndrome are inherited in an autosomal dominant pattern, which

means that only one copy of the defective gene is needed to produce the disorder in the affected child.

Demographics

Cole-Carpenter syndrome is a very rare form of OI. While the more common forms of OI affect about 1 person in every 20,000 to 1 in every 60,000, Cole-Carpenter syndrome is thought to develop in fewer than one person in a million. Only 12 cases had been reported worldwide as of 2021: nine cases of CLCRP1 and three cases of CLCRP2. Males and females appear to be equally affected. As far as is known, all racial and ethnic groups are equally susceptible. The worldwide distribution of Cole-Carpenter syndrome was unknown as of 2021 because the disorder is so rare. Of the 12 known cases, five were reported in Germany, two in the United States, one in China, one in Thailand, one in the United Kingdom, one in Australia, and one in India.

Signs and symptoms

Craniosynostosis, ocular proptosis, hydrocephalus, and distinctive facial features distinguish Cole-Carpenter

syndrome from other forms of OI. Other signs and symptoms of the syndrome are as follows:

- abnormally shaped vertebrae in the spinal column (90% of patients)
- abnormally shaped ribs (90%)
- blue sclerae (90%)
- abnormal vocal quality (90%)
- bowing of the long bones in the arms and legs (90%)
- low bone mineral density (90%)
- delayed eruption of baby teeth (90%)
- short stature (90%)
- kyphosis (50%)
- hypotonia (50%)
- intrauterine growth retardation (50%)
- Wormian bones (50%)

Diagnosis

Diagnosis of Cole-Carpenter syndrome, like other forms of OI, can be made before birth by ultrasound imaging that reveals bone fractures, growth retardation, or deformation of the long bones. Amniocentesis or chorionic villus sampling may be performed to test for the genetic mutations associated with the syndrome.

Diagnosis of the syndrome after birth is based on clinical examination of the infant's physical characteristics together with blood and tissue samples. A tissue sample can be analyzed to determine whether the child's type I collagen is normal. A blood test can be used to detect the presence of the genetic mutations known to cause CLCRP1 and CLCRP2. As of 2021, however, only two laboratories offered molecular genetic testing specifically for Cole-Carpenter syndrome: the Institute of Human Genetics in Germany and Connective Tissue Gene Tests in the United States.

Treatment and management

There is no cure for Cole-Carpenter syndrome or for any other form of OI. Treatment is focused on maintaining the individual's bone strength and preventing new fractures. In general, OI is treated with a combination of braces, physical therapy, and surgery, depending on the severity of each patient's symptoms. Plastic braces and inflatable suits were used as of 2021 to prevent accidental bone fractures, particularly in very young children. Physical therapy is intended to strengthen the individual's weight-bearing bones and joints, improve mobility, and maintain muscle strength. Hydrotherapy—physical therapy in a pool or other body of water—is particularly beneficial because it lowers the risk of fractures during exercise sessions. Surgery may involve the insertion of

QUESTIONS TO ASK YOUR DOCTOR

- Are there any benefits to genetic testing for *de novo* mutations for such rare disorders as Cole-Carpenter syndrome?
- What resources are available to the parents of children with this disorder?
- Can children with Cole-Carpenter syndrome enjoy a reasonably good quality of life?
- Do you think that researchers will discover other genes that cause this disorder?

metal rods in the long bones or procedures to correct malformations of the spinal column.

Medications may be given to patients with OI to treat bone infections (antibiotics in most cases) or to strengthen the bones. Bisphosphonates (a class of drugs that prevent the loss of bone mass) have been tried in some patients with OI to lower the risk of fractures, but the results indicate that these drugs are more helpful in children with OI rather than adults with the condition.

Most patients with OI will eventually need to use such assistive devices as canes, wheelchairs, splints, and grabbing arms to carry out their daily activities. They will also usually need to have their homes or apartments evaluated for the risk of falls or other accidents, and modified with handrails, nonslip rugs, improved lighting, furniture rearrangement, and bathroom redesign.

Prognosis

The prognosis for Cole-Carpenter syndrome is guarded at best. It is significant that two of the 12 cases reported to date were diagnosed after the pregnancies had been terminated, when prenatal diagnosis indicated the presence of multiple bone fractures and bowing of the long bones. While mental development in the patients who have been followed since birth appears to be normal, physical development is severely affected. A follow-up study of the two patients first identified by Cole and Carpenter in 1987 reported that the young men, 18 at the time of the follow-up, were confined to wheelchairs. They have unusually short stature, severe scoliosis, noticeable deformities of the arms and legs, and low bone mineral density.

Although the number of patients identified with Cole-Carpenter syndrome is too small to allow much generalization, it is likely that the disorder shortens the patient's life expectancy, as children with other forms of OI have reduced life expectancy because of the

possibility of fatal bone fractures, breathing difficulties caused by deformities of the spine and rib cage, and complications caused by infections.

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American Academy of Pediatrics (AAP), 345 Park Boulevard, Itasca, IL 60143, (847) 434-4000 or (800) 433-9016, (847) 434-8000, <https://www.aap.org/en-us/Pages/Default.aspx>

Children's Brittle Bone Foundation (CBBF), PO Box 619, Zion, IL 60099, (773) 236-2223, webmaster@cbbf.org, <http://www.cbbf.org/home-page>

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National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS), 6701 Democracy Blvd., Suite 1001, MSC 4874, Bethesda, MD 20892, (301) 402-4336, (301) 480-9655, ordr@nih.gov, <https://rarediseases.info.nih.gov>

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Rebecca J. Frey, PhD

Colitis

Definition

Colitis is a serious, chronic or long-lasting, inflammatory bowel disease (IBD) that is characterized by inflammation and sores on the innermost lining of the large intestine—the colon and rectum.

Description

The two types of colitis—ulcerative colitis (UC) and microscopic colitis—along with Crohn's disease, are the most common IBDs. UC is characterized by open sores (ulcers) on the lining of the colon and rectum that may bleed or produce mucus or pus, as well as by inflammation that causes diarrhea. UC is painful and may lead to potentially life-threatening complications, including malnutrition.

Microscopic colitis is an inflammation of the colon that causes persistent watery diarrhea, and can only be identified by examining colon tissue under a microscope.

UC often runs in families, and susceptibility to the disorder appears to be inherited; nevertheless, most people with UC do not have a family history of the disease. Along with a genetic susceptibility, poor immune system functioning and environmental factors appear to be involved in the development of UC. Certain foods, stress, or emotional distress may trigger or worsen symptoms of UC in some people; however, these triggers do not appear to be involved in the development of UC.

The exact cause of microscopic colitis is unknown. Potential causes include medications or bacterial toxins that irritate the colon, viruses that cause inflammation, or autoimmune disorders, in which the body's immune system attacks healthy tissues.

Genetic profile

The genetic profile of UC is not well-understood. Because its development appears to involve multiple genetic and environmental factors, inheritance patterns are not known. Nevertheless, the risk of UC is increased in individuals with one or more affected family members.

Researchers have identified variants of more than two dozen different genes that may be linked to the development of UC. It has been hypothesized that these gene variants (alleles) affect the protective functioning of the intestinal lining or the body's immune system responses to bacteria that normally reside in the digestive tract. The inner surface of the intestines protects deeper tissues from bacteria and toxins, and a failure in this barrier may trigger an immune response to bacteria or toxins that can

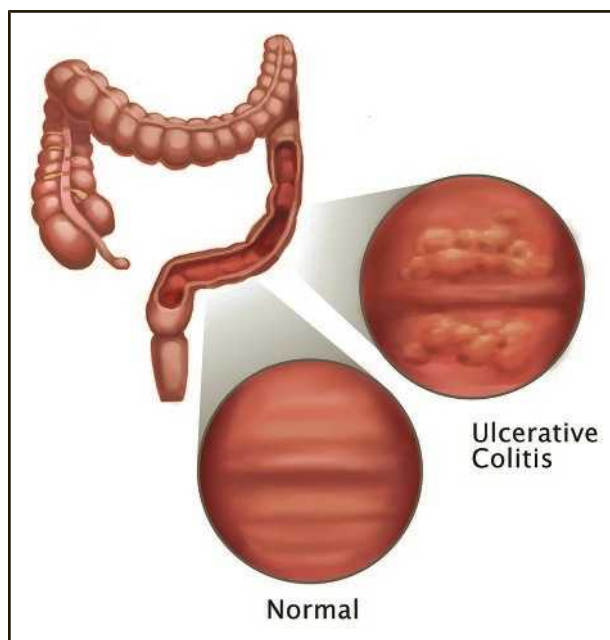


Illustration showing the effects of ulcerative colitis on intestinal walls. (Spencer Sutton/Science Source)

lead to chronic inflammation. In addition to genes that are involved in protecting the intestinal lining, potential UC-associated genes have been identified that affect the maturation and function of immune system T cells that normally protect against infection. Certain gene variants that affect T cells can lead to an overactive immune response or an autoimmune response that results in chronic inflammation. As of 2021, there were 13 molecular genetic tests for UC. Some of these tests involve DNA sequencing of all or part of the protein-coding regions (exons) of an individual's genome to detect variations that are potentially associated with UC. Other tests look for specific changes in the DNA sequence of certain genes, or DNA deletions or duplications.

In 2015, the Genetics Initiative of the Crohn's and Colitis Foundation of America (CCFA) was attempting to identify the exact changes or mutations in specific genes that are associated with IBD risk, with the goal of developing new targeted drugs for IBD treatment. Together, the CCFA Microbiome Initiative and Genetics Initiative have identified IBD-associated genes that affect the types of bacteria that reside in the digestive tract.

Demographics

UC is most common in North America and Western Europe. This may be because of diets that are higher in saturated fats from meat and dairy, sugar, cholesterol, and processed foods. Although these dietary factors do not cause UC, they may contribute to IBD symptoms.

Furthermore, UC prevalence is increasing in other parts of the world, possibly due to the spread of Western-type diets. Estimates of UC in North America range from 37 to 246 cases per 100,000 people, with some estimates as high as 238 cases per 100,000 adults, affecting an estimated 750,000 people. UC affects approximately equal numbers of men and women. It can occur at any age but usually begins between the ages of 15 and 30. It is also more likely to develop in people over age 60. UC affects all races and ethnicities but is much more common in Caucasians and especially in people of Ashkenazi Jewish descent.

Microscopic colitis is more common in women than in men and in people aged 50–70 years. It has been associated with smoking, especially in people aged 16–44 years. Microscopic colitis is more common in people with autoimmune disorders such as thyroid disease, celiac disease, or rheumatoid arthritis.

Signs and symptoms

Symptoms of UC vary depending on the severity of the inflammation and where in the colon it occurs, but most cases have mild to moderate symptoms. About half of UC cases are mild and may be confined to the rectum. About 10% of patients have severe symptoms, which are more likely in patients who develop UC at a younger age. UC frequently begins gradually and worsens over time, although most patients have periods of remission, with no symptoms for weeks or years.

The most common symptoms of UC are abdominal pain and diarrhea with blood or pus. Other symptoms may include the following:

- anemia (low red blood cell count)
- severe tiredness
- weight loss
- loss of appetite
- urgent need for bowel movements
- rectal bleeding
- skin sores
- joint soreness or pain
- growth failure in children
- nausea
- fever
- rashes
- eye irritation

Chronic watery diarrhea is the most common symptom of microscopic colitis. Other symptoms may include the following:

- abdominal pain or cramps
- nausea

- weight loss
- fecal incontinence

Diagnosis

Colitis is usually diagnosed and treated by a gastroenterologist. Personal and family medical histories are taken. The physical exam includes detection of any abdominal swelling or sounds within the abdomen that are heard with a stethoscope. It also includes tapping on the abdomen to identify sites of tenderness or pain. Stool tests are used to rule out diarrhea caused by infection. Blood tests are used to check for anemia, inflammatory markers, and infection. Blood tests can also detect low blood protein (albumin), which is common in people with severe UC.

Colonoscopy and flexible sigmoidoscopy utilize a long, thin, flexible tube with a camera to diagnose UC and rule out other potential causes of symptoms. The colon and rectum are examined for irritation, swelling, ulcers, and polyps. Tissue samples (biopsies) can be removed during these procedures. Since the visualized colon appears normal with microscopic colitis, a biopsy for microscopic examination is necessary for diagnosis.

Treatment and management

The goals of colitis treatment and management are to control symptoms, increase the frequency and duration of remissions, and improve quality of life.

Drugs

A variety of drugs are used to treat colitis symptoms. Many people with colitis continue drug therapy indefinitely. Depending on the severity of the colitis and its location in the large intestine, medications may be administered by mouth, intravenously (IV), as an enema or rectal foam, or as a suppository that dissolves in the rectum and is absorbed.

The following drugs can be used to treat colitis.

- **Aminosalicylates**—such as mesalamine, balsalazide, or olsalazine—contain 5-aminosalicylic acid (5-ASA) for controlling inflammation that causes mild-to-moderate symptoms or for maintaining remission. Oral and rectal aminosalicylates administered by enema or as suppositories are most effective when used in combination.
- **Corticosteroids**—such as prednisone and hydrocortisone—are used for severe symptoms and for patients who do not respond to aminosalicylates. They effectively reduce immune system activity and decrease inflammation, but are not usually prescribed long-term because of serious side effects.

KEY TERMS

Aminosalicylates—Anti-inflammatory medications containing 5-aminosalicylic acid (5-ASA) that are commonly used to treat colitis.

Autoimmune disorders—Conditions caused by inappropriate immune system activity.

Biologics—Pharmaceuticals extracted or semi-synthesized from biological sources.

Colon—The part of the large intestine that connects to the rectum.

Colonoscopy—An examination of the rectum and colon with a long flexible instrument passed through the anus; also used to obtain biopsy samples.

Crohn's disease—A chronic inflammatory autoimmune disease similar to colitis.

Inflammation—An immune system response mediated by tumor necrosis factor that can cause pain and swelling.

Megacolon—Extreme swelling of the colon that is a rare but life-threatening complication of colitis.

Microscopic colitis—A form of colitis that can only be diagnosed by examining tissue under a microscope.

Rectum—The lowermost few inches of the large intestine.

Sigmoidoscopy—Examination of the rectum and lower colon with a flexible instrument passed through the anus; also used to remove polyps and obtain biopsy samples.

T cells—Lymphocytes that originate in the thymus gland and regulate the immune response to infections; variants of genes affecting T cells may be associated with colitis.

Tumor necrosis factor (TNF)—A protein called a cytokine that mediates inflammation throughout the body and activates immune system cells; targeted by biologics for treating colitis.

Ulcerative colitis (UC)—A form of colitis characterized by ulcers in the colon that may bleed and produce pus.

- **Immunomodulators**—such as azathioprine or 6-mercaptopurine—reduce immune system activity and decrease colon inflammation in patients who do not respond to 5-ASA. They can take from several weeks to three months to begin working and may have serious

side effects, including increased risk of infection and certain cancers.

- Biologics—such as adalimumab, golimumab, infliximab, and vedolizumab—decrease inflammation in the colon by inhibiting an immune system protein called tumor necrosis factor (TNF). They are injected or infused intravenously and work very rapidly, but they also increase the risk of infection and certain cancers.
- Acetaminophen can be used for mild pain. Ibuprofen, naproxen, or aspirin may worsen symptoms.
- Antibiotics are used to prevent or treat infections.
- Loperamide can slow or stop diarrhea, but it is usually only used for a short time and cannot be used for very active UC.
- Cyclosporine is used only for severe UC because of its side effects.

Surgery

Surgery to remove the entire colon and rectum is performed when colitis patients also have colon cancer or precancerous cells in the colon, life-threatening complications such as bleeding or megacolon (inflammation that has spread to the deep tissues of the large intestine), or poor responses to medications, severe medication side effects, or a requirement for long-term steroid use. During the surgery, an opening is created in the abdomen that connects to a pouch for collecting fecal waste from the end of the small intestine.

Diet

Because diarrhea and rectal bleeding can cause loss of fluids, nutrients, and electrolytes, nutrition is essential for preventing colitis complications. Deficiencies in iron, magnesium, potassium, calcium, folic acid (folate or vitamin B₉), and other vitamins are fairly common in people with colitis. For many patients, diet is also the most important factor for controlling colitis flare-ups. Keeping a food diary can help people identify foods that appear to make symptoms worse. Important nutrition/dietary factors include the following:

- a low-fat diet
- a variety of fruits and vegetables
- fluids
- five or six small daily meals rather than a few large meals
- magnesium
- vitamin C

People with colitis should avoid the following:

- fats, especially saturated fat and fried or greasy foods

QUESTIONS TO ASK YOUR DOCTOR

- How is colitis diagnosed?
- What causes colitis?
- Do you recommend genetic testing for colitis-associated genes?
- What treatment(s) do you recommend?
- What nutritional/dietary changes should I make?
- What is my prognosis?

- butter, margarine, cream sauces, and pork, which can cause diarrhea if fat absorption by the intestine is incomplete
- beans
- spicy foods
- milk products if lactose intolerant
- high-fiber foods—such as nuts, seeds, corn, and some Chinese vegetables—which can cause abdominal cramping and diarrhea
- sugar
- artificial sweeteners
- chocolate
- alcohol

During colitis flare-ups, patients may experience less discomfort when eating soft, bland foods. They may need to avoid the following:

- high-fiber foods, such as raw fruits and vegetables and whole grains
- gas-producing foods, such as beans, cabbage, onions, and broccoli
- caffeine
- carbonated beverages

Prognosis

There is no cure for colitis, other than surgery to remove the entire colon; however, colitis often can be effectively managed with medications and diet. Complications of severe UC may include the following:

- rectal bleeding from ulcers in the intestinal lining
- dehydration and poor absorption of nutrients
- loss of bone density from corticosteroids
- inflammation from immune system activity in other parts of the body, such as the joints, eyes, skin, or liver

- megacolon—a rare but life-threatening complication in which the deep tissues of the large intestine swell and stop functioning and that usually requires surgical intervention.

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ORGANIZATIONS

American College of Gastroenterology, 6400 Goldsboro Road, Bethesda, MD 20817, (301) 263-9000, info@acg.gi.org, <http://gi.org>

Crohn’s & Colitis Foundation of America, 733 Third Avenue, Suite 510, New York, NY 10017, (800) 932-2423, info@ccfa.org, <http://www.ccfa.org>

National Institute of Diabetes and Digestive and Kidney Diseases, Office of Communications & Public Liaison, NIDDK, NIH Building 31, Room 9A06, 31 Center Drive, MSC 2560, Bethesda, MD 20892-2560, (301) 496-3583, <http://www2.niddk.nih.gov>

Margaret Alic, PhD

Collagenopathy, types II and XI

Definition

Collagenopathy, types II and XI, is a group of genetic disorders that affect the connective tissue—the material between joints and organs. The disorders are caused by defects in either type II or type XI collagen. The conditions are considered together because the two types are components of a particular type of cartilage (hyaline cartilage) in joints, the spine, inner ear, and the jelly-like substance (vitreous body) that fills the inner eyeball. Collagens are complex molecules that give connective tissue strength, structure, and the ability to stretch. There are at least ten subtypes of collagenopathy, types II and XI.

Description

Collagenopathy, types II and XI, is classified as a rare disease by the National Institutes of Health (NIH) since it affects fewer than 200,000 Americans, or less than 1 per 3,000. It is considered a genetic disorder because the genes that encode proteins in the connective tissue have defects or mutations that can be passed from parent to child. Among the subtypes of collagenopathy, types II and XI, are the following:

Achondrogenesis type 2

Achondrogenesis type 2 is a severe disorder that interferes with cartilage and bone development. Symptoms include short arms and legs, a narrow chest with short ribs, and underdeveloped lungs. It causes a lack of bone tissue formation in the spine and pelvis, according to the National Library of Medicine (NLM). Facial abnormalities include a prominent forehead, small chin, and in some cases, a cleft palate (an opening in the roof of the mouth). Also, infants with achondrogenesis type 2 have an enlarged abdomen. Sometimes newborns have hydrops fetalis, an excess buildup of fluids in the fetus.

Czech dysplasia

Czech dysplasia is an extremely rare subtype of collagenopathy, types II and XI, that affects how joints work and bone/skeletal development. The main symptom is joint pain in the hips, knees, shoulders, and spine, to an extent that it can hinder mobility. People generally develop symptoms in adolescence or early adulthood. Czech dysplasia patients frequently have short bones in their third and fourth toes, making their other two toes seem unusually long, according to the NLM. Some people with the condition also have hearing loss that worsens

over time. All 11 known cases of this genetic disorder inherited the mutated gene (*COL2A1*) from a parent with the disease.

Hypochondrogenesis

This disorder is rare but severe, and affects bone development starting in the fetus. Symptoms include a small body, short arms and legs, and abnormal bone development in the spine and pelvis. It is usually fatal at or before birth.

Kniest dysplasia

Kniest dysplasia is a rare bone development disorder characterized by short stature, other bone abnormalities, and problems seeing and hearing. Indications of Kniest dysplasia start at birth and include a short trunk, smaller arms and legs, unusually large joints, and arthritis. There is sometimes pain in the joints that can restrict movement. Other symptoms include a round, flat face with wide-set and bulging eyes; severe nearsightedness; detachment of the retina; and frequent ear infections that can lead to hearing loss. Most cases are caused by new mutations in the *COL2A1* gene and occur in people with no family history of the disease, which is unusual in collagenopathy, types II and XI subtypes.

Otospondylomegapiphyseal dysplasia

Otospondylomegapiphyseal dysplasia (also known as OSMED) is a disorder of the skeletal system. Symptoms include skeletal abnormalities, short stature, enlarged joints, hearing loss, a hole in the roof of the mouth, cleft palate, and distinct facial features such as protruding eyes, a flat nose bridge with an upturned nose and rounded tip, and a small lower jaw. The disease is usually detected at birth. The skeletal abnormalities, mainly to the spine, arms, and legs, usually decrease in severity during childhood. Other problems, including hearing loss, joint pain, and arthritis, continue into adulthood. OSMED is extremely rare and caused by mutations in the *COL11A2* gene that prevent the bones and connective tissues from developing properly, according to the NLM.

Spondyloepimetaphyseal dysplasia, Strudwick type

Spondyloepimetaphyseal dysplasia, Strudwick type, is a genetic disorder that results in short stature, skeletal abnormalities, and vision problems. Symptoms are present at birth and include a short torso, shortened arms and legs, an abnormally curved lower back, flattened vertebrae, breastbone protrusion, upper leg bones that turn inward, and arthritis. This disorder is caused by mutations in the *COL2A1* gene, making it an inherited condition.

Spondyloepiphyseal dysplasia congenita

Spondyloepiphyseal dysplasia congenita is a genetic disorder that is present at birth and disrupts bone growth. Symptoms include short stature, skeletal abnormalities, and problems with hearing and seeing. The disorder affects the spine and the ends of the long bones in the arms. People with the disorder have short stature from birth along with a short trunk, neck, arms, and legs. Their hands and feet are usually of average size. During childhood, a curving of the spine becomes more severe and can cause breathing difficulties and spinal damage.

Spondyloperipheral dysplasia

Spondyloperipheral dysplasia is a genetic disorder that impairs bone development. Symptoms include flattened spinal bones and unusually short fingers and toes (except for the big toe). Other symptoms are short stature, shortened long bones in the arm and legs, feet that point in and down (clubfoot), nearsightedness, hearing loss, and impaired intellect. The disorder is caused by mutations in the *COL2A1* gene that disrupt the normal development of bones and connective tissues throughout the body.

Stickler syndrome

Stickler syndrome is a group of four genetic conditions that is characterized by distinct facial abnormalities, hearing loss, and joint problems, including pain and arthritis. The facial differences include a generally flat-looking face caused by undeveloped bones in the face, a hole in the top of the mouth, a large tongue, and a small lower jaw. These symptoms can lead to eating and breathing difficulties. The disorder is caused by mutations in the *COL2A1*, *COL9A1*, *COL11A1*, and *COL11A2* genes.

Weissenbacher-Zweymuller syndrome

Weissenbacher-Zweymuller syndrome is a genetic disorder that causes short stature in which affected individuals are born with small, underdeveloped jaws, a hole in the roof of the mouth, short arms and legs, dumbbell-shaped arm and leg bones, protruding wide spaced eyes, and incompletely formed back bones. Unlike most other forms of short stature, individuals affected by Weissenbacher-Zweymuller start out being affected by short stature at birth and then have a period of gradual growth and bone change that leads to normal physical development by around the age of five or six.

Risk factors

The primary risk factors for collagenopathy, types II and XI, are:

- One or both parents who have the disorder.
- A family history of the disease.

- Parents that are closely related, such as cousins.
- Parents that are part of a distinct ethnic group, such as Ashkenazi Jews, or are in a geographic community that is rural and isolated, such as areas of low-density population in Afghanistan or Mongolia.
- Parents who do not show symptoms of the disease but carry diseased genes that can be detected through genetic testing. This testing is effective but expensive and is not routinely done in the United States or the rest of the world.

Genetic profile

Types II and XI of collagenopathy are caused by genetic defects that can be passed from parent to child. The defects, or mutations, occur in three specific genes: *COL11A1*, *COL11A2*, and *COL2A1*. These gene mutations disrupt the normal way type II and type XI collagens assemble or reduce the amount of these collagens in the body.

Demographics

Demographics vary between subtypes of the disorder.

- The exact number of achondrogenesis type 2 cases in the United States and the world is not documented. However, the National Library of Medicine (NLM), a branch of the U.S. National Institutes of Health, has combined statistics on this disorder along with hypochondrogenesis, a similar skeletal disorder, that show the two conditions occur in 1 in 40,000 to 60,000 newborns.
- The prevalence of Czech dysplasia is unknown in the United States and the world because it is such an extremely rare disease. As of June 2015, at least 11 families worldwide had been affected with the disorder, with most cases in the Czech Republic.
- Ootospondylomegaepiphyseal dysplasia has been diagnosed in only a handful of families worldwide. The prevalence in the United States and the world is unknown as are the demographics.
- Spondyloepimetaphyseal dysplasia, Strudwick type, is extremely rare with only a handful of cases reported worldwide, making it difficult for researchers to study.
- Spondyloepiphyseal dysplasia congenital is extremely rare, with only about 175 cases reported worldwide. Its incidence and demographics are unknown.
- Spondyloperipheral dysplasia is extremely rare in the United States and world with only a few cases reported worldwide, making it difficult to study.
- Stickler syndrome is not an uncommon disease, affecting 1 in every 7,500 to 9,000 newborns in the

KEY TERMS

Arthritis—An inflammation of one or more joints that causes pain, swelling, stiffness, and limited movement.

Cartilage—A type of connective tissue in the body.

Collagen—Complex molecules that give connective tissue strength, structure, and the ability to stretch.

Connective tissue—The material between the cells of the body that gives tissues form and strength.

Cleft palate—A hole at the top (roof) of the mouth.

Dysplasia—An abnormality in the development of cells within tissue.

Short stature—An abnormally low height.

Stem cells—Cells from which all blood cells are derived.

Vitreous—Describes the jelly-like substance that fills the inner eyeball.

United States and world, according to NML estimates. A study followed 21 known cases in Brazil through 2007.

- Weissenbacher-Zweymuller syndrome is extremely rare, and only a few families with the disease have been reported worldwide.

Signs and symptoms

The symptoms vary between the various subtypes of the disorder but there are a number of common symptoms. These include problems with the bones developing properly that can cause short stature, enlarged joints, a curved spine, and arthritis. Symptoms appear at a young age, often months after birth. Other symptoms include sight and hearing problems, a cleft palate with a small lower jaw, protruding eyes, and a flat nose.

Diagnosis

Diagnosis of collagenopathy, types II and XI, can be made through genetic testing or by bone changes observed on x-ray images. Other factors used in the diagnosis include family history of the disorder, family medical history, and physical examination.

Examination

A physical examination of an infant or child can reveal symptoms such as problems with bone development, short stature, and facial abnormalities, including a cleft palate, small lower jaw, and protruding eyes.

Tests

Genetic testing is the most precise method for detecting the disorder and its subtype. Prenatal testing and newborn screening are also used for diagnosis.

Procedures

The most common procedures are blood tests, ultrasound imaging, and x-ray imaging.

Treatment and management

There is no known way to prevent collagenopathy, types II and XI. There are no treatments or cure for collagenopathy, types II and XI, other than treating specific symptoms, such as medications for joint and other pain, and surgery to correct or lessen the effects of seeing and hearing problems. Also, human growth hormone is sometimes used to treat short stature, although its success is sometimes limited.

Traditional

There are no traditional treatments for collagenopathy, types II and XI.

Drugs

There are no drugs that specifically target collagenopathy, types II and XI. This is because, depending on subtype, the condition is rare to extremely rare and little research has been conducted on it. Medications to treat specific symptoms, such as pain and arthritis, are used.

Alternative

In most cases of collagenopathy, types II and XI, alternative therapies are either not available or have limited use since there are no known vitamins, minerals, herbs, or dietary supplements that can affect this genetic disorder. When pain is involved, therapies such as acupuncture, yoga, and meditation can be useful in older children and adults.

Home remedies

There are no home remedies commonly used to treat the two types of collagenopathy.

Prognosis

Prognosis varies between subtypes. In newborns with hypochondrogenesis, the prognosis is grim. Some fetuses do not survive to birth. Newborns with the condition usually die at birth or soon after due to respiratory failure. Infants who survive after birth are usually reclassified as having a related but milder disorder

QUESTIONS TO ASK YOUR DOCTOR

- What are the chances of my children developing this condition?
- Do you know of any recent research or medical breakthroughs concerning my condition?
- Would alternative or complementary treatments be useful in treating any of my symptoms?
- Are there any current or planned clinical trials or studies of my disorder in which I might be eligible to participate?

(spondyloepiphyseal dysplasia congenita) that hinders bone development. In several subtypes, the disorder is not generally life-threatening. There is little that can be done for short stature since it is caused by genetic defects passed from parent to child. There is cause for hope in finding treatments and cures, and even correcting the defective gene or genes in the womb by using genetic research, including the use of stem cells. Stem cell research is being conducted in North America, Europe, and Asia.

Resources

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ORGANIZATIONS

Genetic and Rare Diseases Information Center (GARD), PO Box 8126, Gaithersburg, MD 20898-4911, (888) 205-2311 or (301) 251-4925 (International), (301) 251-4911, <https://rarediseases.info.nih.gov/gard>

Genetic Science Learning Center, University of Utah, 383 Colorow Dr., Salt Lake City, UT 84108, (801) 585-3470, <http://learn.genetics.utah.edu>

National Institute of Arthritis and Musculoskeletal and Skin Diseases, 1 AMS Circle, Bethesda, MD 20892-3675, (301) 495-4484 or (877) 226-4267, (301) 718-6366, NIAMSinfo@mail.nih.gov, <http://www.niams.nih.gov>

National Organization for Rare Diseases (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Ken R. Wells

Coloboma

Definition

Coloboma is a congenital genetic disorder that results in a piece of tissue missing in or around the eye. There are multiple types of colobomas, some of which are associated with other congenital genetic disorders.

Description

Coloboma describes a condition wherein a portion of a structure of the eye is absent at birth. The affected part

can be the iris, retina, eyelid, or optic nerve. Colobomas may or may not affect vision, depending on their size and location.

Types of colobomas:

- Iris coloboma is also called a uveal or keyhole coloboma, because the shape of the coloboma appears as the shape of a keyhole or an upside-down pear. The iris is the colored part of the eye. The uvea is the middle layer of the eye. The defect may occur in one eye (unilateral) or in both eyes (bilateral).
- Retinal coloboma. In this disorder, a notch or cleft of the retina or part of the retina is missing. The retina is the light-sensitive tissue at the back of the eye.
- Choroidal coloboma. This condition is similar to a retinal coloboma. The choroid is a structure in the eye that lies between the sclera and the retina.
- Optic nerve coloboma. The optic nerve carries nerve impulses from light entering the eye to the brain. This type of coloboma occurs when a uveal coloboma is large enough to cover the optic nerve and may involve the macula, a structure in the eye that is responsible for visual acuity. Alternately, a bit of optic nerve may be missing so that a defect occurs where the optic nerve meets the retina. This condition is sometimes called morning glory syndrome, because it describes the appearance of the optic nerve, which looks like the inside of a morning glory flower.



Coloboma. (Shutterstock/Alina Loseva)

Genetic profile

Colobomas may be isolated abnormalities in otherwise genetically normal individuals, or they may occur as part of a syndrome associated with other congenital genetic disorders. As isolated findings, they generally arise spontaneously, although sometimes they are associated with an autosomal dominant inheritance pattern, meaning that only one copy of the abnormal gene needs to be present for the disorder to occur. Colobomas can also be inherited in an autosomal recessive pattern in which each parent must contribute a changed (mutated) gene for symptoms to be evident. The condition can also be X-linked, meaning that the changed gene is on a sex chromosome. In the case of females who have two X sex chromosomes, the defect might not show symptoms, while in males who have XY sex chromosomes, an X-linked defect will cause symptoms. Some other genetic disorders thought to contribute to coloboma include cat-eye syndrome, trisomy 13, trisomy 18, Sturge-Weber syndrome, and basal cell nevus syndrome.

Demographics

The condition occurs in about one in 10,000 births, although the condition is thought to be underdiagnosed because it does not always affect vision. Uveal colobomas and eyelid colobomas are most common.

Signs and symptoms

Retinal colobomas affect the choroid (light-impermeable lining consisting primarily of blood vessels) and the retina (the photosensitive lining inside the eye). The extent to which vision is impaired depends on the size of the coloboma and its impact on the optic nerve and macula, the center of the retina where fine discrimination occurs.



A woman's eye displaying coloboma. This defect forms because of a failure of the rudimentary eye to join the optic fissure during embryonic development. (Shvaygert Ekaterina/Shutterstock)

KEY TERMS

Choroid—A vascular membrane that covers the back of the eye between the retina and the sclera and serves to nourish the retina and absorb scattered light.

Iris—The colored part of the eye, containing pigment and muscle cells that contract and dilate the pupil.

Macula—A small spot located in the back of the eye that provides central vision and allows people to distinguish colors and fine visual details.

Optic nerve—A bundle of nerve fibers that carries visual messages from the retina in the form of electrical signals to the brain.

Pupil—The opening in the iris through which light enters the eye.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Sclera—The tough white membrane that forms the outer layer of the eyeball.

A coloboma can appear as a black indentation of varying depth at the edge of the pupil, and it gives the pupil an odd or irregular shape. It may also appear as a split in the iris from the pupil to the edge of the iris.

Symptoms usually present as blurred or decreased vision and an appearance of a hole or odd-shaped pupil in the individual's eye. A smaller coloboma, especially if it is not attached to the pupil, often causes a secondary image to focus on the back of the eye, producing blurred vision or decreased visual sharpness. Colobomas are often associated with other eye problems, such as clouding of the eye (cataract), high pressure in the eye (glaucoma), malformation of the retina, and involuntary eye movements.

Diagnosis

A diagnosis is made by a physical exam and includes a detailed eye examination by an ophthalmologist. The ophthalmologist will also ask the individual when the symptoms were first noticed, determine what part of the eye is affected, determine the size and shape of the dark area in the eye, and ask for reports of any changes in the individual's vision.

Certain tests are often used to diagnose coloboma, including a visual acuity test, a refraction test, and an in-depth history of symptoms.

Treatment and management

Colobomas may be accompanied by other problems that may be neurological or chromosomal in nature, including defects in other parts of the body. Some genetic syndromes include coloboma as part of the disorder's potential findings. More importantly, a specific combination of abnormalities identified by the acronym CHARGE must also be considered when a diagnosis of coloboma is made.

The medical condition known as CHARGE association is a very rare and serious condition. Individuals who have the condition will require attention from several specialists and from an early age. Colobomas are usually one of the findings in individuals with CHARGE. The disorder includes these problems:

- (C)oloboma
- (H)eart defects
- (A)tresia of the choanae, which is a blockage of the nasal passages
- (R)etarded growth and development
- (G)enital hypoplasia, which occurs when the testes do not descend properly
- (E)ar abnormalities

While there is no specific treatment for coloboma, some treatments are available that can manage vision problems associated with the disorder. These include glasses or contact lenses to optimize vision in the least affected eye, use of assisted devices for low vision, sunglasses for individuals whose eyesight is adversely affected by bright light, treating or offering preventative treatment for other eye disorders present, such as eye patching to prevent lazy eye. As of 2020, a few individuals have had improvement in iris coloboma through the use of femtosecond laser-assisted cataract surgery (FLACS). This procedure is quite delicate and not widely available. The National Eye Institute offers genetic testing to families with a member who has a coloboma.

Prognosis

The effects of coloboma can be mild or severe, depending upon the extent and location of the gap or cleft. The gap itself is usually located at the bottom of the eye, but it may occur in the iris, choroid, macula, or optic nerve.

A coloboma of the lens, particularly if it is large, may also include abnormalities of the iris and choroids, which increases the risk of retinal tearing. In severe cases of coloboma, the eye may be reduced in size. This condition is called microphthalmia, a disorder that can arise with or without coloboma.

QUESTIONS TO ASK YOUR DOCTOR

- As a parent, how can I recognize coloboma in my child?
- Does coloboma require medical attention, and, if so, should I see some kind of specialist?
- What treatments are available for coloboma?
- Does coloboma lead to more serious vision problems, such as night blindness or loss of vision?

The specific gene or genes responsible for coloboma have not yet been identified, but research continues throughout the United States, Scotland, and England. Clinical trials for treatments of various types of coloboma are underway. Participation in a U.S. clinical trial is voluntary and at no cost to the participant. All clinical trials receiving U.S. government funding, and some supported by private industry, are posted at <https://www.clinicaltrials.gov>. Foreign trials are listed at <https://www.orpha.net>.

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ORGANIZATIONS

National Eye Institute Information Office, 31 Center Drive, MSC 2510, Bethesda, MD 20892-2510, (301) 496-5248, 2020@nei.nih.gov, <http://www.nei.nih.gov>

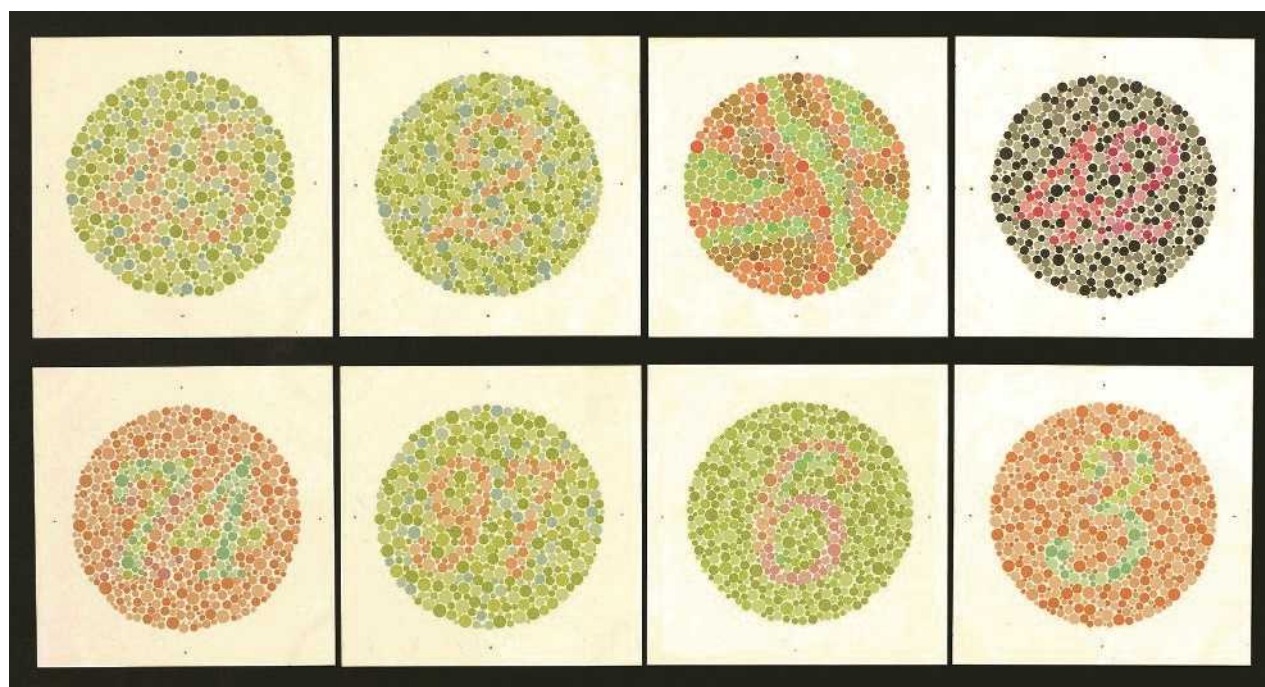
National Federation of the Blind, 200 East Wells Street, Baltimore, MD 21230, (410) 659-9314, nfb@nfb.org, <https://nfb.org>

Bethanne Black
Revised by Tish Davidson, AM

Color blindness

Definition

Color blindness, also called color vision deficiency (CVD), is a group of conditions that affect the perception of color, characterized by the inability to distinguish



Ishihara cards for testing color blindness, invented by Japanese ophthalmologist Shinobu Ishihara (1897–1963). A person with normal vision will be able to see numbers, letters, or designs inscribed in the dots. A person with color blindness may see only dots with no defined image inside. Color blindness is usually caused by an inherited genetic defect in the light-sensitive cells (cones) of the eye. In dichromatism, there is difficulty seeing one of the three primary colors: red, blue, or green. In anomalous trichromatism, there is reduced ability to distinguish certain shades of red and green (usually brighter ones). In the rarer monochromatism, there is no color vision and the world appears in white, black, and grey shades. (Wellcome Images/Science Source)

different colors of the spectrum clearly. The difficulties range from mild to severe. Color blindness is a misleading term, because people with color blindness are not blind. Rather, they tend to see colors in a limited range of hues; a rare few might not see colors at all.

Description

Normal color vision requires the use of specialized receptor cells called cones, which are located in the retina of the eye. There are three types of cones, termed red, blue, and green. Each cone contains a special pigment, called photopigment, that is most sensitive to a particular wavelength of light. The combined input from all three types of cones produces normal color vision. An abnormality or deficiency of any of the types of cones will result in abnormal color vision.

There are three basic variants of color blindness. Red-green color blindness is by far the most common deficiency. Affected persons cannot distinguish well between shades of red and green. They see these colors differently from how most people do, and they may have trouble naming different hues.

Blue-yellow color blindness is an inability to distinguish both blue and yellow, which are seen as white or gray. The condition is quite rare. Red-green and blue-yellow color vision deficiency disrupt the perception of color but do not affect the sharpness of vision.

A total inability to distinguish colors (achromatopsia) is exceedingly rare. These affected individuals view the world in shades of gray. They frequently have poor visual acuity and are extremely sensitive to light (photophobic), which causes them to squint in ordinary light.

Genetic profile

Mutations in the *CNGA3*, *CNGB3*, *GNAT2*, *OPN1LW*, *OPN1MW*, and *OPN1SW* genes are known to cause color vision deficiency. The *OPN1LW* gene makes pigments (L cones) that are more sensitive to light at the red end of the visible spectrum, while the *OPN1MW* gene makes pigments (M cones) that are more sensitive to yellow-green light in the middle of the visible spectrum. As for the *OPN1SW* gene, it makes pigments (S cones) that are more sensitive to blue-violet

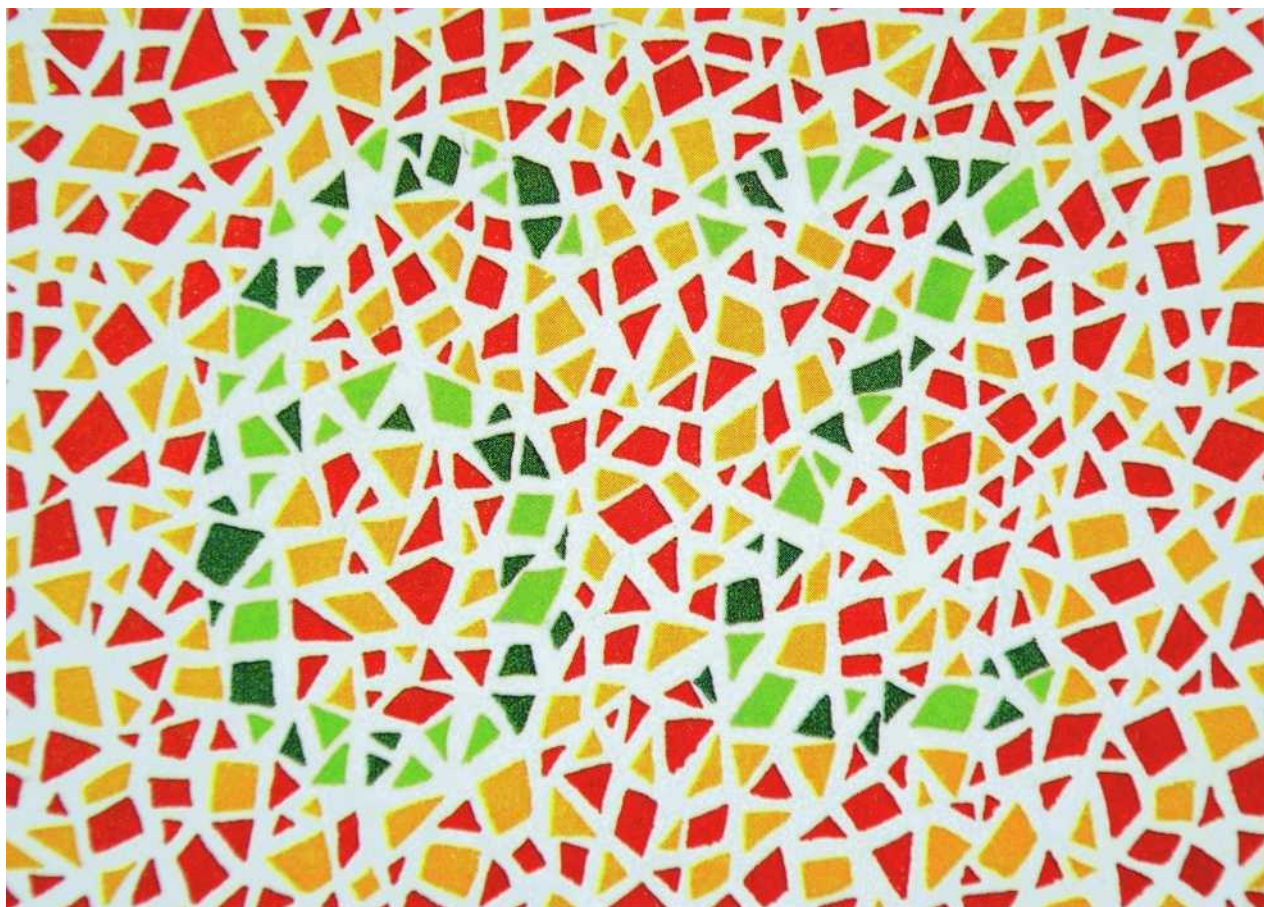
light at the end of the visible spectrum. Genetic changes involving the *OPN1LW* and *OPN1MW* genes accordingly lead to an absence of L or M cones or the production of abnormal cones that affect red-green color vision. Mutations of the *OPN1SW* gene leads to the premature destruction of S cones or the production of defective cones, which impairs perception of the color blue and makes it difficult to detect differences between shades of blue and green. As for the *CNGA3*, *CNGB3*, and *GNAT2* genes, their mutation is responsible for achromatopsia.

Demographics

In the United States, red-green color vision defects are the most common form of color vision deficiency. This condition affects males more often than females. Some ten million American men (7% of the male population) either cannot distinguish red from green or see red and green differently from the way most people do. This is the most common form of color blindness, and it affects only 0.4% of women. Blue-yellow color vision

defects affect males and females equally. This condition occurs in fewer than one in 10,000 people worldwide. Complete achromatopsia affects an estimated one in 30,000 people. The condition is much more prevalent among Pingelapese islanders, who live on one of the Eastern Caroline Islands of Micronesia. Some 5% to 10% of this population have a total absence of color vision.

Color blindness is sometimes acquired. Chronic illnesses that can lead to color blindness include Alzheimer's disease, diabetes mellitus, glaucoma, leukemia, liver disease, chronic alcoholism, macular degeneration, multiple sclerosis, Parkinson's disease, sickle cell anemia, and retinitis pigmentosa. Accidents or strokes that damage the retina or affect particular areas of the brain can lead to color blindness. Some medications such as antibiotics, barbiturates, anti-tuberculosis drugs, high blood pressure medications, and several medications that are used to treat nervous disorders and psychological problems may cause color blindness. Industrial or environmental chemicals such as carbon monoxide, carbon



A common test used to detect color blindness. The number "hidden" in the image will not be visible to an individual with red/green color blindness. (Huaji/Shutterstock)

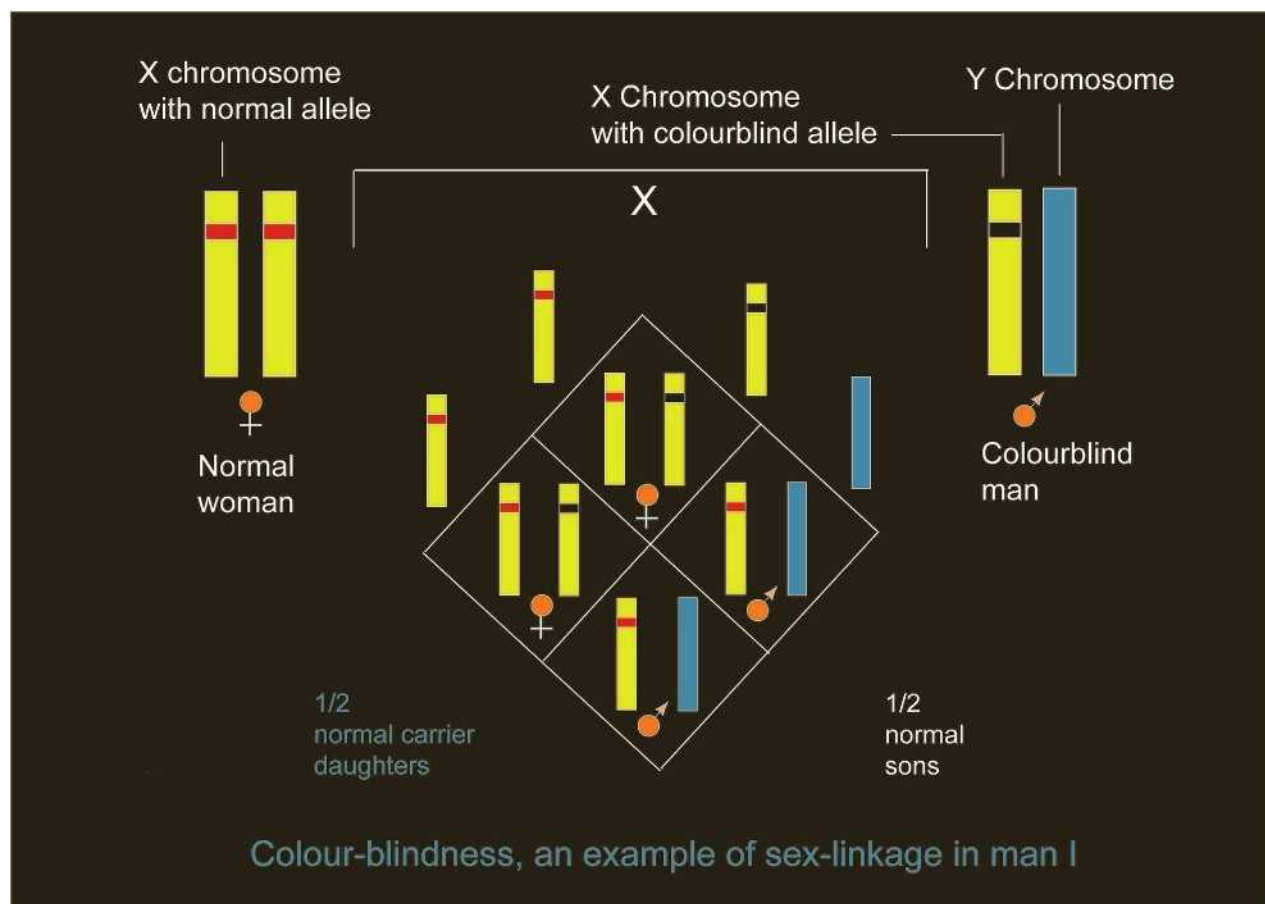


Diagram showing the inheritance of color-blindness genes. X-chromosomes (yellow) and Y-chromosomes (blue) combine at center. The normal color vision allele is a red bar, and the color-blindness allele is a black bar. The male symbol (arrow) and female symbol (cross) show the male and female parents and the offspring (sons and daughters). The cross-table shows the probability for color-blindness in the offspring of a normal woman and color-blind man: half of their sons will be color blind, and half of their daughters will be carriers. This trait is thus classed as X-linked recessive. (Francis Leroy, Biocosmos/Science Source)

disulfide, fertilizers, styrene, and some compounds containing lead can cause loss of color vision. Occasionally, changes can occur in the affected person's capacity to see colors after age 60.

Signs and symptoms

The inability to correctly identify colors is the only sign of color blindness. It is important to note that people with red-green or blue-yellow varieties of color blindness use other cues such as color saturation and object shape or location to distinguish colors. They can often distinguish red or green if they can visually compare the colors. However, most have difficulty accurately identifying colors without any other references. Most people with any impairment in color vision learn colors as do other young children. These individuals often reach adolescence before their visual deficiency is identified.

Diagnosis

There are several tests available to identify problems associated with color vision. The most commonly used is the American Optical/Hardy, Rand, and Ritter pseudoisochromatic test. It is composed of several discs filled with colored dots of different sizes and colors. A person with normal color vision looking at a test item sees a number that is clearly located somewhere in the center of a circle of variously colored dots. A color-blind person is not able to distinguish the number.

The Ishihara test comprises eight plates that are similar to the American Optical Pseudoisochromatic test plates. The individual being tested looks for numbers among the various colored dots on each test plate. Some plates distinguish between red-green and blue-yellow color blindness. Individuals with normal color vision perceive one number. Those with red-green color deficiency

see a different number. Those with blue-yellow color vision see yet a different number.

A third analytical tool is the Titmus II Vision Tester Color Perception test. The subject looks into a stereoscopic machine. The test stimulus most often used in professional offices contains six different designs or numbers on a black background, framed in a yellow border. Titmus II can test one eye at a time. However, its value is limited, because it can only identify red-green deficiencies and is not highly accurate.

Treatment and management

There is no treatment or cure for color blindness. Most color vision-deficient persons compensate well for their abnormality and usually rely on color cues and details that are not consciously evident to persons with typical color vision.

Inherited color blindness cannot be prevented. In the case of some types of acquired color deficiency, if the cause of the problem is removed, the condition may improve with time. But for most people with acquired color blindness, the damage is usually permanent.

Contact lenses

Contact lenses made with millions of gold nanoparticles no bigger than a speck of dust could combat color blindness. These “gold dust” particles filter out certain wavelengths of light so the brain can distinguish different colors, particularly reds and greens, more easily. These contact lenses are discreet and have a slight pink hue. They appear pink (rather than gold)

KEY TERMS

Achromatopsia—The inability to distinguish any colors.

Cones—Receptor cells that allow the perception of colors.

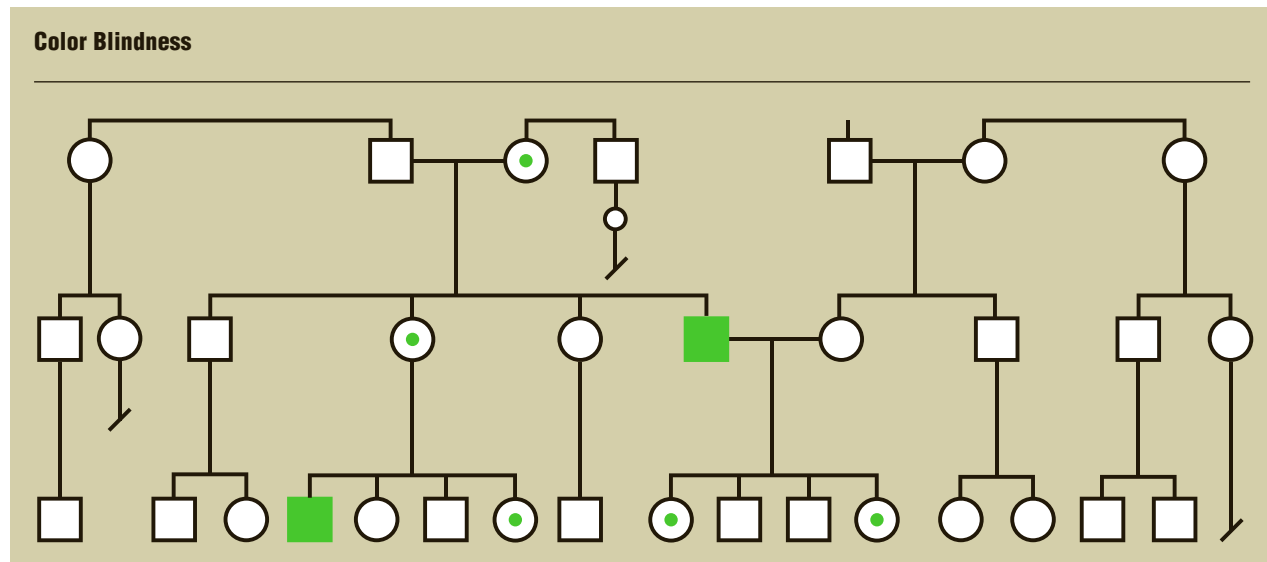
Photophobia—An extreme sensitivity to light.

Photopigment—Pigment that is most sensitive to a particular wavelength of light.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Rod—A photoreceptor that is highly sensitive to low levels of light and transmits images in shades of gray.

because gold in tiny fragments has a small surface area and so, rather than reflecting the whole spectrum of light (which would make it appear gold and shiny), it reflects more red light, which makes the lenses look rose-tinted. Gold particles are used in the lenses because the metal is safe to use in the body. To make the contact lenses, gold particles were mixed into hydrogel polymer, the material used for standard contact lenses. In a lab study, the lenses blocked at least 50% of the light that mixes reds and greens, making it easier to tell the colors apart. These lenses may help some people with color blindness in the same way that tinted glasses do. However, they are not a cure for color blindness.



Color blindness: pedigree analysis chart (Gale)

QUESTIONS TO ASK YOUR DOCTOR

- I have blue-yellow color blindness. What is the long-term prognosis for this condition?
- I would like to participate in a clinical trial on color blindness. Where can I get information about such trials?
- What tests are available to determine whether or not my son is color blind and, if so, what kind of color blindness he may have?

Clinical trials

Clinical trials on color blindness and related conditions are currently sponsored by the National Institutes of Health (NIH) and other agencies. Clinical trial information is constantly updated by NIH, and the most recent information on blindness trials can be found at: <https://www.clinicaltrials.gov/ct2/show/NCT00422721>

Prognosis

Color blindness that is inherited is present in both eyes and remains constant over an individual's entire life. Some cases of acquired color vision loss are not severe, may appear in only one eye, and can last for only a short time. Other cases tend to be progressive, becoming worse with time.

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ORGANIZATIONS

- American Academy of Ophthalmology (AAO), P.O. Box 7424, San Francisco, CA 94120-7424, (415) 561-8500, (415) 561-8533, <http://www.aao.org>
- American Optometric Association, 243 N. Lindbergh Boulevard, Floor 1, St. Louis, MO 63141-7881, (314) 991-4100, (314) 991-4101, <http://www.aoa.org/?sso=y>
- National Eye Institute (NEI), 31 Center Drive MSC 2510, Bethesda, MD 20892-2510, (301) 496-5248, 2020@nei.nih.gov, <https://nei.nih.gov>
- Prevent Blindness, 225 West Wacker Drive, Suite 400, Chicago, Illinois 60606, (800) 331-2020, info@preventblindness.org, <http://www.preventblindness.org>

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Combined pituitary hormone deficiency

Definition

Combined pituitary hormone deficiency (CPHD) is a group of genetic disorders characterized by deficiencies in multiple hormones produced by the pituitary gland. CPHD is characterized by very slow or delayed growth leading to short stature (dwarfism), and can be caused by mutations (changes) in several different genes.

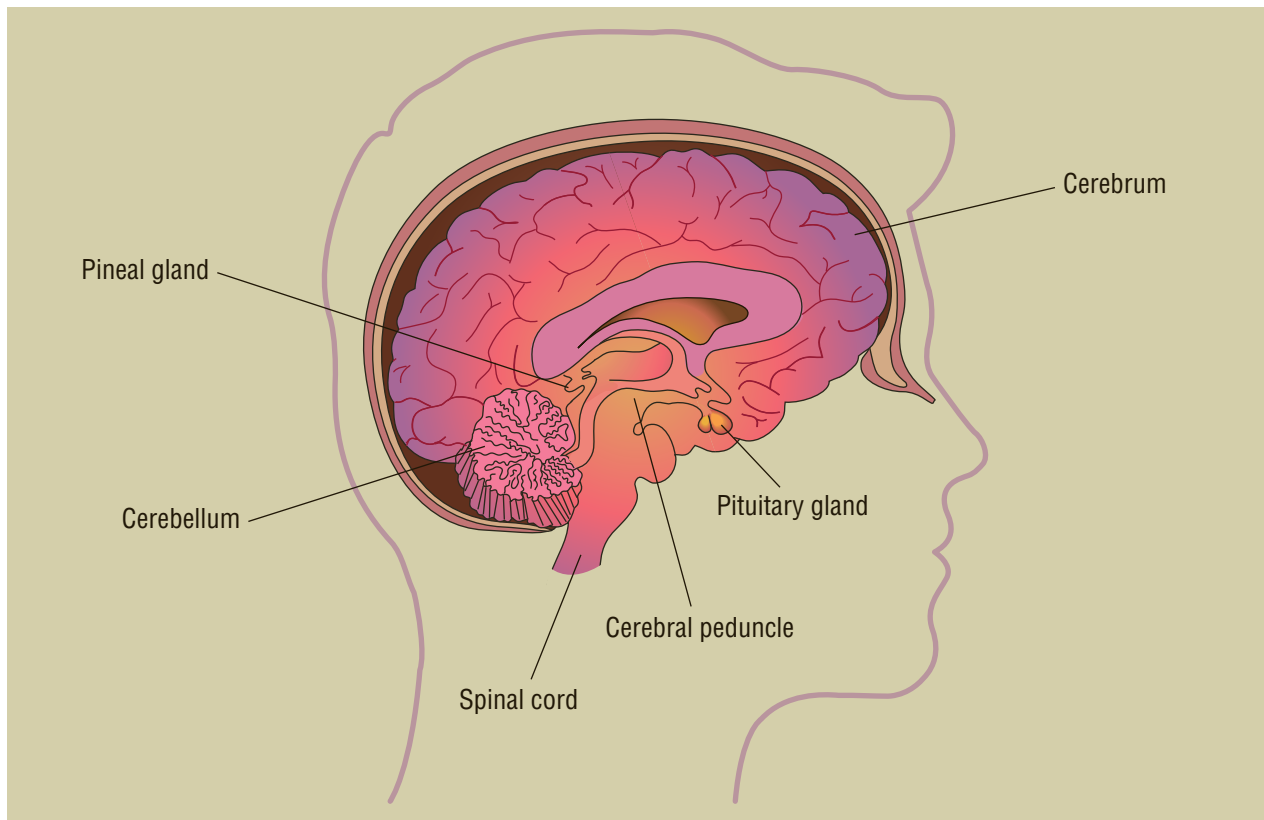


Diagram of brain (Gale)

Description

The pituitary gland is also called the hypophysis. It is divided into two halves: the anterior (front) and the posterior (back). The anterior pituitary produces six hormones: growth hormone (GH), adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), prolactin, and the gonadotropins follicle-stimulating hormone (FSH), and luteinizing hormone (LH). The posterior pituitary gland produces only two hormones: antidiuretic hormone (vasopressin) and oxytocin. Growth and development occur in response to these various hormones. The forebrain contains a small organ called the hypothalamus that is responsible for releasing hormones in response to the body's needs. GH is produced and released by the anterior pituitary gland in response to the release of growth-hormone-releasing hormone (GHRH). GH then stimulates the liver to produce insulin-like growth factor 1 (IGF1).

CPHD most often involves decreased production of hormones from the anterior pituitary gland. The most common form of CPHD is caused by GH deficiency. During childhood, the arms, legs, and other structures develop in normal proportion to the body but at a decreased rate. CPHD was previously known as pituitary

dwarfism. Panhypopituitarism is the lack of production of all anterior pituitary gland hormones.

Mutations in several different genes can cause CPHD. For example, mutations in the *PROPI* gene are associated with GH, TSH, LH, FSH, prolactin, and sometimes ACTH deficiencies. As a result, *PROPI*-associated CPHD (CPHD2) has wide-ranging effects, in addition to underdevelopment of the pituitary gland and short stature. Mutations in the *POUIF1* gene are associated with GH, TSH, and prolactin deficiencies, whereas LH, FSH, and ACTH are still produced.

Genetic profile

Different types of CPHD are caused by mutations in different genes and are inherited in different patterns.

- CPHD type 1, caused by mutations in the *POUIF1* gene located on the short arm (p) of chromosome 3 at 3p11, is inherited in an autosomal recessive pattern. This means that an individual with CPHD1 has inherited two mutated *POUIF1* genes, one from each parent.
- *PROPI*-related CPHD type 2 is also inherited in an autosomal recessive pattern. *PROPI* is located on the long arm (q) of chromosome 5 at 5q35.3.

- CPHD3 is caused by mutations in the *LHX3* gene located on chromosome 9 at 9q34.3.
- CPHD4 is caused by mutations in the *LHX4* gene located on chromosome 1 at 1q25.2.
- CPHD5 is caused by mutations in the *HESX1* gene on chromosome 3 at 3p14.3.
- CPHD6 is caused by mutations in the *OTX2* gene on chromosome 14 at 14q22.3.
- Mutations in other genes, including *SHH* and *HHIP*, may also cause CPHD.

Demographics

CPHD is estimated to affect 1 person in every 8,000 worldwide.

Signs and symptoms

Children with CPHD are usually small with immature-appearing faces and chubby builds. Growth is slowed and does not follow normal growth-curve patterns. However, other signs and symptoms depend on the type of CPHD and the specific gene mutation(s).

- CPHD1 is characterized by severe growth deficiency from birth and distinctive facial features, including a prominent forehead, a depressed nasal bridge, deep-set

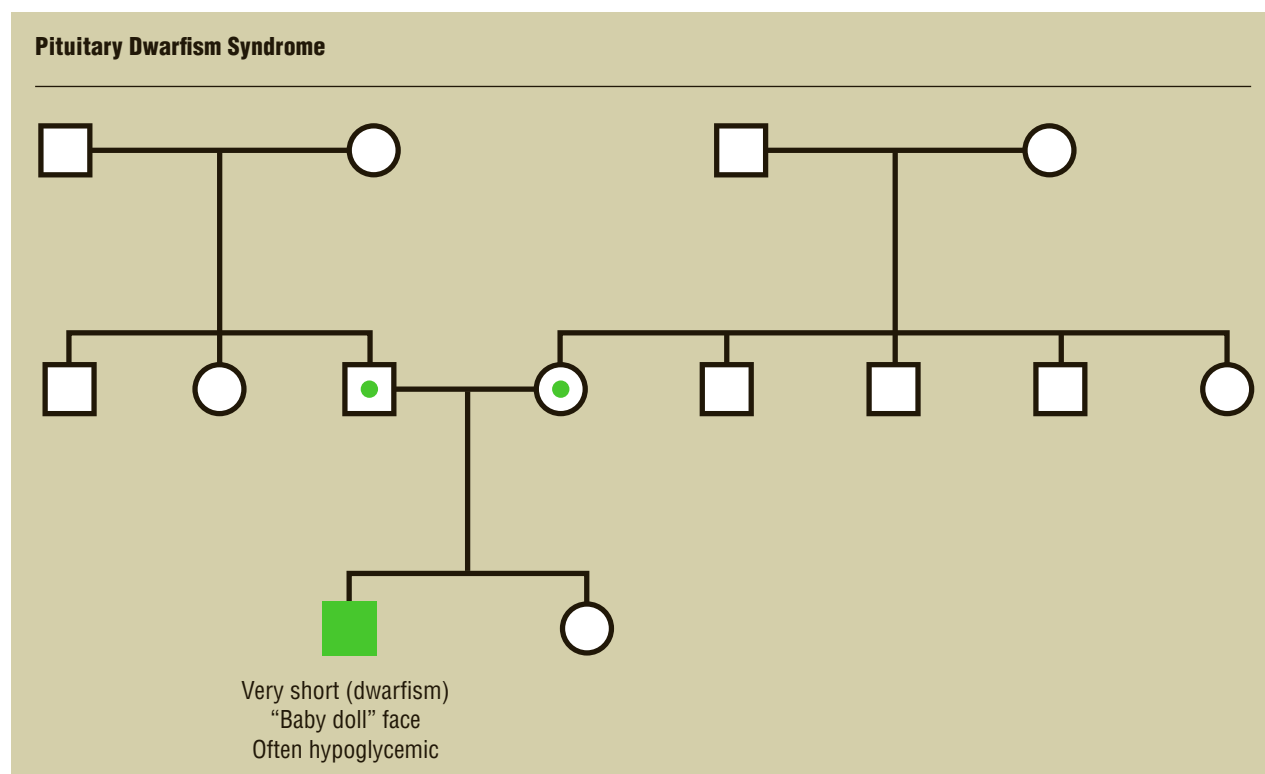
eyes, and a short nose. Short stature is sometimes accompanied by severe intellectual disability.

- CPHD2 is characterized by failure to thrive or growth failure beginning between the ages of nine months and eight years. Secondary sexual development may be delayed, incomplete, or absent, and is accompanied by infertility. Without treatment, males usually have a small penis and testes. Females usually require hormone replacement therapy to undergo sexual development.
- In addition to pituitary dysfunction, children with CPHD6 may have abnormally small eyes (microphthalmia).

Diagnosis

The primary diagnostic symptom of CPHD is short stature. Sometimes a hand is x-rayed to compare “bone age” with the child’s chronological age. Affected children’s bone age is usually two or more years behind chronological age. This means that a ten-year-old child will have bones that appear to be those of an eight-year-old.

However, measuring the levels of GH, TSH, LH, FSH, prolactin, and ACTH establishes the diagnosis of CPHD. Underdevelopment or abnormal development of



Pituitary dwarfism: pedigree analysis chart (Gale)

KEY TERMS

Adrenocorticotrophic hormone (ACTH)—A pituitary hormone that acts on cells of the adrenal cortex to produce male sex hormones and hormones that control water and mineral balance in the body.

Antidiuretic hormone (vasopressin)—A hormone that acts on the kidneys to regulate water balance.

Follicle-stimulating hormone (FSH)—A hormone that stimulates estrogen production in females and sperm production in males.

Gonadotropins—Hormones, such as follicle-stimulating hormone, that stimulate the gonads.

Growth hormone (GH)—A hormone that stimulates growth. Also called somatotropin.

Hormone—A chemical messenger produced by the body that regulates specific bodily functions such as growth, development, and reproduction.

Luteinizing hormone (LH)—A hormone secreted by the pituitary gland that regulates the menstrual cycle and triggers ovulation in females. In males it stimulates the testes to produce testosterone.

Oxytocin—A hormone that stimulates uterine contractions during childbirth and the secretion of breast milk.

Panhypopituitarism—Generalized deficiency of all of the anterior pituitary hormones.

Pituitary gland—A small gland at the base of the brain that is responsible for releasing many hormones, including luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Prolactin—A hormone that helps the breast prepare for milk production during pregnancy.

Puberty—The stage of development when the gonads begin to function and secondary sexual characteristics begin to appear.

Thyroid-stimulating hormone (TSH)—A hormone that stimulates the thyroid gland to produce hormones that regulate metabolism.

the pituitary gland can be seen with magnetic resonance imaging (MRI).

Genetic testing may be available if the parental CPHD-related mutations are known. Molecular genetic testing of younger siblings of an affected child allows for early diagnosis and treatment. In any case, younger siblings should be monitored for growth delays. Prenatal genetic testing may also be possible if the relevant mutations have been identified.

QUESTIONS TO ASK YOUR DOCTOR

- What type of combined pituitary hormone deficiency does my child have?
- What caused my child's disorder?
- Is genetic testing for combined pituitary hormone deficiency available for other family members?
- Is prenatal testing available for combined pituitary hormone deficiency?
- What type of hormone replacement therapy will my child need?

Treatment and management

Treatment of CPHD is directed by a pediatric endocrinologist and depends on the hormones that are deficient.

- GH deficiency is treated with GH injections until about age 17. Treatment must be initiated before the child's growth plates have fused.
- TSH is replaced with oral L-thyroxine.
- A limited course of testosterone is used to treat micropenis in male infants with LH and FSH deficiencies.
- For induction of secondary sexual characteristics and puberty, males are treated with monthly injections of testosterone enanthate beginning at 12–13 years of age, and females are treated with estrogen beginning at 11–12 years, and later by cycling with estrogen and progesterone.
- Treatment with gonadotropins can restore fertility in both males and females.
- ACTH deficiency is treated with oral hydrocortisone.

Prognosis

Prognosis depends on the type of CPHD, but in many cases, hormone treatments can lead to near-normal growth, although adults are usually of short stature. Sexual development and fertility are usually possible. However, it can be difficult to balance the levels of the different hormones in the absence of pituitary function, and panhypopituitarism can be particularly difficult to manage. Furthermore, some types of CPHD cause a variety of other medical problems.

Resources

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Human Growth Foundation, 997 Glen Cove Ave., Suite 5, Glen Head, NY 11545, (800) 451-6434, (516) 671-4055, hgf1@hgfound.org, <http://hgfound.org>

Little People of America, 617 Broadway #518, Sonoma, CA 95476, (888) LPA-2001, info@lpaonline.org, <http://www.lpaonline.org>

MAGIC Foundation, 6645 W. North Ave., Oak Park, IL 60302, (708) 383-0808 or (800) 362-4423, ContactUs@magicfoundation.org, <http://www.magicfoundation.org>

Jason S. Schliesser, DC
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Computational genomics

Definition

Computational genomics involves using computer-based mathematical and statistical calculations to analyze genomes. This analysis can help researchers find genes, investigate systems, compare the genomes of different species, diagnose disease, and do many other things.

Description

Huge amounts of data are collected in the study of genomics. Sequencing just one person's whole genome generates approximately 300 gigabytes of raw data. Analysis of this genome produces an additional 100 gigabytes of data. It has been estimated that we will sequence the DNA of more than 100 million genomes by the year



Human genome project computers that record DNA sequencing. Genes are lengths of DNA (deoxyribonucleic acid) that perform specific tasks within an organism. Human DNA has around 3 billion base pairs, divided into more than 100,000 genes. (James King-Holmes/Science Source)

2025, which equates to about 20 billion gigabytes of raw data. Much of this sequencing data will be analyzed as part of pharmaceutical and national population studies.

Analysis of all these data requires a significant amount of computing power and sophisticated mathematical techniques and has led to many advances in the field of computational genomics. This field connects the disciplines of genomics, mathematics, statistics, computer science, and engineering.

Computational genomics uses

Computational genomics is used in gene discovery, diagnosis of disease, personalizing medicine, and managing infectious diseases.

Gene discovery

Computational genomics has been critical for the discovery of genes and their link to disease. The Human Genome Project, which ended in 2003, was the first large-scale, international computational genomics research project. It used computational genomics to sequence the DNA of human genomes and identify the function and location of genes found on the genome. Since then, many countries have launched large-scale population computational genomics projects. For example, in 2018 the UK finished sequencing for the 100,000 Genomes project. This project sequenced 100,000 genomes from people with rare genetic disease or cancers. The goal of this project is to study the genetic causes, diagnosis, and treatment of diseases and find new targeted medicines.

KEY TERMS

Cell—A building block that provides structure to the body and performs all the functions of the body. Cells contain genetic information and can copy themselves. The four main types of cells are the bases of skin, nerve, muscle, and connective tissue.

DNA (deoxyribonucleic acid)—The genetic material that contains the instructions for creating proteins.

DNA base—One unit in a DNA sequence. The four DNA bases are adenine (A), guanine (G), thymine (T), and cytosine (C). The sequence of these bases is the genetic code that contains the instructions for creating proteins.

DNA sequence—The sequence of DNA bases that contains the instructions for creating proteins. A three-base sequence in the DNA contains the instructions for making a particular amino acid. For example, CGC codes for the amino acid alanine. Proteins are made up of one or more amino acids strung together. The instructions for a particular protein are made up of a number of three base sequences. Because DNA is double-stranded, it has two complementary sequences where the bases pair up together. C always pairs with G, and A always

pairs with T. One example of double-stranded DNA sequence for alanine is GCG/CGC.

Gene—A sequence of bases in a DNA sequence that contains the instructions for one protein.

Genome—The complete set of genetic instructions of an organism.

Genomics—The study of the structure, function, and evolution of genomes and how they interact with each other and the environment.

Mitochondrial genome—The DNA (genetic material) found in the mitochondria. The mitochondrial genome contains the instructions for about 37 genes. These genes produce proteins that help the mitochondria function. Mitochondrial DNA is only passed from the mother to her offspring.

Pathogenic variant—Any change in the sequence of a genome that causes disease.

RNA (ribonucleic acid)—The genetic material that is involved in creating proteins.

Sequence (verb)—To determine the sequence of bases in genetic material like DNA or RNA.

Variant—A change in the sequence of a genome.

The NIH has launched a similar project called the Whole Genome Sequencing Project, which has sequenced over 90,000 genomes and aims to sequence 120,000 more. The goal of this project is to identify genetic variations that increase or decrease the risk of heart, lung, blood, and sleep disorders.

Personalized medicine

The DNA sequence of the genome of each person is unique, which means that different people respond differently to different treatments. Personalized medicine customizes treatments based on an individual's genome. Computational genomics has been critical for advances in personalized medicine. Pharmacogenomics and targeted therapies are two examples of personalized medicine.

Pharmacogenomics studies how certain gene variations affect the safety of certain medications and how well they will work. Advances in this field, fueled by computational genomics, have led to genetic tests that can help doctors choose the optimal medication and best dose for a patient. For example, gene variations involving the *CYP2D6* gene can influence the metabolism of codeine into morphine. People who have a duplication in this gene are called

ultrarapid metabolizers. They turn codeine into morphine at a more rapid rate and make greater amounts of morphine. They are at greater risk for overdose if they use codeine and may have serious problems as a result. Breastfeeding mothers with this variation who use codeine are at increased risk of providing excessive amounts of morphine to their babies, which can result in serious breathing problems and even death. People with another variant in *CYP2D6* do not metabolize codeine very well, and they may need to use an alternative pain reliever.

Targeted drug therapies for cancer have been developed using computational genomics. They target specific genes and proteins based on variations found in an individual genome. For example, 20% to 25% of women with breast cancer produce too much HER2 protein. This protein causes the tumor cells to grow more rapidly. These women can benefit if they are given the antibody trastuzumab along with their chemotherapy.

Diagnosis

Diagnosing genetic disease is very complex. There are at least 7,000 known genetic diseases caused by variations in single genes. There is a lot of overlap in

symptoms amongst these diseases, and variations in different genes can cause the same disorder in different people. There are also complex conditions like cardiovascular disease, asthma, and cancer where multiple genes and environmental factors play roles. Early diagnosis of genetic disease relied on evaluation of the symptoms. Later, limited testing that looks for large changes in the chromosomes and genetic testing that looks for variants in specific genes were added to help make or confirm the diagnosis. These approaches can be very time-consuming. For example, one study found that using these approaches, the average time to make the diagnosis of myotonic dystrophy, a muscle-wasting disease, was 14 years.

Next-generation sequencing approaches, such as whole genome sequencing and whole exome sequencing, can help to expedite the diagnosis. Whole genome sequencing looks for variants in the whole genome. It looks for variants in the parts of the genome that contain the genes. The challenge with these approaches is that they generate a lot of data that needs to be analyzed. Whole exome sequencing, for example, generates approximately 30,000 variants, and whole genome sequencing generates even more. It can be challenging to filter through all of these variants to find the one that might explain the disease. To help find this needle in the haystack, researchers have developed computational genomics tools. For example, some tools filter out common variants and predict how likely they will be to cause the disease. There are also many large databases that link specific variants with specific diseases. Computer programs have also been developed to help match an individual's symptoms with variants that might explain them.

Infectious diseases

Sequencing of the genomes of viruses and bacteria can help determine the cause of an infection and help manage outbreaks and pandemics like COVID-19. Sequencing can also help provide information about which treatments might be most effective and help with the development of new treatments.

Researchers around the world have been sharing large amounts of genomic data and using computational genomics to help control the COVID-19 pandemic. New computational tools, such as those for the detection and analysis of SARS-CoV-2-genomes, were created as the result of this pandemic. Computational genomics was also used to identify and analyze new medicines and other treatments for COVID-19.

RNA and mitochondrial DNA genomes

Most computational genomics research to date has focused on analyzing the DNA genome. Newer research

QUESTIONS TO ASK YOUR DOCTOR

- Could whole genome or exome sequencing help diagnose what is wrong with my child?
- Would sequencing my RNA along with my DNA help with my diagnosis?

is investigating both RNA and mitochondrial genomes. RNA (ribonucleic acid) is the genetic material that is involved in creating proteins. The DNA sequence is transcribed into an RNA sequence, which is turned into proteins by machinery in the cell. The mitochondrial genome is DNA found in the mitochondria. Mitochondria, which make energy for the cell, are found in all cells of the body. The mitochondrial genome contains the instructions for about 37 genes, which produce proteins that help the mitochondria function. The mitochondrial genome is only passed from the mother to her offspring through her eggs.

RNA sequencing (RNA-Seq) can be used to show which RNA is present and how much is present in a particular sample. It can help scientists learn which genes are turned on and which are turned off in different cells and how these processes influence disease. RNA-Seq can also help scientists see which changes may indicate disease, and it can be used for diagnosing disease. Variants in genes can often affect which RNA is present and in what amounts. Doing RNA-Seq in combination with DNA sequencing can help to reveal which genetic variant is responsible for disease in an individual. RNA sequencing produces a significant amount of data that can vary significantly. As a result, an increasing number of computational genomics tools are being developed to help make sense of these data.

Variants in the mitochondrial genome can cause disease. Research involving the mitochondrial genome is complex and often results in large amounts of data. Computational genomics tools are being developed to help analyze the data for both research and diagnosis in the clinic.

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Cone-rod dystrophy

Definition

The cone-rod dystrophies (CRDs) are a clinically heterogeneous group of progressive retinal degenerative disorders that cause deterioration of the cones and rods in the retina and frequently lead to blindness. They are also known as retinal cone-rod dystrophy or cone-rod degeneration.

KEY TERMS

Amelogenesis imperfecta—A hereditary dental defect characterized by discoloration of the teeth.

Cones—Receptor cells that allow the perception of colors.

Nystagmus—Involuntary rhythmic movement of the eye.

Photophobia—An extreme sensitivity to light.

Photoreceptor cells—Specialized cells that convert light into nerve signals that ultimately get transmitted to the brain through the optic nerve.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Rod—A photoreceptor that is highly sensitive to low levels of light and transmits images in shades of gray.

Description

CRDs are characterized by skin pigmentation abnormality; involuntary rhythmic movements of the eyes (nystagmus); degeneration of vision (optic atrophy); and sensitivity to light (photophobia). CRDs are also sometimes accompanied by amelogenesis imperfecta, an abnormality affecting the teeth. But the common link in all CRDs is a problem with the rod and cone photoreceptors. Cones are used to detect color and fine details, and account for central vision. Rods are required for night and peripheral vision.

Genetic profile

CRDs can be inherited as either an autosomal dominant (ad) or autosomal recessive (ar) trait. In autosomal recessive cone-rod dystrophies (arCRDs), both parents have one copy of the faulty cone-rod dystrophy gene but do not have the disease. Their offspring are affected, not affected, or carriers. In autosomal dominant cone-rod dystrophies (adCRDs), one parent has a single faulty gene. When the affected parent mates with an unaffected and noncarrier mate, the offspring are either affected or not affected, but they are not carriers.

CRDs are genetically heterogeneous. Families showing autosomal dominant, autosomal recessive, and X-linked recessive inheritance have been reported, and a number of causative genes and chromosomal loci have now been identified. Mutations in genes that encode proteins involved in phototransduction, transcription,

metabolic pathways, and other processes affecting retinal function have been associated with CRDs. The *CRX* (*Cone-Rod Homeobox*) gene has been shown to contain mutations that cause adCRDs. This genetic form of CRD is clinically known as cone-rod dystrophy 2 (CRD2). Mutations in the *CRX* gene interfere in the development process of embryonic photoreceptor cells during the early stages of life. The result is abnormal photoreceptor cells with reduced function. Currently, six genes have been shown to be associated with adCRDs: *CRX2*, *3GUCY2D*, *6RIM1*, *7Peripherin/RDS*, *13GUCA1A*, *18*, and *AIPL1*, *20* with more remaining to be discovered. Mutations in *ABCA4* are believed to be the most common cause of arCRD. Other studies have identified additional novel mutations in the *RDH12* (*retinol dehydrogenase 12*) gene associated with early onset CRD. The gene *RPGR* is responsible for two-thirds of the X-linked retinitis pigmentosa (RP) and an as yet undetermined percentage of CRDs.

Demographics

CRDs are rare disorders. The current statistics from Orphanet estimate the prevalence at 1 in 40,000.

Signs and symptoms

The earliest symptom of CRD is loss of night vision that usually begins after the age of 20. The vision loss is progressive and unrelenting. Over the next decade, loss of all vision begins, and by age 50, most people with cone-rod dystrophy have gone completely blind.

Cone-rod dystrophy is occasionally accompanied by amelogenesis imperfecta, which is characterized by abnormally shaped teeth and abnormalities in the tooth enamel.

Diagnosis

The earliest symptom of CRD is decreased visual acuity. However, the diagnosis is usually established upon detection of loss of the peripheral visual fields. Cone-rod dystrophy must be distinguished from RP. In CRD, rods and cones are lost at approximately the same rate. It is further distinguished from RP by the absence of night blindness as a presenting symptom.

Diagnostic gene testing is available for 120 genes identified in 36 different CRDs. Sequence analysis of the entire coding region and deletion/duplication analysis are the most common tests used for diagnosis.

Treatment and management

There is no therapy that stops the evolution of CRDs or restores vision, and the visual prognosis is poor. It has been suggested that people with cone-rod dystrophy may

QUESTIONS TO ASK YOUR DOCTOR

- I have cone-rod dystrophy, but my partner does not. What are the chances that our son will inherit the condition?
- I have read a lot about retinitis pigmentosa. How is my cone-rod dystrophy related to this condition?
- How likely is it that I will completely lose my vision as a result of my cone-rod dystrophy?

be able to slow the progression of their blindness by wearing sunglasses and avoiding bright light. Treatment aims at slowing down the degenerative process, treating the complications, and helping patients to cope with the social and psychological impact of blindness.

In 2008, a novel gene was identified, *NPHP4*, as causing CRD in dogs; in 2017, the gene *IQCB1* was identified as causing CRD in a species of African cat known as *Felis nigripes*. Since CRDs affect humans, felines, and canines, further studies into the complex genetics of this retinopathy has potential for the development of potential therapies.

Prognosis

Studies of individuals thought to have CRD reveal that central vision loss begins in the first decade of life with the onset of night blindness occurring sometime after age 20. Little visual function remains after the age of 50.

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ORGANIZATIONS

- American Academy of Ophthalmology (AAO), PO Box 7424, San Francisco, CA 94120-7424, (415) 561-8500, (415) 561-8533, patientinfo@aao.org, <http://www.aao.org>
- American Optometric Association, 243 N. Lindbergh Blvd., Louis, MO 63141, (800) 365-2219, <http://www.aoa.org>
- National Eye Institute (NEI), Information Office, 31 Center Dr. MSC 2510, Bethesda, MD 20892-2510, (301) 496-5248, 2020@nei.nih.gov, <http://www.nei.nih.gov>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06813, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>
- Prevent Blindness America, 211 W. Wacker Dr., Suite 1700, Chicago, Illinois 60606, (800) 331-2020, <http://www.preventblindness.org>

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Congenital adrenal hyperplasia

Definition

Congenital adrenal hyperplasia (CAH) is a group of common autosomal recessive genetic conditions that result from an abnormality in one of the enzymes required by the adrenal glands to convert cholesterol into the steroid hormones cortisol and aldosterone. CAH is characterized by cortisol and aldosterone deficiencies and overproduction of androgens (male sex hormones), with effects ranging from mild to severe.

Description

The first likely description of CAH occurred in 1865 when anatomist Luigi De Crecchio reported on a cadaver that had what appeared to be a penis with the urinary opening on its underside, and undescended testicles. What was remarkable about this cadaver was that it also had a vagina, a uterus, fallopian tubes, ovaries, and very enlarged adrenal glands. From four years of age until death, this person had lived as a male, although at birth he had been declared a female. He died in his 40s after repeated episodes of vomiting, diarrhea, and prostration. This genetic female with masculinized external genitals

and abnormalities in salt regulation had all the symptoms of severe untreated CAH.

CAH results from an abnormality in one of the enzymes required by the adrenal glands to convert cholesterol into cortisol, aldosterone, and androgens such as testosterone. Cortisol helps the body cope with stress, such as injury or illness, as well as maintain blood sugar levels and suppress inflammation; aldosterone helps to ensure that the body retains normal amounts of salt and fluids, which helps control blood pressure; and androgens such as testosterone are involved in the production of masculine traits such as body hair and the development of male sex organs.

There are many different enzymes necessary for the normal production of cortisol, aldosterone, and testosterone. Each type of CAH results from a deficiency in one of these enzymes. Most cases of CAH (90%–95%) are caused by a deficiency of adrenal steroid 21-hydroxylase, which is involved in the conversion of cholesterol to cortisol and aldosterone but not in the conversion of cholesterol to testosterone. A deficiency or absence of 21-hydroxylase (CAH21) decreases the levels of cortisol and aldosterone, which prompts the body to compensate by forcing the adrenal glands to increase the conversion of cholesterol. This does not significantly increase cortisol and aldosterone levels, but it does increase the levels of testosterone, which is produced by another enzyme. Both men and women normally produce some testosterone, although men typically produce larger amounts.

Increased levels of testosterone can result in premature puberty in males and females and can prevent menstrual periods and increase body hair (hirsutism) in women. Females who produce high levels of testosterone in utero can be born with masculinized external genitals. Decreased levels of cortisol can also result in increased levels of two other hormones: 17-hydroxyprogesterone and androstenedione. Increased levels of 17-hydroxyprogesterone in conjunction with decreased levels of aldosterone can result in the inability of the body to retain normal amounts of salt.

There are three major types of CAH21: (1) the classic salt-wasting form, (2) the classic non-salt-wasting form or simple virilizing form, and (3) the nonclassic (late-onset) form. The classic forms of CAH, if untreated, can result in premature puberty in boys, girls born with an enlarged clitoris or external male genitals, and increased growth in childhood but short adult height in both males and females. The salt-losing form of CAH21 results in reduced levels of salt in the body, which can sometimes result in an adrenal crisis—a life-threatening condition characterized by severe dehydration, very low blood pressure, and vomiting. The nonclassic, or late-onset,

form of CAH21, caused by a partial enzyme deficiency, is milder but can cause an absence of menstruation and increased body hair in women and a low sperm count in men. Some people with nonclassic CAH21 are only diagnosed because of an affected family member.

CAH due to a deficiency in the enzyme 11-beta-hydroxylase (CAH11) also results in excess androgen and virilization, as well as hypertension (high blood pressure) caused by salt retention. CAH11 accounts for 5%–8% of CAH cases. Females with the classic form of CAH11 have external genitalia that are not clearly male or female, but the internal reproductive organs develop normally. Males and females experience early puberty and an early growth spurt that can lead to short stature in adulthood. About two-thirds of individuals with CAH11 have hypertension, usually developing within the first year of life. Females with the nonclassic form of CAH11 have normal genitalia but develop excess body hair and irregular menstruation. Short stature is usually the only sign of nonclassic CAH11 in males. Nonclassic CAH11 does not cause hypertension.

Genetic profile

All types of CAH are autosomal recessive genetic conditions. An autosomal recessive condition is caused by a change (mutation) in both genes of a pair, one inherited from each parent. A person with CAH has mutations in both copies of the gene responsible for producing one of the enzymes involved in steroid production from cholesterol. The parents of a child with CAH are called carriers, since they each possess one mutated CAH gene and one normal CAH gene. Carriers usually do not have any symptoms of disease, since their normal gene produces enough enzyme to prevent symptoms of CAH. Each child born to parents who are both carriers for the same type of CAH has a 25% chance of having CAH, a 50% chance of being a carrier, and a 25% chance of being neither a carrier nor having CAH.

CAH21 results from mutations in the *CYP21A2* gene that produces steroid 21-hydroxylase. *CYP21A2* is located on the short arm (p) of chromosome 6 at 6p21.3. A number of different mutations in *CYP21A2* can reduce or abolish 21-hydroxylase production. The types and combinations of *CYP21A2* mutations at least partially determine the severity of CAH21 symptoms.

CAH11 is caused by mutations in the *CYP11B1* gene that produces 11-beta-hydroxylase. Classic CAH11 is typically caused by mutations that produce 11-beta-hydroxylase that has little or no activity. Nonclassic CAH11 is typically caused by *CYP11B1* mutations that have moderately reduced function.

Rare forms of CAH are caused by mutations in other genes. Lipoid CAH is caused by mutations in the gene encoding steroidogenic acute regulatory protein (*STAR*) located on chromosome 8 at 8p11. CAH due to 17-alpha-hydroxylase deficiency is caused by mutations in the gene encoding steroid 17-monooxygenase (*CYP17A1*).

Demographics

CAH is the most common disorder of the adrenal glands. It affects both females and males of all ethnic backgrounds. CAH21 is the most common form of CAH, accounting for 90%–95% of cases. Approximately 1 person in 60 is a carrier for CAH21. Classic CAH21 occurs in approximately 1 in 15,000 births worldwide. Nonclassic CAH21 is one of the most common genetic disorders, affecting about 1 in 1,000 people overall; however, in some communities it may affect as many as 1 in 20. It is particularly common among Ashkenazi Jews, Hispanics, Italians, and people of Balkan descent. CAH11 accounts for 5%–8% of all CAH cases. It is estimated to occur in 1 in 100,000–200,000 newborns. However, among Moroccan Jews living in Israel, it occurs in about 1 in 5,000–7,000 newborns. The classic form of CAH11 appears to be much more common than the nonclassic form. Lipoid CAH is rare worldwide but is common in Japanese, Korean, and Palestinian Arab populations.

Signs and symptoms

CAH symptoms depend on the particular enzyme deficiency and its extent. CAH can cause congenital masculinization of the female external genitals or feminization of the male genitals, but it does not affect the internal reproductive organs of either males or females. CAH can prevent menstruation in women and increase body hair, and is associated with premature puberty in both males and females.

Classic salt-losing CAH21

The classic salt-losing form is the most severe form of CAH21, resulting from little or no production of 21-hydroxylase. Untreated girls may be mistaken for boys at birth since they are typically born with masculinized external genitals. Their internal sexual organs are, however, normal. Males with untreated CAH21 have normal external genitalia but may experience premature puberty. Signs of puberty such as pubic hair, enlarged penis, deepened voice, and increased muscle strength can occur long before normal puberty, sometimes as early as two to three years of age. An abnormal growth spurt in childhood can prevent later growth, resulting in short

KEY TERMS

Adrenal crisis—A life-threatening complication of salt-losing (salt-wasting) congenital adrenal hyperplasia with 21-hydroxylase deficiency.

Adrenal gland—A triangle-shaped endocrine gland located above each kidney that synthesizes aldosterone, cortisol, and testosterone from cholesterol. The adrenal glands are responsible for salt and water levels in the body, as well as for protein, fat, and carbohydrate metabolism.

Aldosterone—A steroid hormone produced by the adrenal gland that regulates salt and fluid balance in the body and is deficient in congenital adrenal hyperplasia.

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Androgens—Steroid hormones that contribute to the development of male sex organs and male secondary sexual characteristics.

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are required to express the trait or disease.

Carrier—An individual who possesses an unexpressed abnormal gene of a recessive genetic disorder.

Carrier testing—Testing performed to determine if a person carries one mutated copy of a particular gene.

Chromosomes—The gene-containing structures found in all of the body's cells; in each normal cell, there are 46 chromosomes that come in 23 pairs.

Congenital—Refers to a disorder that is present at birth.

Cortisol—Hydrocortisone; a glucocorticoid hormone produced by the adrenal glands that mediates various metabolic process and responds to stress; deficient in congenital adrenal hypoplasia.

Deoxyribonucleic acid (DNA)—The genetic material in cells that carries the inherited instructions for growth, development, and cellular functioning.

DNA testing—Genetic analysis of DNA (the genetic component of cells) to determine changes in genes that may cause specific disorders.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Gene—A building block of inheritance that contains the instructions for the production of a particular protein and is made up of a molecular sequence found on a section of DNA. Each gene is found at a precise location on a chromosome.

Glucocorticoids—Corticosteroids, such as cortisol and dexamethasone, that regulate metabolism, along with other functions; medications used to treat congenital adrenal hyperplasia.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Hypertension—Abnormally high blood pressure in an artery.

In utero—While in the uterus; before birth.

Labia—The two pairs of skin folds that form the externally visible female genitalia. The outer pair is called the labia majora; the labia minora are smaller and lie within the labia majora.

Mutation—An inherited or *de novo* change in the DNA sequence of the genome.

Prenatal testing—Testing for a disease such as a genetic condition in an unborn baby.

Virilization—Masculinization; the development of male sexual characteristics in a female or increased male characteristics in a male caused by excess androgen production.

stature in both males and females. This form of CAH21, if untreated, results in a loss of salt that can trigger an adrenal crisis, which is a life-threatening condition characterized by severe dehydration, very low blood pressure, weakening of the heart muscles, and vomiting. Adrenal crisis typically occurs by 6 to 12 weeks of age. On occasion, salt loss is not noticed until precipitated by an infection in early childhood.

Classic non-salt-losing CAH21

The classic non-salt-losing form of CAH21 results from a low amount of 21-hydroxylase production. In this form of CAH21, enough enzyme is present to prevent abnormally low levels of salt in the body and adrenal crises. Girls are born with slightly masculinized external genitals such as an enlarged clitoris and a partial fusion of the labia. If untreated, they may also experience early

puberty and absence of menstruation. Untreated boys have normal genitals but may have premature puberty. This form of CAH21 can also cause increased growth in childhood and short adult stature.

Nonclassic CAH21

The nonclassic form is the mildest type of CAH21. It results from mildly decreased levels of 21-hydroxylase. Males and females with this form of CAH21 appear normal at birth and do not have salt deficiency. Symptoms may arise in infancy, childhood, or adulthood. Untreated women may have an increase in body hair, irregular or absent menstruation, and/or cysts on their ovaries. Many men have no symptoms. Some men and woman have short stature, severe acne, and decreased fertility.

Diagnosis

Diagnostic testing

Most forms of CAH can be diagnosed by a clinical examination, family history, and the amount of specific hormones in a urine sample. CAH21 can be diagnosed by elevated 17-hydroxyprogesterone in a urine sample. However, CAH21 is best diagnosed with a blood test called an ACTH (adrenocorticotrophic hormone) stimulation test. ACTH is a hormone that stimulates the adrenal glands to convert cholesterol to cortisol. The ACTH stimulation test measures the amount of 17-hydroxyprogesterone in the blood before and after stimulation with ACTH. People with CAH21 have excess production of 17-hydroxyprogesterone after stimulation with ACTH. The ACTH stimulation test can usually identify the type of CAH21.

CAH can also be diagnosed by genetic testing. Detection of a *CYP21* gene alteration can confirm an uncertain diagnosis and can facilitate prenatal diagnosis and carrier testing of relatives.

Carrier testing

Carrier testing may be recommended for relatives of a person with CAH or parents of a child with CAH. Carriers for CAH21 can sometimes be identified through the ACTH stimulation test, although DNA testing is more accurate. If a change in the *CYP21* gene is detected in an affected person, carrier testing can be performed on siblings and parents with an accuracy of greater than 99%. Carrier testing should be considered by anyone whose partner is a known carrier or is affected by CAH. Genetic testing can also identify approximately 95% of carriers for CAH21 who do not have a family history of CAH21.

Prenatal testing

If both parents are carriers for the same type of CAH or one parent is a carrier and the other parent is affected with by the same type of CAH, prenatal testing should be considered. Prenatal testing for CAH21 can only be performed if both parents have detectable mutations in *CYP21A2*. If the relevant gene mutations in the parents have not been identified, prenatal diagnosis of the salt-losing form of CAH21 can be performed by measuring the amount of 17-hydroxyprogesterone in amniotic fluid obtained through amniocentesis. Prenatal testing is especially important for mothers who are undergoing dexamethasone therapy to help prevent their daughters from being born with masculine genitalia. Although treatment must be started before prenatal testing can be performed, treatment can be discontinued if the baby is found to not have CAH21.

Newborn screening

Most states and several foreign countries screen newborns for CAH21 by measuring the amount of 17-hydroxyprogesterone in a drop of blood obtained through a heel prick. The same specimen is tested for thyroid function and various other inherited diseases. Newborn screening is recommended because newborn boys have no outward signs of CAH21 and the death rate from adrenal crisis is high but preventable by early diagnosis and treatment. However, a 2012 study found that routine newborn screening failed to identify approximately 20% of infants with CAH.

Treatment and management

Medications

Most people with CAH are treated with cortisol-like medications called glucocorticoids—oral hydrocortisone for children and prednisone or dexamethasone for adults. In most cases, this therapy is life-long. The goal of treatment is to return cortisol, aldosterone, and testosterone to near-normal levels. Patients with salt-wasting classic CAH21 also require fludrocortisone, an aldosterone-like drug, in order to retain salt and prevent adrenal crises. Babies with the salt-losing form of CAH21 must have salt added to their formula or breast milk. Children and adults do not need salt supplements if they have a high-salt diet. Adrenal crisis is treated by intravenous administration of fluids containing sugars and salt.

Medications usually achieve hormonal balance, but CAH patients can have periods of fluctuating hormones that require modifications in steroid therapy. Because classic CAH can cause short adult stature and high-dose

QUESTIONS TO ASK YOUR DOCTOR

- What are the risks of surgery for my child with congenital adrenal hyperplasia?
- How early in pregnancy (or in utero) can congenital adrenal hyperplasia be diagnosed?
- What treatments are available for congenital adrenal hyperplasia?
- What is the risk that we will have another child with congenital adrenal hyperplasia?
- Is prenatal genetic testing available for congenital adrenal hyperplasia?

glucocorticoids inhibit growth, adjusting steroid doses in the first two years of life is extremely important to maintain near-normal growth and prevent weight gain and/or hypertension. Because of the difficulties in maintaining hormonal balances with medications, clinical trials are testing various new drug combinations. People with the nonclassic form of CAH21 are treated with very-low-dose oral glucocorticoids if required.

Surgery

Adrenalectomy, a surgical procedure to remove the adrenal glands, is a more radical treatment for people with the salt-losing form of CAH21 who have little or no enzyme activity. This surgery allows them to be treated with lower doses of steroids. Adrenalectomy was common before the advent of steroid therapy and is again being recommended for some patients, especially females with little or no enzyme activity and severe virilization that requires high-dose glucocorticoids. Laparoscopic surgery has greatly simplified adrenalectomy, and the life-long replacement hormone doses are lower than those necessary for treating CAH.

Girls born with masculinized genitals may undergo surgery to create female genitals. This surgery is often performed at about 6 to 12 weeks of age. Sometimes an initial surgery is followed by surgery to correct the opening to the vagina when the girl becomes sexually active. Some people believe that any genital surgery should be delayed until individuals are old enough to decide for themselves. Girls with nonclassic CAH do not require genital surgery.

Prenatal treatment

Some mothers who are at risk for having a child with CAH21 take a type of steroid called dexamethasone during

pregnancy. This can often prevent masculinization of the external genitals in female fetuses. To be fully effective, treatment must be started at approximately five to six weeks of gestation, prior to the formation of the external genitals. Treatment can be stopped if prenatal testing shows that the baby is male or an unaffected female; otherwise, the treatment continues throughout the pregnancy. Although this treatment does not appear to have many adverse effects on the fetus, the long-term risks are not known. The mother may experience side effects such as weight gain, fluid accumulation, sugar intolerance, high blood pressure, gastrointestinal problems, and mood swings.

Prognosis

If appropriately treated, the prognosis for CAH, and particularly CAH21, is very good, and most people with CAH have normal lifespans. However, the prognosis for patients with the salt-losing form of CAH21 is dependent on early identification and treatment. Even with treatment, some people with CAH21 have short adult stature and may have decreased fertility. Females treated with feminizing hormones or surgery for masculinized genitals may experience physical and/or psychological difficulties with sexual activity and sexual identity, as well as gender confusion.

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ORGANIZATIONS

- CARES Foundation, 2414 Morris Ave., Suite 110, Union, NJ 07083, (908) 364-0272, (866) 227-3737, contact@caresfoundation.org, <http://www.caresfoundation.org>

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), 31 Center Dr., Building 31, Room 2A32, Bethesda, MD 20892-2425, (800) 370-2943, (866) 760-5947, NICHDInformationResourceCenter@mail.nih.gov, <https://www.nichd.nih.gov>

National Adrenal Diseases Foundation, P.O. Box 566, Lake Zurich, IL 60047, (847) 726-9010, nadfsupport@nadf.org, <http://www.nadf.us>

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Congenital contractural arachnodactyly

Definition

Congenital contractural arachnodactyly (CCA) is a rare genetic disorder of the connective tissue of the skeleton. It is also known as Beals syndrome, Beals contractural arachnodactyly (BCA), or Beals-Hecht syndrome.

Description

Individuals with CCA usually have long, thin fingers and toes that cannot be straightened out because of contractures, resulting in a limited range of motion in the joints of the fingers, hips, elbows, knees, and ankles. They also have unusual external ears that appear crumpled. Contractures of the elbows, knees, and hips at birth are very common. Some babies also have clubfoot, causing one or both feet to be turned in toward each other at the ankles. In most individuals, the contractures improve with time and the clubfoot responds well to physiotherapy.

CCA occurs when fibrillin-2, an important component of the body's connective tissue (the glue and scaffolding of the body, including bones, cartilage, tendons, and fibers) is not made properly. The gene responsible for making fibrillin-2 is called *FBN2* and is located on chromosome 5. Mutations (changes) in the *FBN2* gene result in CCA.

Genetic profile

CCA is caused by a mutation occurring in a gene. Genes are units of hereditary material passed from parents to a child through the egg and sperm. The information contained in genes is responsible for the development of all the cells and tissues of the body. Most genes occur in pairs: one copy of each pair is inherited from the egg cell produced by the mother, and the other copy of each pair comes from the sperm cell of the father.

The gene known as *FBN2* instructs the body how to make fibrillin-2, a specific type of protein. Proteins are substances made in the body that consist of chains of amino acids. Fibrillin-2 is an important part of connective tissue, which provides structural support and elasticity to the body. It is made up of various components, including elastic-like fibers, and fibrillin-2 is thought to play a role in ensuring that the elastic fibers of the connective tissue are assembled properly early in development. Fibrillin-2 binds with other proteins and substances to form microfibrils that form the fibers that provide strength and flexibility to connective tissue. Microfibrils also have a role in regulating growth factors. People with CCA have a mutation in one copy of their *FBN2* gene. As a result, their fibrillin-2 is unable to function properly, resulting in the symptoms of CCA.

CCA is inherited as a dominant condition. Dominant conditions require the presence of only one altered copy of a gene. The mutation in the *FBN2* gene that causes CCA can be inherited from a parent who is also affected with CCA. Individuals with CCA have a 50% chance in each pregnancy to have a child with the condition.

Sometimes CCA cannot be traced back to a parent with the condition. In these cases, the genetic change is said to be a spontaneous mutation. This means that the *FBN2* gene (which functions normally in the parents) mutated in either the sperm of the father or the egg of the mother. If fertilization occurs, the resulting child will have CCA. People with CCA due to a spontaneous mutation can then pass on their altered *FBN2* gene to their children.

Demographics

CCA affects males and females of all ethnic groups. It is a rare condition, estimated to affect fewer than 1 in 10,000 people worldwide.

Signs and symptoms

Besides the general appearance of people with CCA (tall and thin, contractures, with typical crumpled ears), symptoms of the disorder vary from one affected individual to the next. Sometimes the arms are disproportionately long for the person's height. Other less common features may include a small chin, a protruding forehead, and a high arch in the roof of the mouth (palate).

An abnormal bending or twisting of the spine (kyphosis/scoliosis) is seen in about half of individuals diagnosed with CCA and can occur in early infancy. This bending and twisting of the spine tends to worsen over time. Some individuals may also have an abnormal

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman’s abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chromosome—A microscopic threadlike structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Connective tissue—Tissues responsible for support throughout the body, including cartilage, bone, fat, and tissue underlying skin and supporting organs, blood vessels, and nerves.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

FBN2—The gene that encodes fibrillin-2; mutations in this gene can cause congenital contractural arachnodactyly.

Fibrillin-2—A protein that helps form microfibrils that provide strength and flexibility to connective tissue.

Kyphosis—An abnormal outward curvature of the spine, with a hump at the upper back.

Mitral valve prolapse—A heart defect in which one of the valves of the heart (which normally controls blood flow) becomes floppy. Mitral valve prolapse may be detected as a heart murmur, but there are usually no symptoms.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual or manifest as disease and can be transmitted to offspring.

Proteins—Important building blocks of the body, composed of amino acids and involved in the formation of body structures and controlling the basic functions of the human body.

Scoliosis—An abnormal side-to-side curvature of the spine.

indentation or protrusion of their chest wall. Decreased muscle bulk, especially in the lower legs, is also a common sign of CCA.

Less common symptoms of CCA include heart and eye problems. The most frequent heart problem involves one of the heart valves (mitral valve prolapse) and may necessitate medication prior to dental or other surgeries so as to prevent infection. More serious heart problems may occur but are rare. Rarely, the aorta—the major blood vessel carrying blood away from the heart—may be enlarged. This condition usually requires medication to prevent further enlargement, or occasionally surgery. A small number of individuals with CCA are nearsighted and require eyeglasses.

Diagnosis

The diagnosis of CCA is based on the presence of specific characteristics. The diagnosis is suspected in anyone with the typical features of CCA, such as tall, slender stature; contractures of many joints including the elbows, knees, hips, and fingers; abnormal curvature of the spine; decreased muscle bulk; and crumpled ears. Genetic testing is available for CCA.

Testing during pregnancy (prenatal diagnosis) to determine whether the unborn child of at-risk parents may be affected may be available. Using a procedure called amniocentesis, fluid surrounding the developing fetus is removed, and cells from the fluid are submitted for genetic testing. However, because of the relatively mild nature of the condition in most individuals, prenatal diagnosis may not be requested.

Treatment and management

There is no cure for CCA. Management of the disorder usually involves physiotherapy in early childhood to increase joint mobility and to lessen the effects of low muscle bulk. The contractures have been known to spontaneously improve, with surgery sometimes required to release them.

The abnormal curvature of the spine tends to worsen with time. A bone specialist should be consulted for advice on the appropriate treatment. Some individuals may require a back brace and/or surgery to correct the curvature.

A heart specialist should be consulted because some individuals with CCA have heart defects. An ultrasound

QUESTIONS TO ASK YOUR DOCTOR

- Can you explain why my child's CCA is a genetic disorder?
- Will surgery be necessary to deal with the condition and if so, what risks are associated with the surgery?
- What other kinds of treatment will my child require for CCA?
- What effect will my child's CCA have on lifespan?
- What are my risks of having another child with CCA?

of the heart usually can assess any abnormalities. Medications may be used to treat some types of heart problems. An eye specialist should also be consulted because of the possibility of eye problems such as myopia (nearsightedness). Prescription eyeglasses may be necessary.

Individuals with CCA and their families may benefit from genetic counseling for information on the condition and the risk of CCA in future pregnancies.

Prognosis

There tends to be gradual improvement in the joint contractures with time. The abnormal spinal curvature tends to get worse over time and may require bracing or surgery. The lifespan of individuals with CCA is not affected.

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ORGANIZATIONS

Marfan Foundation, 22 Manhasset Ave., Port Washington, NY 11050, (800) 8-MARFAN x126, (516) 883-8712, staff@marfan.org, <http://www.marfan.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Congenital familial hypertrophic synovitis
see **Arthropathy-campodactyly syndrome**

Congenital heart disease

Definition

Congenital heart disease, also called congenital heart defect, includes a variety of malformations of the heart or its major blood vessels that are present at the birth of a child.

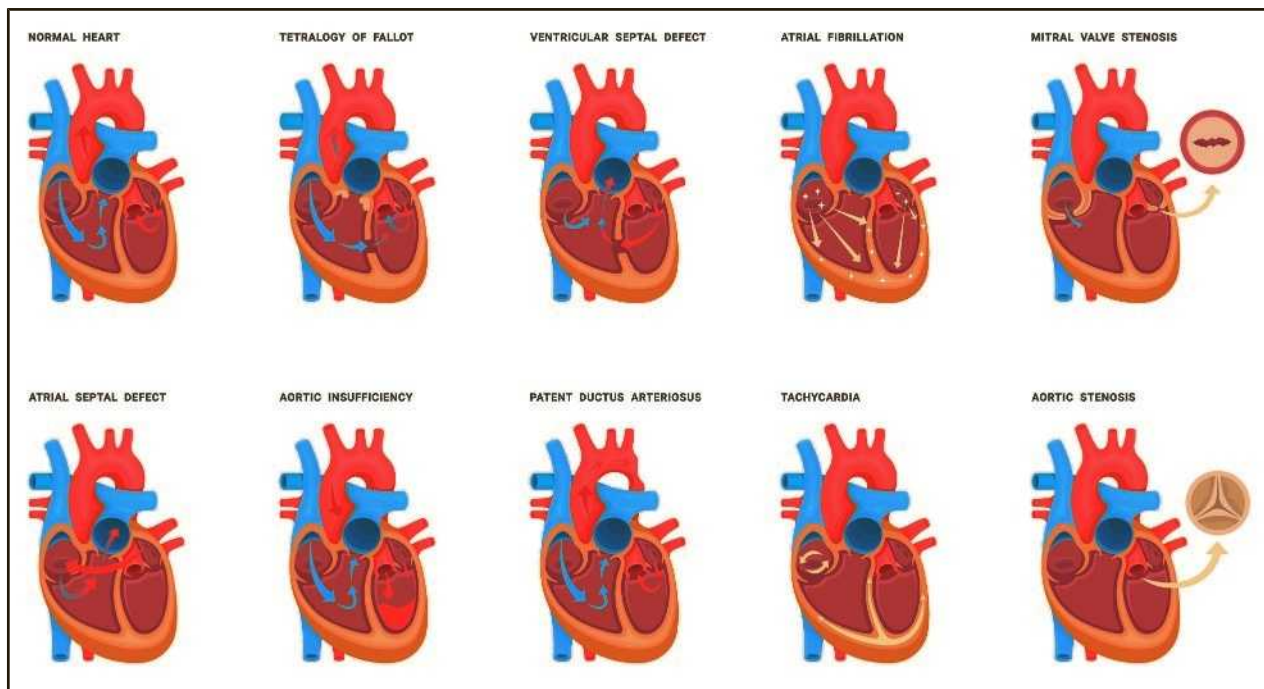
Description

Congenital heart disease occurs when the heart or blood vessels near the heart do not develop properly before birth. Some infants are born with mild types of congenital heart disease, but most need surgery in order to survive. Patients who have had surgery are likely to experience other cardiac problems later in life.

Most types of congenital heart disease obstruct the flow of blood in the heart or the nearby vessels or cause an abnormal flow of blood through the heart. Rarer types of congenital heart disease occur when the newborn has only one ventricle, when the pulmonary artery and the aorta come out of the same ventricle, or when one side of the heart is not completely formed.

Patent ductus arteriosus

Patent ductus arteriosus refers to the opening of a passageway—or temporary blood vessel (ductus)—to carry the blood from the heart to the aorta before birth,



Various heart defects. (Shutterstock/N.Style)

allowing blood to bypass the lungs, which are not yet functional. The ductus should close spontaneously in the first few hours or days after birth. When it does not close in the newborn, some of the blood that should flow through the aorta then returns to the lungs. Patent ductus arteriosus is common in premature babies but rare in full-term babies. It has also been associated with mothers who had German measles (rubella) while pregnant.

Hypoplastic left heart syndrome

Hypoplastic left heart syndrome, a condition in which the left side of the heart is underdeveloped, is rare, but it is the most serious type of congenital heart disease. With this syndrome, blood reaches the aorta, which pumps blood to the entire body only from the ductus, which then normally closes within a few days of birth. In hypoplastic left heart syndrome, the baby seems normal at birth, but as the ductus closes, blood cannot reach the aorta and circulation fails.

Obstructive defects

When heart valves, arteries, or veins are narrowed, they partly or completely block the flow of blood. The most common obstructive defects are pulmonary valve stenosis, aortic valve stenosis, and coarctation of the aorta. Bicuspid aortic valve and subaortic stenosis are less common.

Stenosis is a narrowing of the valves or arteries. In pulmonary stenosis, the pulmonary valve does not open

properly, forcing the right ventricle to work harder. In aortic stenosis, the improperly formed aortic valve is narrowed. As the left ventricle works harder to pump blood through the body, it becomes enlarged. In coarctation of the aorta, the aorta is constricted, reducing the flow of blood to the lower part of the body and increasing blood pressure in the upper body.

A bicuspid aortic valve has only two flaps instead of three, which can lead to stenosis in adulthood. Subaortic stenosis is a narrowing of the left ventricle below the aortic valve, which limits the flow of blood from the left ventricle.

Septal defects

When a baby is born with a hole in the septum (the wall separating the right and left sides of the heart), blood leaks from the left side of the heart to the right, or from a higher pressure zone to a lower pressure zone. A major leakage can lead to enlargement of the heart and failing circulation. The most common types of septal defects are atrial septal defect, an opening between the two upper heart chambers; and ventricular septal defect, an opening between the two lower heart chambers. Ventricular septal defect accounts for about 20% of all cases of congenital heart disease in the United States.

Cyanotic defects

Heart disorders that cause a decreased, inadequate amount of oxygen in blood pumped to the body are called

cyanotic defects. These defects, including truncus arteriosus, total anomalous pulmonary venous return, tetralogy of Fallot, transposition of the great arteries, and tricuspid atresia, result in a blue discoloration of the skin due to low oxygen levels. About 10% of cases of congenital heart disease in the United States are tetralogy of Fallot, which includes four defects. The major defects are a large hole between the ventricles, which allows oxygen-poor blood to mix with oxygen-rich blood, and narrowing at or beneath the pulmonary valve. The other defects are an overly muscular right ventricle and an aorta that lies over the ventricular hole.

In transposition (reversal of position) of the great arteries, the pulmonary artery and the aorta are reversed, causing oxygen-rich blood to re-circulate to the lungs while oxygen-poor blood goes to the rest of the body. In tricuspid atresia, the baby lacks a tricuspid valve, and blood cannot flow properly from the right atrium to the right ventricle.

Other defects

Ebstein's anomaly is a rare congenital syndrome that causes malformed tricuspid valve leaflets, which allow blood to leak between the right ventricle and the right atrium. It also may cause a hole in the wall between the left and right atrium. Treatment often involves repairing the tricuspid valve. Ebstein's anomaly may be associated with maternal use of the psychiatric drug lithium during pregnancy.

Brugada syndrome is another rare congenital heart defect that appears in adulthood and may cause sudden death if untreated. Symptoms, which include rapid, uneven heartbeat, often appear at night. Scientists believe that Brugada syndrome is caused by mutations in the gene *SCN5A*, which involves cardiac sodium channels.

Infants born with DiGeorge sequence can have heart defects such as a malformed aortic arch and tetralogy of Fallot. DiGeorge is the most common microdeletion syndrome and is often caused by mutations in genes in the region 22q11.2.

Williams-Beuren syndrome or Williams syndrome (WS) is a gene deletion syndrome caused by deletion at 7q11.23. It is characterized by specific cardiovascular defects such as vascular stenoses and elastin arteriopathy, distinctive personality characteristics, growth abnormalities, connective tissue and skeletal abnormalities, and endocrine abnormalities including infantile hypercalcemia, hypercalciuria, hypothyroidism, and early puberty.

Jacobsen syndrome (JS) is gene deletion syndrome involving deletions from 11q23 to the telomere. More than half of affected individuals have congenital heart disease along with growth retardation, cognitive and behavioral problems, recurrent infections, immune deficiency, and

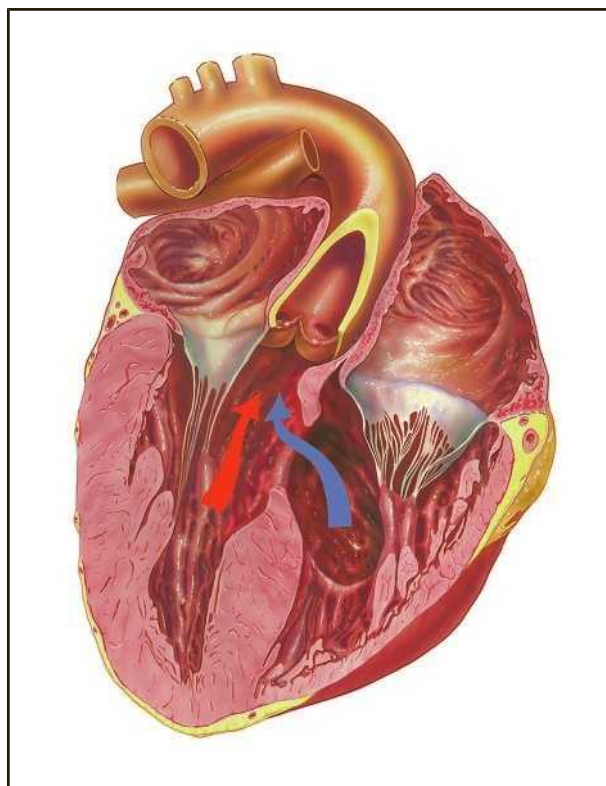


Illustration of a defective heart viewed from behind. The defect is a hole in the wall between the two ventricles. This results in deoxygenated blood (blue arrow) mixing with oxygenated blood (red arrow), which can lead to pulmonary hypertension and breathlessness. (Bo Veisland/Science Source)

blood, ophthalmologic, gastrointestinal, and genitourinary problems.

The 1p36 deletion syndrome is the second most common deletion syndrome, and about 90% of affected individuals have severe intellectual disability and behavioral problems along with brain abnormalities and structural heart defects, including septal defects, valvular abnormalities, tetralogy of Fallot, coarctation of the aorta, stenosis of the right ventricle, and Ebstein's anomaly.

1q21.1 deletions are associated with microcephaly, mild intellectual disability, short stature, eye abnormalities and hearing loss in addition to many types of congenital heart disease.

8p23.1 deletions are associated with diaphragmatic hernia, growth impairment, microcephaly, behavioral problems (including hyperactivity and impulsivity), mild to moderate intellectual disability, and developmental delays as well as congenital heart disease.

Marfan syndrome is a connective tissue disorder that causes tears in the aorta. Since the disease also causes

KEY TERMS

Aorta—The main artery located above the heart, which pumps oxygenated blood out into the body. Many congenital heart defects affect the aorta.

Congenital—Referring to a disorder that is present at birth.

Cyanotic—Marked by bluish discoloration of the skin due to a lack of oxygen in the blood. It is one of the types of congenital heart disease.

Ductus—The blood vessel that joins the pulmonary artery and the aorta. When the ductus does not close at birth, it causes a type of congenital heart disease called patent ductus arteriosus.

Electrocardiograph (ECG, EKG)—A test used to measure electrical impulses coming from the heart in order to gain information about its structure or function.

Hypoplastic—Incomplete or underdevelopment of a tissue or organ. Hypoplastic left heart syndrome is the most serious type of congenital heart disease.

Nuchal translucency—A pocket of fluid at the back of an embryo's neck visible via ultrasound. When thickened, it may indicate that the infant will be born with a congenital heart defect.

Septal—Relating to the septum, the thin muscular wall dividing the right and left sides of the heart. Holes in the septum are called septal defects.

Stenosis—The constricting or narrowing of an opening or passageway.

excessive bone growth, most Marfan syndrome patients are over six feet tall. In athletes, and others, it can lead to sudden death. Researchers believe the defect responsible for Marfan syndrome is found in gene *FBNI*, on chromosome 15.

Other syndromes that involve congenital heart defects are caused by single-gene variants (formerly called mutations) that are genetically heterogeneous, which means that an individual variant in more than one gene is capable of causing a similar condition.

Genetic profile

Some of the genes that are responsible for, or associated with, congenital heart defects have been identified; others are as yet unknown. Single-gene disorders are responsible for 3% to 5% of congenital heart defects,

and gross chromosomal anomalies and aneuploidy (an abnormal number of chromosomes) are present in 8% to 10% of cases. Pathogenic (disease-causing) copy number variants (involving large insertions or deletions of DNA, greater than 1,000 nucleotides long, that can occur anywhere in the genome) are present in 3% to 25% of persons with congenital heart disease as part of a syndrome, and in 3% to 10% among persons for whom congenital heart disease is the sole problem. When feasible, genetic testing can help families determine the risk that their child will be born with a heart defect.

Demographics

Congenital heart disease is the most commonly occurring birth defect, affecting about one percent of live births. In the United States, about 40,000 infants are born every year with congenital heart disease and about half of these require medical treatment. More than one million people with heart defects are currently living in the United States. It is not yet known why racial and ethnic minorities are disproportionately affected by this congenital heart disease. It is possible that certain variants or genetic loci are more prevalent in certain ethnic or racial groups.

Signs and symptoms

In most cases, the causes of congenital heart disease are unknown. Genetic and environmental factors and lifestyle habits can all be involved. Environmental causes can be identified in many as 30% of cases. The likelihood of having a child with a congenital heart disease increases if the mother or father, another child, or another relative had congenital heart disease or a family history of sudden death. Viral infections, such as German measles, can produce congenital heart disease. Women with diabetes and phenylketonuria also are at higher risk of having children with congenital heart defects. Many cases of congenital heart disease result from the mother's excessive use of alcohol or illegal drugs, such as cocaine, while pregnant. The mother's exposure to certain anticonvulsant and dermatologic drugs during pregnancy can also cause congenital heart disease. There are many genetic conditions, such as Down syndrome, that affect multiple organs and can cause congenital heart disease.

Symptoms of congenital heart disease include shortness of breath, difficulty feeding in infancy, sweating, cyanosis (bluish discoloration of the skin), heart murmur, respiratory infections that recur excessively, stunted growth, and limbs and muscles that are underdeveloped.

Symptoms of specific types of congenital heart disease are as follows:

- Patent ductus arteriosus: quick tiring, slow growth, susceptibility to pneumonia, rapid breathing. If the ductus is small, there are no symptoms.
- Hypoplastic left heart syndrome: ashen color, rapid and difficult breathing, inability to eat.
- Obstructive defects: cyanosis (skin that is discolored blue), chest pain, tiring easily, dizziness or fainting, congestive heart failure, and high blood pressure.
- Septal defects: difficulty breathing, stunted growth. Sometimes there are no symptoms.
- Cyanotic defects: cyanosis, sudden rapid breathing or unconsciousness, and shortness of breath and fainting during exercise.

Diagnosis

Echocardiography and cardiac magnetic resonance imaging are used in the diagnosis of congenital heart disease when it is suggested by the symptoms and physical examination. An echocardiograph will display an image of the heart that is formed by sound waves. It detects valve-related and other heart problems. Fetal echocardiography is used to diagnose congenital heart disease in utero, usually after 20 weeks of pregnancy. Between the 10th and 14th weeks of pregnancy, physicians also may use an ultrasound to look for a thickness at the nuchal translucency, a pocket of fluid in back of the embryo's neck, which may indicate a cardiac defect in 55% of cases. Cardiac magnetic resonance imaging, a scanning method that uses magnetic fields and radio waves, can help physicians evaluate congenital heart disease, but it is not always necessary. Physicians may also use a chest x-ray to look at the size and location of the heart and lungs, or an electrocardiogram (ECG), which measures electrical impulses to create a graph of the heartbeat.

Treatment and management

Congenital heart disease is treated with drugs and/or surgery. Drugs used include diuretics, which aid the baby in excreting water and salts; and digoxin, which strengthens the contraction of the heart, slows the heartbeat, and removes fluid from tissues.

Surgical procedures seek to repair the defect to the greatest extent possible and to restore circulation to as close to normal as possible. Sometimes, multiple surgical procedures are necessary. Surgical procedures include arterial switch, balloon atrial septostomy, balloon valvuloplasty, Damus-Kaye-Stansel procedure, Fontan procedure, pulmonary artery banding, Ross procedure, shunt procedure, and venous switch or intra-atrial baffle.

QUESTIONS TO ASK YOUR DOCTOR

- What are some of the physical characteristics of congenital heart disease?
- What kinds of tests are needed to confirm a diagnosis of congenital heart disease?
- What types of surgery may be necessary to treat various forms of congenital heart disease?
- What lifestyle adaptations (such as increased or decreased levels of exercise) should we consider for a child born with congenital heart disease?

Arterial switch, to correct transposition of the great arteries, involves connecting the aorta to the left ventricle and connecting the pulmonary artery to the right ventricle. Balloon atrial septostomy, also done to correct transposition of the great arteries, enlarges the atrial opening during heart catheterization. Balloon valvuloplasty uses a balloon-tipped catheter to open a narrowed heart valve, improving the flow of blood in pulmonary stenosis. It is sometimes used in aortic stenosis. Transposition of the great arteries can also be corrected by the Damus-Kaye-Stansel procedure, in which the pulmonary artery is cut in two and connected to the ascending aorta and the farthest section of the right ventricle.

For tricuspid atresia and pulmonary atresia, the Fontan procedure connects the right atrium to the pulmonary artery directly or with a conduit, and the atrial defect is closed. Pulmonary artery banding, narrowing the pulmonary artery with a band to reduce blood flow and pressure in the lungs, is used for ventricular septal defect, atrioventricular canal defect, and tricuspid atresia. Later, the band can be removed, and the defect can be corrected with open-heart surgery.

To correct aortic stenosis, the Ross procedure grafts the pulmonary artery to the aorta. For tetralogy of Fallot, tricuspid atresia, or pulmonary atresia, the shunt procedure creates a passage between blood vessels, sending blood into parts of the body that need it. For transposition of the great arteries, venous switch creates a tunnel inside the atria to redirect oxygen-rich blood to the right ventricle and aorta, and venous blood to the left ventricle and pulmonary artery.

When all other options fail, some patients may need a heart transplant. Children with congenital heart disease require lifelong monitoring, even after successful surgery. The American Heart Association recommends regular dental check-ups and the preventive use of antibiotics to

protect some, but not all, patients with congenital heart disease, such as those with prosthetic heart valves, unrepaired cyanotic congenital heart defects, and cardiac transplant with valve regurgitation due to an abnormal valve from heart infections, or endocarditis.

Prognosis

The outlook for children with congenital heart disease has improved markedly in the past two decades. Many types of congenital heart disease that would have been fatal can now be treated successfully. Research on diagnosing and repairing heart defects when the fetus is in the womb enables physicians to correct some defects before birth. Promising new prevention methods and treatments include genetic screening and the cultivation of cardiac tissue in the laboratory that could be used to repair congenital heart defects.

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American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721 or (888) 474-8483, inquire@heart.org, <http://www.heart.org>

Texas Heart Institute, MC 3-116, P.O. Box 20345, Houston, TX 77225-0345, (832) 355-3792, <http://www.texasheart.org/index.cfm>

Melissa Knopper
Revised by Barbara Wexler, MPH

Congenital hypothyroid syndrome

Definition

Congenital hypothyroid syndrome is a condition in which a child is born with a deficiency in thyroid gland activity or thyroid hormone levels.

Description

The thyroid gland is a small gland in the front of the neck that secretes hormones called thyroxine (T₄) and triiodothyronine (T₃) into the bloodstream. Some of the T₄ is converted into T₃ by the liver and kidney. These thyroid hormones help regulate a large number of processes. A deficiency in the level of these hormones can affect the brain, heart, muscles, skeleton, digestive tract, kidneys, reproductive function, blood cells, other hormone systems, heat production, and energy metabolism.

In most cases of congenital hypothyroidism, the thyroid gland is either completely absent or severely underdeveloped. Sometimes thyroid tissue is located in ectopic, or abnormal, locations along the neck.

Other abnormalities can lead to congenital hypothyroidism including the following:

- abnormal synthesis of thyroid hormones
- abnormal synthesis of thyroid-stimulating hormone (TSH) or thyrotropin-releasing hormone (TRH), which are regulatory hormones that affect the production of thyroid hormones
- abnormal response to thyroid hormones, TSH or TRH
- inadvertent administration of harmful drugs or substances to the pregnant mother, possibly resulting in temporary congenital hypothyroidism in the newborn
- dietary deficiency of iodine, a raw component vital to the manufacturing of thyroid hormones

Genetic profile

Most causes of congenital hypothyroidism are not inherited. Some abnormalities in thyroid hormone synthesis (TSH synthesis), or the response to TSH, are inherited in autosomal recessive fashion. This means that both parents have one copy of the changed (mutated) gene but do not have the condition. Abnormal response to thyroid hormones may be an autosomal dominant condition, meaning that only one parent has to pass on the gene mutation in order for the child to be affected with the syndrome.

Demographics

Congenital hypothyroidism occurs in 1 in every 4,000 newborns in the United States. It is twice as common in girls as in boys. The condition is less common in African Americans, and more common in Hispanics and Native Americans.

Signs and symptoms

The signs and symptoms of congenital hypothyroidism are difficult to observe because the mother passes along some of her thyroid hormones to the fetus during pregnancy. Even if the newborn is completely lacking a thyroid gland, it may not be obvious in the early stages of life. Ectopic thyroid tissue may also provide enough thyroid hormones for a short period of time.

Rarely, the affected newborn will exhibit jaundice (yellow skin), noisy breathing, and enlarged tongue. If hypothyroidism continues undetected and untreated, the

KEY TERMS

Congenital—Refers to a disorder that is present at birth.

Ectopic—Tissue found in an abnormal location.

Hypothyroid—Deficiency in thyroid gland activity or thyroid hormone levels.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Levothyroxine—A form of thyroxine (T_4) for replacement of thyroid hormones in hypothyroidism.

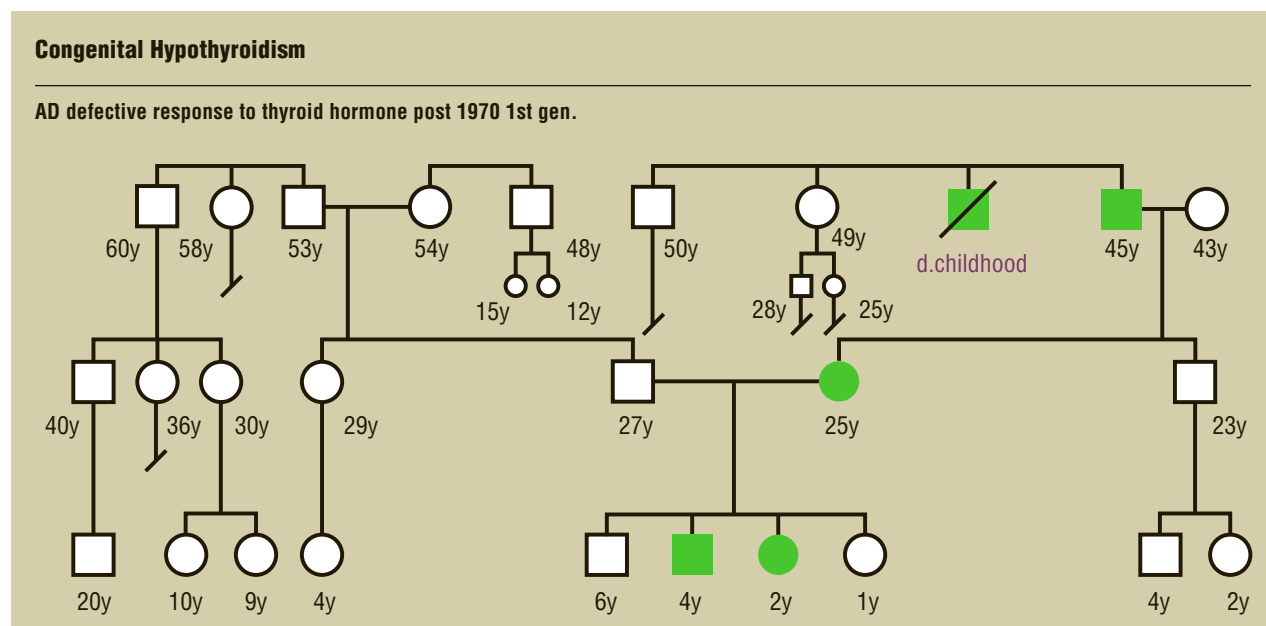
Myxedema—Swelling of the face, hands, feet, and genitals due to hypothyroidism.

Scintigraphy—Injection and detection of radioactive substances to create images of body parts.

Thyroxine (T_4)—The major thyroid hormone; it has a longer half-life than triiodothyronine.

Triiodothyronine (T_3)—The minor thyroid hormone.

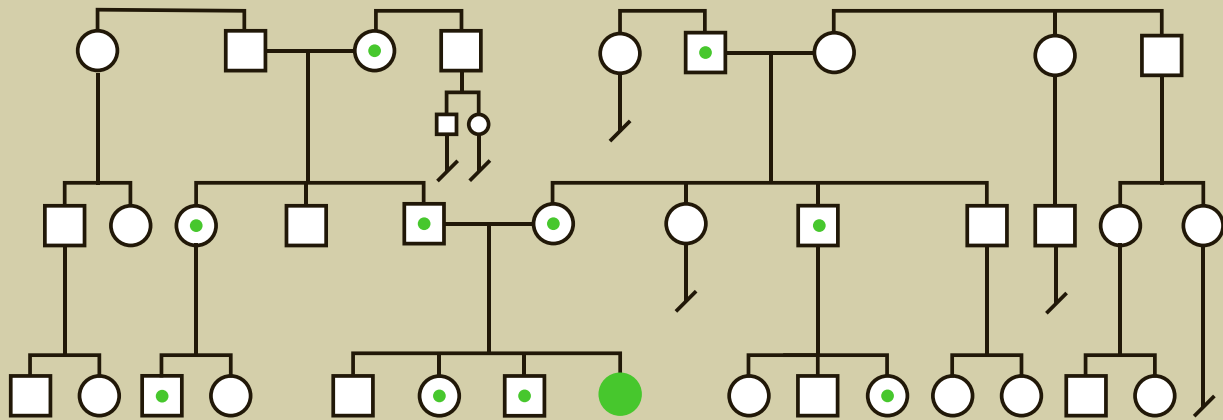
infant may gradually demonstrate feeding problems, constipation, sluggishness, sleepiness, cool hands and feet, and failure to thrive. Other signs include protruding abdomen, slow pulse, enlarged heart, dry skin, delayed teething, and coarse hair. Affected children may also have myxedema, which is swelling of the face, hands, feet, and genitals. Hypothyroidism eventually leads to marked



Congenital hypothyroid syndrome: pedigree analysis chart (Gale)

Congenital Hypothyroidism

AR abnormalities in thyroid hormone syndrome, TS synthesis, or TS response



Congenital hypothyroid syndrome: pedigree analysis chart (Gale)

retardation in physical growth, mental development, and sexual maturation.

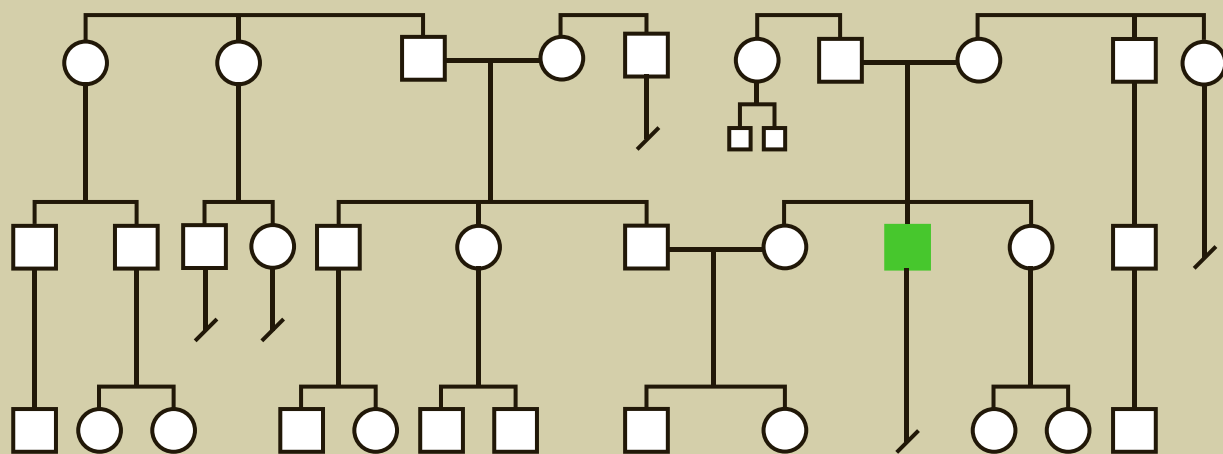
Diagnosis

Prompt diagnosis and treatment are critical to avoid the profound consequences of hypothyroidism. The signs and symptoms of hypothyroidism are often subtle in newborns, only to manifest themselves later in life when permanent damage has been done. Before the implementation of screening for hypothyroidism in the

1970s, most children with the disease suffered growth retardation and intellectual disability, as well as neurological and psychological deficits.

Most cases of congenital hypothyroid syndrome are now detected by a screening test performed during a newborn's first few days of life. Every state offers testing, and most states require it. The test for hypothyroidism is part of a battery of standard screening tests designed to diagnose important conditions. A sample of the child's blood is analyzed for levels of thyroxine (T_4), thyroid-stimulating

Congenital Hypothyroidism (Sporadic)



Congenital hypothyroid syndrome: pedigree analysis chart (Gale)

QUESTIONS TO ASK YOUR DOCTOR

- What are the causes of congenital hypothyroidism?
- What tests will you use to diagnose the disorder in my child?
- What treatments are available for congenital hypothyroidism, how effective are they, and what side effects should we expect from these treatments?
- What factors affect the long-term prognosis of my child's congenital hypothyroidism?

hormone (TSH), or both, depending on the individual state or country. Some states also require a second round of screening performed one to four weeks later.

Once the diagnosis of congenital hypothyroidism is made, other tests can pinpoint the nature of the abnormality. X-rays of the hip, shoulder, or skull often reveal characteristically abnormal patterns of bone development. Scintigraphy is a method by which images of the thyroid gland and any ectopic thyroid tissue are obtained to determine if the thyroid is absent or ectopic. However, treatment should not be delayed for these other tests. Early treatment offers a good probability of normal development.

Treatment and management

Treatment of congenital hypothyroidism requires replacement of deficient thyroid hormones with levothyroxine, an oral tablet form of T_4 . There is no need to directly replace T_3 , since T_4 is converted to T_3 by the liver and kidney. Hypothyroid children usually require more levothyroxine per pound of body weight than hypothyroid adults do. The importance of prompt and adequate treatment cannot be overemphasized. Delays in treatment result in permanent stunting of physical, mental, and sexual development.

Blood levels of T_4 should be checked regularly to ensure appropriate replacement. The blood levels of TSH should also be monitored since TSH is an indicator of the effectiveness of T_4 replacement. As the child develops, the physical growth rate also provides a good measure of treatment.

Prognosis

If congenital hypothyroidism is detected and treated early in life, the prognosis is quite good. Most children will

develop normally. However, the most severely affected infants may have mild intellectual disability, speech difficulty, hearing deficit, short attention span, or coordination problems.

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ORGANIZATIONS

American Thyroid Association, 2000 Duke Street, Suite 300, Alexandria, VA 22314, (703) 998-8890, thyroid@thyroid.org, <http://www.thyroid.org>

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Congenital ichthyosis-mental retardation-spasticity syndrome see **Sjögren-Larsson syndrome**

Congenital isolated hemihypertrophy see **Hemihypertrophy**

Congenital megacolon see **Hirschsprung disease**

Congenital microcoria

Definition

Congenital microcoria (MCOR) is a rare genetic disorder characterized by unusually small pupils of the eye resulting from the absence or underdevelopment of the

dilator pupillae muscle of the iris. It is associated with extreme myopia (nearsightedness) and juvenile-onset glaucoma. The word “microcoria” comes from two Greek words that mean “small” and “pupil.” Other names for the disorder include congenital miosis and chromosome 13q32 deletion syndrome.

MCOR as a condition is also associated with Pierson syndrome, a genetic disorder characterized by severe kidney disease (congenital nephrotic syndrome) and neuromuscular defects as well as abnormalities of the eye. Pierson syndrome is also called microcoria-congenital nephrotic syndrome.

Description

MCOR by itself is a disorder limited to the eye; that is, it does not affect other body systems. It has been described as a failure of normal development of the anterior chamber of the eye, which is the front portion of the eye between the cornea and the iris. A muscle in the iris known as the dilator pupillae is either underdeveloped or missing altogether; as a result, the pupil cannot dilate normally even when mydriatics (drugs used to prevent the pupil from contracting in bright light, usually given as part of an eye examination) are administered. The average size of the pupil in patients with MCOR is only about 0.8 mm and cannot be dilated beyond 1.4 mm.

In contrast to MCOR, Pierson syndrome involves severe and progressive kidney disease as well as microcoria and other neurological and muscular problems. Patients require lifelong monitoring for kidney function; some suffer from kidney failure within a few weeks or months after birth, while others reach adult maturity before their kidneys fail.

Genetic profile

MCOR has been traced to a deletion on chromosome 13 at 13q32.1. The deletion encompasses two genes: *TGDS*, which has no known function in regard to muscle cells, and *GPR180*, which regulates the growth of smooth muscle cells. The international team of geneticists that identified the deletion suggests that loss of the *GPR180* gene is the cause of congenital microcoria. MCOR is known to be transmitted in an autosomal dominant pattern, which means that only one copy of chromosome 13 with a defective *GPR180* gene is required to produce the disorder in affected individuals.

Pierson syndrome is caused by a mutation in a different gene, the *LAMB2* gene on chromosome 3 at 3p21.31. The *LAMB2* gene codes for a protein called laminin beta-2, which is an important component of the basement membranes of the glomeruli (clusters of capillaries within the nephrons) in the kidneys, and the smooth muscle cells that

form the inner lining of blood vessels. Unlike MCOR, Pierson syndrome is transmitted in an autosomal recessive pattern, which means that affected persons must receive two copies of the defective gene in order to develop the disorder.

Demographics

MCOR is a rare disease, described in only 50 families worldwide as of 2021. Affected families have been identified in France, Mexico, and Japan, with males and females equally affected. The worldwide incidence of MCOR was unknown as of 2021.

Pierson syndrome is also a rare disease, first identified in a French family in 1963. Other cases have been reported in Turkey, Saudi Arabia, Norway, and the United States. As with MCOR, Pierson syndrome affects males and females equally. In the United States, the only known cases as of 2021 had occurred within Old Order Amish families in eastern Pennsylvania. Genetic counseling and testing for persons from an Amish or Mennonite background is available from the New Leaf Center Clinic for Special Children in Ohio, a program founded on the science of genomics that works to detect and treat inherited health issues.

Signs and symptoms

The signs and symptoms of MCOR include loss of pigmentation, as well as other structural abnormalities in the iris; the absence or underdevelopment of the dilator pupillae muscle; extreme nearsightedness (in 83% of affected individuals) that worsens as the child grows older; glaucoma that manifests as early as age ten and frequently requires treatment; and intraocular pressure (IOP) that is difficult to control with medications. Unlike Pierson syndrome, however, MCOR is not associated with defects in the retina of the eye.

Pierson syndrome is marked by systemic symptoms in addition to congenital microcoria.

- **Neuromuscular symptoms:** Infants with Pierson syndrome typically show delayed motor (movement) development, hypotonia (poor muscle tone, sometimes referred to as “floppy baby syndrome”), some degree of mental retardation, and failure to reach normal developmental milestones.
- **Ocular symptoms:** Like patients with MCOR, infants with Pierson syndrome typically have unusually small pupils that do not dilate normally, together with incomplete development of the iris and an increased risk of glaucoma. Unlike patients with MCOR, however, infants with Pierson syndrome also have an unusually thin retina at the back of the eye, an increased risk of retinal detachment, an increased risk of cataract formation in the lens of the eye, and a lifelong risk of total blindness.

KEY TERMS

Anterior chamber—The fluid-filled front portion of the eye that lies between the iris and the cornea (the transparent front part of the eye that covers the iris and pupil).

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a nonsex chromosome is required for a disease or inherited trait to develop in an individual.

Autosomal recessive—A pattern of inheritance in which two copies of a defective gene on a nonsex chromosome must be present for a disease or inherited trait to develop in an individual.

Autosome—Any human chromosome other than a sex chromosome.

Basement membrane—A thin fibrous noncellular layer of tissue that anchors and separates the epithelium (the skin and the tissue that lines body cavities) from the underlying connective tissue.

Congenital—Present at birth.

Glaucoma—A group of eye disorders resulting in damage to the optic nerve, in most cases as the result of increased intraocular pressure (fluid pressure within the eye). Untreated glaucoma can result in permanent loss of vision.

Glomeruli (singular, glomerulus)—The tiny networks of capillaries in the nephrons (filtering units) of the kidneys that serve to filter the blood during the first stage of urine formation.

Hypotonia—A state of low muscle tone that often involves loss of muscle strength as well. Infants with hypotonia are often described as having “floppy baby syndrome”; they may have difficulty lifting their heads and usually have problems with feeding.

Iris—The thin circular structure in the eye that controls the size of the pupil and thus the amount of light that enters the eye and stimulates the retina. The color of the iris determines an individual’s eye color.

Laminin, beta-2—A protein involved in various biological processes that include cell migration, adhesion, and the formation of basement membranes in the kidneys and the smooth muscle lining of arteries and veins. Mutations in the gene that encode this protein are responsible for Pierson syndrome.

Miosis—The medical term for constriction of the pupil of the eye.

Mydriatics—Medications given to induce dilation of the pupil, usually as part of an eye examination.

Nephrotic syndrome—A kidney disorder caused by damage to the filtering units (glomeruli) of the kidneys and resulting in high levels of protein in the urine, excess fluid in body tissues, and abnormally low blood levels of albumin. It has a variety of genetic and nongenetic causes.

Pierson syndrome—A rare genetic disorder characterized by congenital nephrotic syndrome as well as congenital microcoria. It is named for Michel Pierson, the French physician who first described it in 1963.

Pupil—The circular opening in the iris of the eye that allows light to strike the retina at the back of the eye.

Retina—The light-sensitive layer of tissue at the back of the eye.

Transillumination—A diagnostic technique that involves shining a strong light through body tissues in order to detect defects. Transillumination of the iris may be used to diagnose congenital microcoria.

- **Kidney function:** Patients with Pierson syndrome have a shortened life expectancy due to eventual kidney failure. They have high blood pressure and high levels of protein in the urine. About 90% also have hematuria (blood in the urine).
- **Other:** About 50% of male infants with Pierson syndrome have an underdeveloped penis.

Diagnosis

MCOR may be diagnosed clinically by an ophthalmologist using transillumination of the iris, which usually reveals defects in its tissue structure along with some loss

of color. The pupil of the eye will also be seen to be unusually small and will not dilate when the examiner applies topical mydriatic eye drops. The patient will usually be found to be nearsighted when visual acuity is tested, and the intraocular pressure will often be higher than normal. The clinical diagnosis could potentially be confirmed by genetic testing; however, no genetic testing laboratories were offering tests specifically for MCOR as of 2021.

Pierson syndrome can be diagnosed clinically at birth or shortly afterward by an ophthalmologist or pediatrician on the basis of the abnormalities in the infant’s eyes, hypotonia, slow development of motor (movement)

QUESTIONS TO ASK YOUR DOCTOR

- I am related to the Amish on both sides of my family. What are the chances that I will have a child with Pierson syndrome?
- Should I consider genetic testing for congenital microcoria?
- Would you recommend kidney transplantation for a child with Pierson syndrome?
- Do you think that a genetic test for congenital microcoria will be developed in the near future?

skills, and high blood pressure. Blood and urine tests will show high levels of protein in the urine and low levels of albumin in the blood. The diagnosis can be confirmed by genetic testing. As of 2021, the only laboratory that offered genetic testing specifically for Pierson syndrome was the Institute of Human Genetics in Cologne, Germany. The test performed is sequence analysis of the entire coding region of the *LAMB2* gene.

Treatment and management

MCOR can be managed by regular eye examinations that include careful monitoring of intraocular pressure as well as changes in visual acuity. Because the intraocular pressure in patients with MCOR does not respond to medications, surgery is necessary to treat glaucoma.

There is no cure for Pierson syndrome. Life expectancy varies according to the time of the onset of kidney failure, with death in infancy or early childhood commonplace. Lifelong monitoring by a kidney specialist is essential. While a kidney transplant may extend the patient's life, the severe neuromuscular and intellectual impairments characteristic of the syndrome may not justify the complications that often accompany organ transplantation. Retinal detachment, cataracts, and glaucoma can be treated surgically in selected patients.

Prognosis

Patients with MCOR have a normal life expectancy, although their nearsightedness typically worsens as they age, and they have a lifelong increased risk of glaucoma.

The prognosis of Pierson syndrome is poor, with slow motor development and hypotonia complicating the patient's defects in vision and kidney function. Individuals who survive past infancy typically do not reach such normal developmental milestones as sitting, standing, and walking.

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ORGANIZATIONS

- American Academy of Ophthalmology (AAO), PO Box 7424, San Francisco, CA 94120-7424, (415) 561-8500, (415) 561-8533, <http://www.aao.org/>
- Institute of Human Genetics, Cologne University, Kerpener Strasse 34, Cologne, Germany 50931, +49 (221) 478-86811, +49 (221) 478-86812, alexandra.neke@uk-koeln.de, <http://www.humangenetik.uk-koeln.de/>
- National Human Genome Research Institute (NHGRI), 31 Center Drive, MSC 2152, 9000 Rockville Pike, Building 31, Room 4B09, Bethesda, MD 20892-2152, (301) 402-0911, (301) 402-2218, <http://www.genome.gov>
- New Leaf Center Clinic for Special Children, PO Box 336, 16014 E. Chestnut Street, Mt. Eaton, OH 44659, (330) 359-9888, <http://newleafclinic.org/>
- Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS), 6701 Democracy Blvd., Suite 1001, MSC 4874, Bethesda, MD 20892, (301) 402-4336, (301) 480-9655, ordr@nih.gov, <https://rarediseases.info.nih.gov>

Rebecca J. Frey, PhD

Conjoined twins

Definition

Conjoined twins are an extremely rare type of identical twins who are born physically joined.

Description

Scientists believe that conjoined twins form because of a delay in the division of an early embryo to form identical twins. With normal identical twins, the embryo starts to divide within the first 12 days to form two separate embryos. In conjoined twins, however, the split occurs



An x-ray image of conjoined twins. (Biophoto Associates/Science Source)

sometime after day 12. Instead of forming two separate embryos, the twins remain partially attached as they develop inside the womb. There are two theories of why this happens. The fission theory proposes that if the division starts after day 12, the embryos never fully separate, resulting in conjoined twins. The fusion theory proposes that two initially separate identical twins rejoin for unknown reasons.

In most cases, conjoined twins do not survive more than a few days past birth because of malformed organs and other severe birth abnormalities. However, surgery often can separate surviving conjoined twins. The phrase “Siamese twins,” which is now considered derogatory, originated with the famous conjoined twins Eng and Chang Bunker, who were born in Siam (Thailand) in 1811.

Conjoined twins may be connected at virtually any point of their bodies, but they are most often connected at the chest, pelvis, or buttocks. They may share one or more internal organs, such as a heart, liver, or brain. Conjoined twins are classified according to where they are joined.

Upper body

- Cephalopagus is a rare form of fused upper bodies and two faces on opposite sides of a single head.

- Craniopagus—conjoined twins with separate bodies and one shared head—occurs in only 2% of cases.
- Thoracopagus occurs in about 35% of conjoined twin births. These twins usually share a heart, making surgical separation nearly impossible.

Lower body

- Ischiopagus—attachment at the lower half of the body—occurs in about 6% of conjoined twins.
- Omphalopagus, in which conjoined twins are attached at the abdomen and often share a liver, accounts for approximately 30% of all cases.
- Parapagus—attachment along the side of the lower bodies—accounts for about 5% of conjoined twins.
- Pygopagus—joined back-to-back with fused buttocks—accounts for about 19% of conjoined twins.

Rare types

- Dicephalus are twins who share one body but have two separate heads and necks.
- Parasitic twins include one smaller malformed twin who is dependent on the larger, stronger twin for survival.

- Fetus in fetu is an unusual case in which one fetus grows inside the body of the other twin.

Genetic profile

The cause of conjoined twins is unknown. It is believed that a combination of genetic and environmental factors may be responsible for this rare condition.

Demographics

Conjoined twins occur in one out of every 50,000 births. Many such pregnancies are terminated before



Skeleton of conjoined twins showing that each had its own head, neck, and trachea, but shared the rest of the body. The medical name for this condition is dicephalus dibrachius, and most afflicted infants are stillborn or die soon after birth. As with identical twins, conjoined twins result from the fertilization of a single egg cell, but in these cases the spitting of the embryo into two identical bodies is incomplete. (Arno Massee/Science Source)

KEY TERMS

Breech delivery—Birth of an infant feet- or buttocks-first.

Craniopagus—Conjoined twins with separate bodies and one shared head.

Dicephalus—Conjoined twins who share one body but have two separate heads and necks.

Fetus in fetu—A fetus growing inside the body of the other twin.

Ischiopagus—Conjoined twins who are attached at the lower half of the body.

Omphalopagus—Conjoined twins who are attached at the abdomen.

Parapagus—Conjoined twins who are joined at the side of their lower bodies.

Parasitic twins—Twins who include a smaller, malformed twin who is dependent on the larger, stronger twin for survival.

Pygopagus—Conjoined twins who are joined back-to-back with fused buttocks.

Thoracopagus—Conjoined twins joined at the upper body who share a heart.

birth, or the infants are stillborn. Conjoined twins are always identical and of the same sex. They are more often female than male, by a ratio of three to one. Conjoined twins are more common in Africa, India, China, and Latin America than in the United States or Europe. Conjoined twins have occurred as part of a triplet or quadruplet pregnancy but not as one single conjoined group of more than two. Most parents of conjoined twins are younger than age 35.

Signs and symptoms

Approximately 50% of women who are pregnant with conjoined twins will develop excess fluid surrounding the fetuses, which can lead to premature labor and an increased risk of miscarriage. Conjoined twins joined at the abdomen (omphalopagus) are more likely to be a breech presentation at delivery. In breech births, infants are born feet- or buttocks-first instead of head-first. However, most conjoined twins are born by cesarean delivery to increase their odds of survival.

Conjoined twins can be born with a complication called hydrops, which causes excessive fluid to build up in the infant's body and can be life-threatening. Those who survive past birth may experience congenital heart disease, liver or kidney disease, physical or mental disabilities, and/or intestinal blockages.

QUESTIONS TO ASK YOUR DOCTOR

- What is the process by which conjoined twins are formed?
- Are there ways to prevent the formation of conjoined twins?
- On what factors does the success of surgical separation of conjoined twins depend?
- What is the prognosis for conjoined twins who are surgically separated after birth?
- What is the risk of having conjoined twins in a subsequent pregnancy?

Diagnosis

Physicians usually diagnose conjoined twins early in pregnancy through ultrasound, a technique in which high-frequency sound waves create a picture of a developing fetus inside the uterus. Initial diagnosis is possible at 10–12 weeks of gestation, but it is difficult to determine which body structures are involved until 20 weeks of gestation. Before ten weeks of gestation, identical twins who share an amniotic sac may appear to be conjoined. Halfway through the pregnancy, more detailed ultrasounds and echocardiograms can be used to determine the connection and the sharing and functioning of organs.

Treatment and management

Early diagnosis is key so that families and healthcare providers can plan for the birth of conjoined twins or end the pregnancy. Because of the high rate of miscarriage and difficult labor, most conjoined twins are delivered by cesarean delivery. Some conjoined twins have survived and lived full lives without serious medical interventions. If the twins do not share a large number of organs, however, physicians typically recommend a surgical separation.

A large medical team must be assembled for a surgical separation. Physicians prefer to wait for a few months after birth before attempting surgical separation, but that may not be possible if the twins are born with life-threatening abnormalities. An emergency surgical separation may be required if one twin dies, develops a life-threatening condition, or otherwise threatens the survival of the other twin. The type of surgery that is performed is determined by where the twins are connected. Doctors will often insert tissue-expansion devices into the twins' skin before the operation to promote better healing at the site of separation.

Conjoined twins who survive a surgical separation will have many ongoing healthcare needs, from wound care to reconstructive surgeries, prosthetic limbs, and special diets. As the twins grow up and start school, they may need counseling to help them adjust.

Prognosis

About 40%–60% of conjoined twins are stillborn. Of those born alive, fewer than half survive long enough for separation surgery. The prognosis for separation surgery depends on where the twins are joined and what organs are shared. However, advances in prenatal imaging and critical care have improved separation surgery outcomes.

In 2011, 11-month-old Sudanese twins joined at the head were successfully separated in a series of four surgeries. In 2020, a set of Californian twins conjoined at the head were successfully separated after 24 hours of surgery by 30 surgical health providers. They were separated at nine months of age in the midst of the Covid-19 pandemic. The twins were diagnosed at 11 weeks of gestation. Before birth, doctors created doll replicas of the twins. That helped the team plan how to deliver the babies. After birth, in preparation for the surgery, the doctors placed tissue expanders underneath the babies' skin so that more skin would grow. That was necessary so that there would be enough skin to cover the skulls of both girls after surgery. The surgeons also used 3D printing of models of the twins' skulls to prepare for surgery.

Other conjoined twins have lived successful lives without being separated. For example, Abby and Brittany Hensel were born in 1990. Their parents decided not to separate them because of the risk that one of the girls would die. The twins share their body from their pelvis down and each twin controls one side of their body. It was a challenge for them to learn how to coordinate their movements. They even each have a driver's license. They have different personalities and hobbies. In 2021, thirty-one years later, they are still doing well. Both are teachers, but Abby studied and teaches math, while Brittany studied and teaches English. They hope to each marry a different man and have children. Although they prefer privacy now, they had their own reality TV show in 2012.

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- Center for Loss in Multiple Birth, Inc. (CLIMB), P.O. Box 190401, Anchorage, AK 99519, (907) 222-5321, climb@climb-support.org, <http://www.climb-support.org>
- Center for Study of Multiple Birth, 333 E. Superior Street, Suite 464, Chicago, IL 60611, (312) 695-1677, (312) 908-8777, lgk395@northwestern.edu, <http://www.multiplebirth.com>
- Multiples of America, 2000 Mallory Lane, Suite 130-600, Franklin, TN 37067-8231, (248) 231-4480, info@multiplesofamerica.org, <https://multiplesofamerica.org/>

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Connectome genetics

Definition

The connectome is a comprehensive map of all the neural connections in the brain. Much like a blueprint or a schematic, a connectome includes the mapping of all neural connections within an organism's nervous system.

Connectome genetics is the scientific attempt to discover and record how genetic factors affect the neural connections of the brain. The term "connectome" was coined by Dr. Olaf Sporns and Dr. Patric Hagmann in 2005 to describe a literal map of the entirety of the neurological connections of the brain. Connectome genetics applies the methods of genetic research to the concept of neural mapping to determine the genetic factors involved.

Description

Researchers study the genetics of the connectome in an attempt to identify the ways that different regions of the brain are connected and work cooperatively as one integrated system to accomplish the various functions of the brain such as emotion, thought, and activity, and how that system is influenced by genetics. The regions of the brain are organized into parallel systems that interact and are physically connected. The human connectome seeks to provide methods and mapping so that connectivity may be measured and its influence understood. Discovering the genetic factors involved in this connectivity will determine the inherited aspects of neural connection, and help identify abnormal development and the origins of degenerative processes.

While it is not currently possible to assess the entire human connectome and all genetic influences, significant discoveries may be made by employing multiple research methods. In order to understand the genetic influences of neural connections on a scale as large as the human connectome, multiple scientific research tools have been employed. Researchers have compared results from genetic analysis methods such as genome-wide association studies (GWAS); linkage and candidate gene studies; neural imaging tests such as resting state and functional magnetic resonance imaging (fMRI and R-fMRI); and groups working to compile large databases with information of genetic inheritance, such as the Evidence-Based Network for the Interpretation of Germline Mutant Alleles (ENIGMA), to understand the genetics of the connectome on an individual or group level.

According to the National Human Genome Research Institute, GWAS is an approach that involves rapidly scanning markers across the complete sets of DNA, or genomes, of many people to find genetic variations associated with a particular disease. Once new genetic associations are identified, researchers can use the information to develop better strategies to detect, treat, and prevent the disease. This methodology was made possible by the Human Genome Project and the tools it provided researchers around the world such as large databases of the reference human genome sequence, a map of human genetic variation, and innovative new technologies that

allow the quick and accurate analysis of entire genome samples.

Linkage and candidate gene studies use a single gene approach rather than the entire genome approach used in GWAS. After a candidate gene (a gene believed to be responsible for causing a specific condition or disease) is selected, that gene is compared to the same gene from another individual with the same condition and to genes from other individuals who do not have the condition to determine whether the candidate gene is responsible.

Imaging studies are especially useful in connectome research because they provide a detailed image of neural connections. Two types of MRI used in connectome and genetic research are resting state functional connectivity MRI (fcMRI) and high angular resolution diffusion imaging (HARDI).

An fcMRI is often used to investigate networks in the brain, especially those that demonstrate correlated fluctuations. Even though this test does not offer the ability to provide direct measurement of anatomic connectivity, research data suggests that the neural anatomy seen in fcMRI images shows enough distinct brain system architecture to be useful in drawing conclusions. It is particularly useful for characterizing large-scale systems that span widespread areas such as polysynaptic cortical pathways, cerebro-cerebellar circuits, and cortical-thalamic circuits.

HARDI is another MRI technique used to help identify the genetics of the connectome. This technique uses the distribution of water molecules in tissue to map fiber tracts inside the brain. HARDI is preferred over another more common technique called diffusion tensor imaging (DTI) because HARDI is able to image fiber tracts that cross, fan out, or become intertwined as many neural pathways do.

The advantage of both fcMRI and HARDI is that they are noninvasive ways to map the human brain. Previously, mapping was conducted after death by actual physical examination and dissection of the brain, or by using invasive tracing methods that required a tissue sample from the brain. HARDI and fcMRI technologies cause little discomfort to the patient and provide a much richer body of data.

The ENIGMA Consortium was established in order to analyze brain measures and genotypes from multiple sites across the world. This analysis is designed to improve the power to detect genetic variants that influence the brain. One ENIGMA working group analyzed high-resolution DCI images from multiple imaging sites across North America, Australia, and Europe to address the challenge of combining imaging data collected from multiple sites.

This research has already uncovered how some diseases and genetic mutations affect the brain. Researchers

KEY TERMS

Allele—One member of a pair of genes.

Amnesic mild cognitive impairment (aMCI)—An early symptom of Alzheimer's disease in which there is mild impairment but normal cognitive functioning is still present.

Biomarker—A measurable indicator of a biological function.

Cerebro-cerebellar circuits—Neural pathways that originate in the cerebral cortex and travel through the deeper structures of the brain and back to the cerebral cortex. They control verbal working memory and other higher-order brain functions.

Cortical-thalamic circuits—A circular connection within the brain that travels between the cerebral cortex and the thalamus and back to the cerebral cortex. Scientists believe it helps the brain monitor its status.

Genetic locus (plural, loci)—The specific location of a gene on a chromosome.

Genome—An organism's complete set of DNA.

Polysynaptic cortical pathways—The pathway by which stimuli enter the brain.

have also identified new genetic loci and interrelated genetic networks that influence and control neural networks within the brain.

Genetic profile

In order to analyze the significance of genetic contributions to the human connectome, quantitative classical genetics techniques may be employed to determine which trait variance may be attributed to genetic factors, which are attributable to environmental factors, which are epistatic (a result of the influence of one gene on another), and which are due to the interaction between environment and inheritance. The proportion of trait variance within a population that is due to genetic factors is the heritability of that trait. Calculating heritability estimates is a valuable exercise for novel traits that have been identified using complex image analyses such as the connectome. These methods are particularly helpful in efforts to discover genetic variants affecting brain measures because they can help identify traits that are more likely to be inherited or passed on to offspring. Once these traits are identified, researchers can use valuable resources to perform genetic analysis on the heritable traits.

Demographics

The connectome project is ongoing. In 2015, the demographics of the genetics of the connectome had not been determined.

Signs and symptoms

An important component of the Human Connectome Project is discovering clinical applications for connectomics (the science of the connectome). One important functional discovery is the function and validity of biomarkers. Biomarkers (biological markers) are a biological measure of a biological state. Using R-fMRI, a type of fcMRI, variations in the functional connectome may be identified and combined with known genetic factors; these variations can be connected to clinical or diagnostic features of diseases and condition of the brain. For example, Alzheimer's disease currently affects 2.4 million to 4.5 million in the United States alone. Researchers have discovered that mutations in the *APP*, *PSEN1*, or *PSEN2* genes cause Alzheimer's disease. In 2013, using fcMRI and functional connectome methodologies, researchers discovered that even in amnesic mild cognitive impairment (aMCI), the earliest stage of Alzheimer's disease, there is evidence that the entire connectome is disrupted. This finding may be helpful for diagnostic purposes in this population and for use as a biomarker.

There are still many challenges to the routine use of the connectome and biomarker identification for diagnostic purposes. By applying clinical test evaluation measures such as validity, reliability, sensitivity, specificity, and applicability, researchers hope to expand these prospects to include risk assessment, treatment response, and prognosis prediction.

Diagnosis

The genetics of the connectome are particularly relevant for the field of psychiatry. Disorders that affect behavior and mental functioning may be attributed to specific identifiable abnormalities in the very neural pathways and connections that the connection will map.

There are many psychiatric conditions caused by interruptions in the human connectome. In particular, schizophrenia has been shown to be a condition caused by interruptions of the neural connections and pathways of the brain. The human connectome project has identified areas of interest related to schizophrenia. Using the imaging technologies of structural, diffusion, resting-state, and task-related functional imaging, and advanced computational analysis methods such as graph theory, more than 200 publications have addressed different aspects of structural and/or functional connectivity in schizophrenia in 2015 alone. This research and the

discoveries made help identify the genetic components of the connectome as it relates to schizophrenia. More than 45 different single-gene mutations have been associated with an increased risk of developing schizophrenia. Research in the connectome may lead to the identification of how each of these genes affects neural pathways in the brain and improved diagnosis and treatment.

Many more discoveries may be expected related to the genetics of the connectome. Eventually, the results of the connectome will help diagnose multiple conditions and diseases that affect the brain.

Treatment and management

There are currently no treatment options for diseases using the genetics of the connectome. Researchers are investigating the connectome as a tool to identify biomarkers for psychiatric and neurological conditions and diseases. In the course of this research, it is expected that treatment options may be discovered as well.

Prognosis

Using the science of connectomics, researchers are attempting to use R-fMRI and the connectome to improve the prognosis of patients with psychiatric disorders such as schizophrenia and conditions of brain deterioration such as Alzheimer's disease. They have had success identifying biomarkers useful for diagnosis and for identifying disease progression. These discoveries have led them to believe prognosis prediction may be possible using the same methodologies.

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Deborah L. Nurmi, MS

Corneal dystrophy

Definition

Corneal dystrophy is a condition that causes a layer of the cornea to cloud over and impair visual clarity. It is usually a bilateral problem, which means it occurs in both eyes equally. There are more than 20 different forms of inherited corneal dystrophies. A corneal dystrophy can occur in otherwise healthy individuals. Depending on the type of condition and the age of the individual, a corneal dystrophy may cause no problems, moderate vision impairment, or severe difficulties that require surgery.

Description

The cornea is the outside layer of the eye, and is comprised of five layers, including the outer epithelium; the Bowman's layer; the stroma, or middle layer that takes up about 90% of the entire cornea; Descemet's membrane; and the endothelium. In most cases, the central (stromal) layer of the cornea is involved.

Some corneal dystrophies are named after the individual who discovered them, while others are descriptive of the pattern seen with the dystrophy or the location of the disease. The key forms of corneal dystrophy are congenital hereditary endothelial dystrophy (CHED), epithelial basement membrane dystrophy ("map-dot-fingerprint" dystrophy), Fuchs' endothelial dystrophy, granular dystrophy, lattice dystrophy, macular corneal dystrophy, Meesmann's corneal dystrophy, posterior polymorphous dystrophy (PPD), and Reis-Bücklers' dystrophy.

According to the International Committee for Classification of Corneal Diseases (IC3D), corneal dystrophies are classified by the anatomic layer of corneal involvement, but they are increasingly defined on a genetic basis.

Genetic profile

As of 2021, some 293 genetic alterations (mutations) causing corneal dystrophies had been mapped to 18 different genes that include *COL8A2*, *TGFBI*, *VSX1*, *CHST6*, *KRT3*, *KRT12*, *GSN*, *TACSTD2*, *CYP4V2*, *SOD1*, *TCF8/ZEB1*, *UBIAD1*, *PIKFYVE*, *DCN*, and *SLC4A11*. Genetic variations in these genes have been associated with several corneal dystrophies, which are linked to epithelium, stroma, and endothelium.

Some corneal dystrophies have the same genetic address. Mutations on the *BIGH3* gene on chromosome 5q31 cause granular corneal dystrophy and Reis-Bücklers' dystrophy. Macular corneal dystrophy has been mapped to an altered gene on chromosome 16. The mutation causing congenital hereditary endothelial dystrophy

KEY TERMS

Basement membrane—Part of the epithelium, or outer layer of the cornea.

Bowman's layer—Transparent sheet of tissue directly below the basement membrane.

Corneal transplant—Removal of impaired and diseased cornea and replacement with corneal tissue from a recently deceased person.

Descemet's membrane—Sheet of tissue that lies under the stroma and protects against infection and injuries.

Edema—Extreme amount of watery fluid that causes swelling of the affected tissue.

Endothelium—Extremely thin innermost layer of the cornea.

Epithelium—The layer of cells that cover the open surfaces of the body such as the skin and mucous membranes.

Hyaline—A clear substance that occurs in cell deterioration.

Stroma—Middle layer of the cornea, representing about 90% of the entire cornea.

has been mapped to 20p11-20q11. Lattice type I is linked to the 5q31 locus (location), while lattice type II dystrophy is linked to the 9q34 locus. Posterior polymorphous corneal dystrophy has been linked to the 20q11 locus.

Most corneal dystrophies, with the exception of congenital endothelial corneal dystrophy and macular dystrophy, are autosomal dominant. In dominant disorders, a single copy of the mutated gene (received from either parent) dominates the normal gene and results in the appearance of the disease. The risk of transmitting the disorder from parent to offspring is 50% for each pregnancy.

Both congenital endothelial corneal dystrophy and macular dystrophy are autosomal recessive. This means the affected person inherits the same abnormal gene for the same trait from both parents; each parent is a carrier for the disease but usually does not have symptoms of the disease. The risk of transmitting the disease to each pregnancy is 25%.

Demographics

The diversity of corneal dystrophy diseases makes it difficult to provide specific demographic data. Some dystrophies appear in early childhood or even infancy, such as Reis-Bücklers' dystrophy. Others may not appear until

middle age or beyond, as with Fuchs' dystrophy. It generally begins at 30–40 years of age and gradually progresses, affecting women slightly more than men. Epithelial basement membrane dystrophy generally occurs in adults after the age of 40, and it can come as late as age 70.

Signs and symptoms

The symptoms vary with the type of corneal dystrophy and the location of the site. Most experts categorize these diseases based on whether they are located on the anterior (outer) layer, stromal (middle) layer, or endothelial (inner) layer.

Anterior corneal dystrophies

The epithelium, or the basement membrane, and the Bowman's layer together comprise the anterior, or outer part, of the cornea. Epithelial basement membrane dystrophy, also known as Cogan's map-dot-fingerprint dystrophy, is a disorder that causes errors in refractions of the eye and may also present with microscopic cysts. This disease results from excessive fluid (edema) and swelling of the basement membrane into the epithelium. Symptoms of this disease are map-like dots, opaque circles, or thin lines that are formed in a swirled pattern like fingerprints. Individuals with this disorder feel like they have something irritating in the eye and experience pain and light sensitivity (photophobia).

The tiny opaque collagen fibers that cause Reis-Bücklers' dystrophy create a linear or ring-like pattern. People with this disease have recurrent painful erosions of the cornea and may also suffer from severe visual impairment. Reis-Bücklers' is usually noticed in an infant or young child who suddenly has very red eyes. To the ophthalmologist, the cornea looks like frosted glass. This disorder may recur several times per year and disappear when affected individuals are in their 20s or 30s.

Stromal dystrophies

The primary dystrophies found in the stromal layer are granular dystrophy, lattice dystrophy, and macular dystrophy. Granular dystrophy is so named because of the small opaque areas caused by deposits of hyaline, a substance that accumulates as cells deteriorate. Lattice dystrophy is caused by deposits of amyloid, the same substance that accumulates in the brain in people with Alzheimer's disease. Both granular dystrophy and lattice dystrophy have been identified in family members in Avellino, Italy, and these dystrophies are sometimes grouped together and called Avellino corneal dystrophy. Lattice and granular dystrophies can cause severe eye pain. With lattice dystrophy, by about age 40, an affected

QUESTIONS TO ASK YOUR DOCTOR

- My partner has corneal dystrophy. Is he or she a candidate for a corneal transplant?
- What changes in vision can I expect as a result of a corneal transplant?
- Are there symptoms that we should watch for in assessing the ongoing status of corneal dystrophy?
- I have diabetes and hypertension in addition to corneal dystrophy. Will other medical conditions such as these affect my condition?

person's vision can be very obscured and a corneal transplant is required.

Endothelial dystrophies

Fuchs' dystrophy is the most common of the endothelial dystrophies and is inherited as an autosomal dominant trait. It is characterized by blurred vision, hypersensitivity to light (photophobia), and two to eight acute inflammatory attacks per year. It may also cause ulceration and erosion of the cornea. Fuchs' can cause deterioration of endothelial cells and result in corneal guttata, which are thickenings or leakages from the Descemet's membrane of the cornea. These guttata eventually cause edema (excessive fluid) to leak into the stromal or epithelial areas.

Posterior polymorphous dystrophy (PPD), an autosomal dominant disease, also causes edema, although it affects a larger area than Fuchs' dystrophy. It usually does not cause vision impairment.

Congenital hereditary endothelial dystrophy (CHED) comprises two types. The autosomal dominant form is CHED 1, and the recessive form is CHED 2. CHED 1 can occur in early childhood and may also cause hearing loss. The key symptoms of CHED 1 are sensitivity to light and excessive tearing. CHED 2 is present at birth and is more severe than CHED 1. In both CHED 1 and 2, the cornea presents with a milky haze or the appearance of ground glass.

Macular dystrophy is inherited as an autosomal recessive trait. It can present as early as age three, and up to about age nine, and is very debilitating. This disorder is caused by deposits of keratin sulfate (sulfur-containing fibrous proteins) and becomes increasingly painful. The child will have a feeling of something in

the eye and also experience photophobia (sensitivity to light).

Diagnosis

Corneal dystrophy may be identified by an optometrist and diagnosed by an ophthalmologist. The findings determine the existence and type of corneal dystrophy. The presence, size, and shape of any opaque material in the eyes are considered.

The affected cornea of a person with lattice dystrophy will have a ground-glass appearance, while granular deposits indicate granular dystrophy. The examination can also reveal the presence of amyloid deposits, which are typical of individuals with lattice dystrophy.

Treatment and management

Treatment depends on the severity of the disease. If the affected person is in acute pain, treatment with eye drops, antibiotics, and other solutions is necessary. Some doctors advise affected people with eye edema to use a hair dryer at arm's length to dry some of the edema. Soft contact lenses may also help. Individuals with increasingly severe vision problems may need a corneal transplant.

For other forms of corneal dystrophy, affected people may need artificial tears and other medications. Some individuals may need laser treatment, such as phototherapeutic keratectomy (PK), which is the removal of part of the corneal stroma, or they may need a corneal transplant. Endothelial keratoplasty, a cornea-sparing transplant technique that replaces only the diseased endothelial cell layer of the patient's cornea, may also be recommended by an ophthalmologist.

Clinical trials

Clinical trials on corneal dystrophies are currently sponsored by the National Institutes of Health (NIH) and other agencies. In 2021, NIH reported 95 ongoing or active studies.

Clinical trial information is constantly updated by NIH and the most recent information on corneal dystrophy trials can be found at: <http://clinicaltrials.gov/ct2/results?term=corneal+dystrophy>.

Prognosis

With most forms of corneal dystrophy, the disease progresses as the affected person ages. The severity of the conditions varies and a particular form of the disease may cause few or no problems or may also cause severe visual difficulties requiring surgery. Cases must be evaluated individually.

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ORGANIZATIONS

American Academy of Ophthalmology (AAO), PO Box 7424, San Francisco, CA 94120-7424, (415) 561-8500, (415) 561-8533, <http://www.aao.org>

American Optometric Association, 243 N. Lindbergh Blvd., Flr. 1, St. Louis, MO 63141-7881, (800) 365-2219, <http://www.aao.org/?sso=y>

Corneal Dystrophy Foundation, 6066 McAbee Rd., San Jose, CA 95120, (866) 807-8965, execdir@cornealdystrophyfoundation.org, <http://www.cornealdystrophyfoundation.org>

National Eye Institute (NEI), 31 Center Drive MSC 2510, Bethesda, MD 20892-2510, (301) 496-5248, 2020@nei.nih.gov, <http://www.nei.nih.gov>

Prevent Blindness America, 211 West Wacker Drive, Suite 1700, Chicago, Illinois 60606, (800) 331-2020, <http://www.preventblindness.org>

Royal National Institute of Blind People (RNIB), 105 Judd Street, London, UK WC1H 9NE, 0303 123 9999, helpline@rnib.org.uk, <http://www.rnib.org.uk>

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Cornelia de Lange syndrome

Definition

Cornelia de Lange syndrome (CdLS) is a genetic disorder characterized by multiple birth defects, including

distinctive facial features, prenatal and postnatal growth delays, feeding difficulties, psychomotor delay, behavioral problems, and associated malformations that primarily involve the upper extremities. CdLS is caused by mutations in genes that are important for prenatal and postnatal development.

Description

CdLS is named for Cornelia de Lange, the Dutch physician who first described it as a distinct syndrome in 1933. It is sometimes called Brachmann-de Lange syndrome, after W. Brachmann, who described a severe form of the syndrome in 1916.

Three distinct forms of CdLS are recognized. Type I is the most severe or “classic” form. Children with this type have a prenatal growth deficiency that continues after birth. They have distinctive facial features and moderate-to-profound mental retardation. Major deformities of the gastrointestinal tract and heart may lead to severe disability or death. Type II is the mild form of CdLS. Facial features are similar to those of Type I but may not become apparent until later in life. Pre- and postnatal growth deficiencies are less severe, and major malformations are less likely. Type III CdLS, called a phenocopy, includes patients with characteristics of CdLS that are caused by chromosomal aneuploidies (an abnormal number of chromosomes) or teratogenic (birth-defect-inducing) factors.

Genetic profile

CdLS can be caused by mutations (changes) in a gene called *NIPBL*, located on chromosome 5. Although the exact function of the protein produced by *NIPBL* (known as delangin in humans) is unknown, the corresponding proteins in other species are involved in the regulation of development and in the joining of sister chromatids during chromosome duplication prior to cell division. More than half of patients with CdLS appear to have mutations in the *NIPBL* gene. Many different mutations in *NIPBL* have been reported to result in CdLS, although the severity of the syndrome varies, depending on the specific mutation.

Mutations in four other genes—*SMC1A*, *SMC3*, *HDAC8*, and *RAD21*—have been identified as resulting in CdLS. Mutations in *SMC1A* and *SMC3* have been reported in 5% and 1% of patients with CdLS respectively. Like *NIPBL*, *SMC1A* and *SMC3* produce proteins that are involved in the cohesion of sister chromatids. Thus, CdLS is considered to be a “cohesinopathy,” in which the separation of sister chromatids during cell division is disrupted, resulting in daughter cells that may lack one chromosome of a chromosome pair, a condition



A young male patient with Cornelia de Lange syndrome. This genetic disorder affects both the physical and mental development of a child, with features such as widely spaced teeth, autistic-like behaviors, and excessive hairiness. (SPL/Science Source)

known as haploinsufficiency. These proteins are important for the structure and organization of chromosomes. They are also involved in repairing damaged DNA and in regulating other genes that direct the development of the limbs, face, and other body parts. Mutations in *SMC1A* and *SMC3* cause milder forms of CdLS than mutations in *NIPBL* do. Severe limb defects and other structural anomalies are absent. In some patients with these gene mutations, mental retardation is the only obvious symptom.

It is believed that other genes may also be involved in CdLS, since in about 35% of cases, the cause has not been identified. The fact that CdLS can be caused by mutations in several different genes probably helps explain the variability in signs and symptoms of CdLS.

NIPBL and *SMC3* gene mutations can be inherited in an autosomal dominant pattern, meaning that only one copy of the mutated gene is sufficient to cause CdLS, even when the second copy of the gene is normal. *SMC1A* gene mutations are inherited as X-linked

dominants, which means that the gene is located on the X sex chromosome, and mutations cause CdLS even when a second copy of the gene on the other X chromosome in females is normal. (Males have only one X chromosome, inherited from their mother.) In a few known cases of inherited CdLS, a parent was mildly affected by the syndrome. However, more than 99% of CdLS cases are sporadic—resulting from new, spontaneous mutations in the egg or sperm or during fetal development—rather than inherited from a parent.

Demographics

CdLS is estimated to affect one in 10,000 newborns. It appears to affect males and females of all races equally.

Signs and symptoms

Musculoskeletal abnormalities

Most newborns with CdLS have low birth weight, cleft palate, and a low-pitched growl or cry. Characteristic facial features include thin eyebrows joined at the midline (known as synophrys), long eyelashes, excessive facial and body hair (hypertrichosis), and thin, downturned lips. In mild cases, this classic appearance might not be present at birth, and it might not become obvious for two or three years. CdLS can also result in:

- microcephaly—an abnormally small head accompanied by a small brain, resulting in mild-to-profound mental retardation
- micrognathia—an abnormally small mandible or lower jaw bone
- a small nose
- anteversion, or turning, of the nostrils
- a long philtrum (the area between the nose and upper lip)
- relatively short limbs
- limitations of elbow extension in mild forms
- small hands and/or feet
- oligodactyly—fewer than five digits on the hands or feet
- clinodactyly, or bending of the fifth finger and thumb
- webbing of the toes (syndactyly)

Gastrointestinal abnormalities

The upper and lower gastrointestinal (GI) tract is the body system most commonly affected by CdLS:

- Gastroesophageal reflux disease (GERD) is caused by acid from the stomach refluxing back into the esophagus, which can lead to severe heartburn and, if left untreated, can damage the esophagus (reflux esophagitis) due to

repeated irritation. Gastroesophageal reflux can also cause symptoms of pulmonary congestion and irritation due to chemical pneumonitis (inflammation of the lung).

- Barrett's esophagus is a change in the tissue type of the lower esophagus. It is usually a complication of GERD and may develop into an adenocarcinoma (carcinoma of glandular tissue).
- Esophageal stenosis is a narrowing of the esophagus, which may decrease esophageal motility and make feeding difficult.
- Gastric ulcers are usually caused by bacteria and can lead to abdominal discomfort.
- Pyloric stenosis is a narrowing of the pyloric canal that leads from the stomach to the duodenum. It may result in vomiting and diarrhea complicated by electrolyte imbalances.
- Intestinal malrotation is a failure of the normal rotation of the small intestine during fetal development. It can cause a volvulus—a twisting of the intestine back on itself—cutting off blood supply to the tissue or possibly causing intestinal obstruction.
- Meckel diverticula are tiny pouches that protrude into the small intestine. Sometimes ulceration develops, and bleeding occurs.

Cardiac abnormalities

Heart problems are not uncommon in patients with CdLS.

- Ventricular septal defect is a condition in which the septum of the ventricles (the wall between the lower chambers of the heart) is not fully closed, resulting in a



Syndactyly (fusion) of the toes in a young male patient with Cornelia de Lange syndrome. This syndrome is a genetic disorder that affects both the physical and mental development of a child. (SPL/Science Source)

heart murmur. It can possibly lead to congestive heart failure.

- Infective endocarditis is an infection of the endothelium, the tissue that lines the heart.
- Atrial septal defect is a defect of the septum between the upper chambers of the heart. It is caused by the persistence of the foramen ovale, which is a hole normally present in the fetal heart that closes at birth. Individuals with this condition may also have a heart murmur. Symptoms are normally not present in patients with atrial septal defects, but there is an increased risk of infective endocarditis.
- Patent ductus arteriosus is a failure of the ductus arteriosus—a blood vessel between the pulmonary artery and the aorta found only in the fetus—to close. Severe cases may require surgery.
- Pulmonary valve stenosis is a narrowing of the valve that allows blood to move from the right ventricle to the lungs. It may result in right-sided heart enlargement and heart failure.
- Tetralogy of Fallot is a condition consisting of pulmonary stenosis, ventricular septal defect, enlarged right ventricle, and a displaced aorta. This condition results in a decrease in oxygenated blood pumped to the body. It can normally be corrected by surgery.

Growth and developmental deficiencies

Most infants afflicted with CdLS have both prenatal and postnatal growth deficiencies as well as developmental delays, which may be due to endocrine system involvement, including growth hormone delivery problems. Most CdLS patients have a characteristically short stature but often have a pubertal growth spurt at a comparable age to normal teens.

Developmental delays are numerous and affect most patients with CdLS. They can include walking, speaking, toilet training, and dressing. Some children never reach these milestones. The average IQ is 53—within the mild-to-moderate range for mental retardation.

Disorders of ears and eyes

Many patients with CdLS have some form of hearing loss, ranging from mild to severe and affecting one or both ears. This loss can be attributed to a lack of prenatal development of some of the important bony structures associated with the inner ear. Developmental failure of important neural elements also plays a role in hearing loss.

A significant number of CdLS patients have eye and/or vision problems including:

- myopia—nearsightedness or shortsightedness
- nystagmus—rhythmical oscillations of the eyes slowly to one side followed by a rapid reflex movement in the

opposite direction—usually horizontal, although rotatory or vertical nystagmus also occur

- ptosis, or drooping eyelid(s), possibly resulting from lesions in either the brainstem or the nerves supplying the muscles that raise the eyelid
- nasolacrimal duct fistula that prevents tears from draining from the eyeball, which may develop into chronic tearing and discharge from the eyes

Dysfunctional placenta

Researchers have demonstrated that a dysfunctional placenta can play a formerly unknown role during the earliest phases of development in mouse models of CdLS. People with CdLS often harbor mutations in cohesins, ring-like proteins that help DNA organize and repair itself. Mice with cohesin mutations had placentas that built up damage to their DNA, assumed a permanent growth-arrested state called senescence, and released pro-inflammatory cytokines that impacted the growth of the embryos. Targeting cytokine signaling could offer a way to safeguard the health of the placenta and support healthy pregnancies.

Other symptoms

Other malformations include undescended testicles, which can cause fertility problems. Diaphragmatic hernia is a complication that may lead to GI difficulties. CdLS patients may also have seizures, feeding difficulties, and behavioral and communication problems.

Diagnosis

CdLS diagnosis is based on signs and symptoms, which are often apparent at birth; however, the syndrome varies considerably. Characteristic facial features may be the most prominent diagnostic clues. Prenatal diagnosis is possible through the use of ultrasound. The association of intrauterine growth retardation, oligodactyly, an absent ulna (one of the two long bones of the forearm), underdevelopment of hands, diaphragmatic hernia, and cardiac defects leads to the differential diagnosis. The most distinctive abnormalities are those of the upper limbs. Researchers have also found that maternal serum samples collected from women who gave birth to a child with CdLS had low levels of pregnancy-associated plasma protein-A (PAPP-A) during the second trimester. In addition, it has been noted that an amniotic molecule (5-OH-indole-3-acetic acid) and a fetal serum protein (galactose-1-phosphate-uridylyltransferase) are increased prenatally. Genetic testing for relevant gene mutations can be diagnostic, but many patients with CdLS test negative for the known mutations.

Treatment and management

The treatment and management of patients with CdLS are strictly symptomatic. Treatment is prescribed according to presenting symptoms. However, treatment and management are usually complex and lifelong, requiring the involvement of numerous specialists.

Musculoskeletal concerns

For patients with limb and digit malformations, a variety of prostheses may be necessary. Physical and occupational therapy may also be needed. Surgery may be necessary to correct more severe deformities.

Gastrointestinal treatment

GERD can be treated with special diets and a number of different drugs that either block acid secretion from the stomach or neutralize acid once it is produced. Drugs may include antacids, histamine receptor blockers, and proton pump inhibitors. If these treatments prove unsuccessful, surgery may be performed to eliminate the possibility of further complications such as Barrett's esophagus or esophageal stenosis. Patients with CdLS should have endoscopic evaluation with biopsies for Barrett's esophagus. If Barrett's esophagus occurs, treatment will include the aforementioned drugs to reduce stomach acid, and removal of the precancerous tissue may be indicated. Surgery to shorten the esophagus may also be performed. Esophageal stenosis treatment may include a procedure for dilating the esophagus. Some patients may require surgery to implant a stent or to replace part of the esophagus.

Gastric ulcers are often treated by the same means used to treat GERD. In addition, antibiotics are used to eliminate any bacteria that may be the cause of the ulcers. Sucralfate may be used to form a barrier over the ulcer that protects it from stomach acid and allows it to heal.

Patients with pyloric stenosis normally require surgery to widen the canal leading from the stomach to the duodenum. In addition, those with intestinal malrotation may require surgery, depending on the severity of the condition. Surgery may also be required for patients with Meckel diverticulum if bleeding is a problem.

Cardiovascular treatment

In mild cases of cardiovascular involvement, no treatment plan is initiated other than to monitor the dysfunctions. Some septal defects may be asymptomatic and heal on their own. Since most of these abnormalities can lead to infective endocarditis, patients should be given antibiotics before undergoing dental procedures or surgeries.

KEY TERMS

Autosomal dominant—A pattern of inheritance in which one copy of a mutated gene on a non-sex chromosome is sufficient to cause disease.

Chromosomal aneuploidy—A condition in which the chromosomal number is either increased or decreased.

Clinodactyly—An abnormal inward curving of the fingers or toes.

Cohesinopathy—A condition, such as Cornelia de Lange syndrome, that affects the cohesion complex that separates chromosomes during cell division.

Fistula—An abnormal passage or communication between two different organs or surfaces.

Gastrointestinal reflux disease (GERD)—A chronic condition, usually accompanied by heartburn, that can damage the esophagus.

Haploinsufficiency—A condition caused by the loss of one copy of a gene.

Hypertrichosis—Excessive hair growth; also called hirsutism.

Infective endocarditis—An infection of the tissue lining the walls of the heart.

Oligodactyly—The absence of one or more fingers or toes.

Sporadic—Occurring at irregular intervals in no particular pattern or order.

Syndactyly—Webbing or fusion between the fingers or toes.

Synophrys—A feature in which the eyebrows join in the middle; also called blepharophimosis.

Teratogenic factor—Any factor that can produce congenital abnormalities.

For patients who develop congestive heart failure, a regimen of drugs known as beta blockers may be useful for slowing down the heart. Other drugs that may be used include diuretics, to prevent fluid retention, or ACE inhibitors.

For more serious cardiac involvement, surgery is recommended. Surgery for tetralogy of Fallot involves widening the pulmonary valve and repairing the ventricular septal defect. This surgery is normally performed on patients between the ages of eight months and three years. Ventricular septal defects can be repaired, usually with a synthetic patch. Atrial septal defects are normally performed by catheterization to

QUESTIONS TO ASK YOUR DOCTOR

- What are the factors on which preliminary and definitive diagnoses of Cornelia de Lange syndrome are based?
- Should my child have genetic testing for Cornelia de Lange syndrome? Should family members be tested?
- What are the characteristic symptoms of Cornelia de Lange syndrome?
- What factors determine how long children with Cornelia de Lange syndrome will live and their quality of life?
- What is the likelihood of having a second child with Cornelia de Lange Syndrome?

place a device between the atria in the septum. Patent ductus arteriosus correction is done by either ligating the vessel or cutting it off.

Hearing and visual concerns

Patients diagnosed with CdLS should be examined for hearing loss as soon as possible because of the likelihood of speech delay. Patients should be fitted with hearing aids and may be considered for pharyngeal-esophageal tubes.

It is important to identify vision problems early. Glasses may be necessary for nearsightedness. Children should be seen by an ophthalmologist in order to assess limitations and develop a treatment plan.

Other issues

CdLS-specific developmental charts and growth charts are available to guide treatments and therapies. Since development of speech is often delayed, children with CdLS should be seen by a speech pathologist at an early age. Alternative communication strategies, such as sign language, may be employed, depending on the level of speech development. Children and family members may also benefit from therapy available from a number of organizations. Patients may qualify for health-related support services from a variety of national organizations for retarded persons. Children with persistent behavioral problems such as hyperactivity, severe impulsive behavior, aggression, or self-injury may require specialist psychological or psychiatric treatment. CdLS also affects multiple oral structures, and early dental evaluation and

treatment are very important. Treatment for cleft palate may be required.

Prognosis

Patients with CdLS can live well into adulthood, although lifespan is typically shortened. Gastrointestinal and respiratory complications are the most common causes of death in patients with CdLS. Prognosis can be improved by early diagnosis and intervention. These two factors can influence not only patients' life expectancy but also quality of life for them, their family, and their caregivers.

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Cornelia de Lange Syndrome Foundation, Inc., 30 Tower Lane, #400, Avon, CT 06001, (860) 676-8166, (800) 223-8355. (800) 753-2357, (860) 676-8337, info@cdlsusa.org, <http://www.cdlsusa.org>

Genetic Alliance, Inc., 26400 Woodfield Road, #189, Damascus, MD 20872, (202) 966-5557, (202) 966-8553, info@geneticalliance.org, <http://www.geneticalliance.org>
 March of Dimes National Office, 1550 Crystal Drive, Suite 1300, Arlington, VA 22202, (888) 663-4637, <http://www.marchofdimes.org>
 National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 263-9938, <http://www.rarediseases.org>

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Costello syndrome

Definition

Costello syndrome is an extremely rare genetic disorder caused by mutations in the *HRAS* gene. It affects many aspects of growth and development, and is characterized by newborn feeding problems, poor growth, loose and wrinkled skin, and mental retardation.

Description

The *HRAS* gene produces a protein called H-Ras that helps regulate cell growth and division. Costello syndrome results from mutations in *HRAS* that produce an overactive H-Ras protein that directs cells to constantly grow and divide. This apparently results in many of the characteristic features of Costello syndrome, although the exact mechanisms are unclear. H-Ras-promoted uncontrolled cell growth also can lead to the development of cancerous (malignant) and non-cancerous (benign) tumors. For this reason, *HRAS* is called an oncogene—a gene in which mutations can cause cancer.

H-Ras is a type of enzyme called a GTPase that converts a molecule called GTP into GDP. This acts as a switch, relaying signals from outside the cell to the cell nucleus to instruct the cell to grow or divide. The *HRAS* gene mutations responsible for Costello syndrome result in an H-Ras protein that is always turned on so that cells throughout the body grow and divide out of control. This abnormal process apparently leads to the other characteristics of Costello syndrome, including delayed development, intellectual disabilities, and distinct facial features, including a large mouth, loose skin folds, and very flexible joints. Children with Costello syndrome also commonly have structural heart defects, an abnormal heart rhythm, and an enlarged and weakened heart muscle.

KEY TERMS

Arrhythmia—Abnormal heart rhythm; examples are a slow, fast, or irregular heart rate.

Autosomal dominant—A pattern of inheritance in which one copy of a mutated gene on a non-sex chromosome is sufficient to cause disease.

HRAS—The gene encoding the H-Ras protein that helps regulate cell growth and division; mutations in *HRAS* can cause Costello syndrome.

Larynx—The voice box or the organ that contains the vocal cords.

Oncogene—A gene, such as *HRAS*, that can cause cancer if mutated.

Papillomatous papules—Skin-colored, raised bumps (not warts) found on the skin; most of these growths are benign (noncancerous) and rarely become malignant (cancerous).

Polyhydramnios—A condition in which there is too much fluid around the fetus in the amniotic sac.

Rhabdomyosarcoma—A malignant tumor of the skeletal muscle.

Somatic mutation—Sporadic mutation; a gene mutation that is not inherited from a parent carrying the mutation but rather occurs in an egg or sperm cell or during fetal development.

They are of relatively short stature and may have reduced levels of growth hormone.

From early childhood, patients with Costello syndrome are at increased risk for various cancers, as well as benign tumors called papillomas—small growths usually around the nose and mouth or anus. The most common childhood cancer associated with Costello syndrome is rhabdomyosarcoma, which originates in muscle tissue. Neuroblastomas that arise in developing nerve tissue have also been reported. Adolescents with Costello syndrome can be at risk for a type of bladder cancer associated with older adults. Individuals with Costello syndrome may also be at increased risk for thyroid, kidney, and other cancers.

Genetic profile

The capital letters in *HRAS* gene stand for “Harvey rat sarcoma viral oncogene homolog.” This gene is located on the short arm (p) of chromosome 11 at position 15.5 (11p15.5). At least 15 mutations in *HRAS* are known to cause Costello syndrome. These mutations change

single amino acids in an essential region of the H-Ras protein. More than 80% of Costello syndrome cases are caused by a mutation that changes the amino acid glycine to the amino acid serine at position 12 in the H-Ras protein (Gly12 Ser or G12S).

Costello syndrome is an autosomal dominant condition. This means that only one copy of a mutated *HRAS* gene is sufficient for the development of Costello syndrome, even when the second copy of *HRAS* is normal. Almost all known cases of Costello syndrome occur in children without a family history of the disorder; rather, they are new gene mutations—known as somatic or sporadic mutations—that were not inherited from a parent but that occurred in an egg or sperm cell, or during early embryonic or fetal development.

Some individuals who have been diagnosed with Costello syndrome do not have an identified mutation in the *HRAS* gene. It is possible that they may actually have Noonan syndrome or cardiofaciocutaneous (CFC) syndrome, which are caused by mutations in genes that interact with the H-Ras protein to control cell growth and division.

Demographics

In 1971 and 1977, Dr. J. Costello described the mental and growth delays and distinctive facial and skin features of the syndrome that carries his name. After these initial descriptions, there were no further reports of Costello syndrome until 1991. Costello syndrome is now estimated to affect 200–300 people worldwide, with an estimated prevalence ranging from 1 in 300,000 to 1 in 1.25 million people. It affects both males and females equally and most likely occurs in all racial and ethnic groups.

Signs and symptoms

The first signs of Costello syndrome may appear even before birth. Mothers carrying Costello syndrome babies may have polyhydramnios (an excess of amniotic fluid in the womb). This may be because of the fetus's poor swallowing ability. Many Costello syndrome babies are large at birth, especially with respect to weight, and have a large head. However, they begin life with severe feeding problems. They do not grow and thrive; rather, they lose weight and become quite ill. This poor growth continues until about two years of age. Then, for unknown reasons, growth, especially weight gain, begins to normalize. However, the children continue to grow slowly and will remain short throughout life. Most adults with Costello syndrome are approximately 4.5 ft. (1.5 m) tall. X-ray studies at different ages show that bone growth is delayed, leading to reduced height.

Infants with Costello syndrome have a slight downward slant of the eyes, full cheeks, thick lips, and an

upturned nose. The neck is short. The ears are low-set (below the level of the nose) with large, fleshy earlobes. These features seem to coarsen and become more noticeable over time. However, the signature feature of Costello syndrome is the soft, deeply wrinkled skin, especially on the hands and feet. This is evident at birth and becomes even more striking in the first few months of life. All individuals with Costello syndrome have deeply creased loose skin. Some physicians have described the distinct, deep creases in the skin as resembling “bathtub hands”—similar to the puffiness seen after soaking one's hands in water. Other skin characteristics may include dark-colored moles on the palms of the hands and the bottoms of the feet, brownish-colored birthmarks almost anywhere on the body, and small red marks on the surface of the skin caused by broken blood vessels. Unusual skin growths called papillomatous papules, which are skin-colored, raised bumps, form inside the nose and mouth, on the tongue, and around the anus in late childhood or early adolescence. These rarely become cancerous.

Most individuals with Costello syndrome have sparse, curly hair and a hoarse voice. The hair turns gray at a very early age, sometimes even during adolescence. Along with the loose wrinkled skin, the gray hair makes Costello syndrome patients appear much older than their age. The Costello syndrome voice, described as low and hoarse, may possibly be due to weakness in the tissues or muscles of the larynx.

All individuals with Costello syndrome have significant mental delays and delays in walking and talking. They are usually a few years behind other children their age. These learning disabilities continue as they get older and require special education. IQ testing shows mild to moderate retardation (IQs of 30–68). Although they have special needs, Costello syndrome individuals are outgoing, with friendly personalities, which helps them make the most of their abilities.

Other signs and symptoms of Costello syndrome may include:

- tight Achilles tendons
- weak muscle tone (hypotonia)
- a structural brain abnormality called a Chiari I malformation
- skeletal abnormalities
- dental problems
- vision problems

Diagnosis

The pattern of overgrowth in the womb, poor growth after birth, and short height is typical of individuals with Costello syndrome. However, the signs and symptoms

QUESTIONS TO ASK YOUR DOCTOR

- Are there prenatal signs or symptoms that might suggest that my child will be born with Costello syndrome?
- Should my child have genetic testing for Costello syndrome?
- Should other family members have genetic testing?
- What is the risk that my partner and I will have another child with Costello syndrome?
- What health problems will an infant with Costello syndrome likely experience?
- What ongoing treatments or other procedures will be needed to assist a child born with Costello syndrome?

overlap considerably with those of Noonan and CFC syndromes, and it may be difficult to distinguish these syndromes based on newborn appearance. Later in childhood, the skin papules and graying hair can be diagnostic of Costello syndrome. Genetic testing for *HRAS* mutations is available for a definitive diagnosis.

Treatment and management

Individuals with Costello syndrome require extensive treatment and management throughout life to address multiple physical and intellectual conditions as they arise. Children will require special education and treatment by a team of specialists.

Heart disease is seen in almost half of individuals with Costello syndrome. The heart problems are sometimes apparent at birth. These include holes in the muscular wall of the heart, abnormal thickening of the walls of the heart, and an abnormal heartbeat or arrhythmia. An echocardiogram (ultrasound of the heart) is usually performed early in life to assess heart function. Heart function is closely monitored as patients age.

Individuals with Costello syndrome frequently develop rare types of cancer. These cancers may occur early in life, even in infancy. Therefore, continual cancer surveillance throughout life is required.

Prognosis

The severe problems with feeding and growth that characterize Costello syndrome can be life-threatening. Most of these infants require a feeding tube to survive. Complications of heart disease are another life-threatening

concern, even in early life. For most individuals, the heart problems are not severe and usually can be successfully treated without surgery, although some individuals with Costello syndrome have experienced heart failure and sudden death. Lastly, individuals with Costello syndrome are at risk for developing and possibly dying of cancer.

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ORGANIZATIONS

- Costello Kids, 90 Parkfield Rd. N, New Moston, Manchester, UK M40 3RQ, <http://www.costellokids.com>
- Magic Foundation, 6645 W. North Ave., Oak Park, IL 60302, (708) 383-0808, (800) 3MAGIC3 (362-4423), ContactUs@magicfoundation.org, <https://www.magicfoundation.org>

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Cowden syndrome

Definition

Cowden syndrome is a rare genetic disorder whose main symptom is the presence of many benign (noncancerous) growths that are known as hamartomas. People with Cowden syndrome have a higher risk of developing certain types of cancers.

Description

Because Cowden syndrome is caused by mutations in the *PTEN* gene, it is often referred to as *PTEN* hamartoma tumor syndrome, along with other disorders caused by *PTEN* mutations, including Bannayan-Riley-Ruvalcaba syndrome and Cowden-like syndrome. Most people with Cowden syndrome have hamartomas on the skin and mucous membranes. Hamartomas also may occur inside the body, such as within the intestines.

Because people with Cowden syndrome are at high risk for developing certain types of cancer, it is considered a familial or hereditary cancer syndrome.

- Women with Cowden syndrome have an estimated 85% lifetime risk of developing breast cancer.
- Men and women are at a 10% risk of developing cancer of the thyroid.
- Women have a 5%–10% chance of developing cancer of the endometrium (uterine lining).

Women with Cowden syndrome may also develop benign disorders of the breast, including a 67% risk of fibrocystic breast disease. Men and women have a 75% chance of developing benign conditions of the thyroid, such as goiter or benign tumors. They are also more likely than the general population to have polyps in the stomach, small intestine, or colon; fibroids in the uterus; and lipomas (fatty tumors) and hemangiomas (tumors involving blood vessels).

PTEN (Phosphatase and TENsin homolog) is a member of the protein tyrosine phosphatase (PTP) gene family. It encodes the instructions for making a PTP protein that is found almost everywhere in the body. The *PTEN* protein is a tumor suppressor that regulates cell division to prevent cells from growing and dividing uncontrollably. The *PTEN* protein is an enzyme that removes a phosphate (PO₃) group from other proteins and from fats (lipids) as part of a cell-signaling pathway that instructs cells to stop growing and dividing, and/or triggers cells to self-destruct (apoptosis). Thus, mutations in the *PTEN* gene that result in the dysfunction or lack of the *PTEN* protein can cause cells to grow and divide uncontrollably, leading to the formation of benign and cancerous tumors in various parts of the body. The *PTEN* protein may also help control cell migration (movement), adhesion (sticking) of cells within tissues, and the formation of new blood vessels (angiogenesis). In addition, the *PTEN* protein may help maintain the stability of the genetic information within a cell. As a result of these multiple roles, *PTEN* mutations can cause a variety of problems throughout the body.

KEY TERMS

Apoptosis—Programmed cell death.

Autosomal dominant—A pattern of genetic inheritance in which only one abnormal gene is needed to display the trait or disease.

Endometrium—Lining of the uterus.

Hamartomas—Masses resembling tumors.

Hemangioma—A benign growth in a blood vessel.

Keratosis—Horny overgrowths of skin.

Lhermitte-Duclos disease—A rare form of benign brain tumor.

Lipomas—Benign fatty tumors.

Macrocephaly—A larger-than-normal head.

Protein tyrosine phosphatase (PTP)—A member of a protein family, including the *PTEN* protein, that modifies other proteins by removing a phosphate group.

PTEN—The gene that encodes a protein tyrosine phosphatase that is a tumor suppressor active in nearly all cells of the body; mutations in *PTEN* result in Cowden syndrome.

Genetic profile

The *PTEN* gene is located on the long arm (q) of chromosome 10 at position 10q23.3. More than 300 different mutations in the *PTEN* gene have been identified as causing Cowden syndrome, Cowden-like syndrome, or Bannayan-Riley-Ruvalcaba syndrome. These mutations range from small changes in the DNA sequence of *PTEN*, to large deletions within the gene. They cause a dysfunctional or abnormally functioning *PTEN* protein that fails to inhibit cell division or signal apoptosis in abnormal cells, resulting in hamartomas and cancerous tumors.

PTEN mutations are inherited in an autosomal dominant pattern. This means that only one mutated copy of the *PTEN* gene, inherited from one affected parent, is required to develop Cowden syndrome. Each child of an affected parent has a 50% risk of inheriting the mutated gene and the disorder. About 15% of *PTEN* mutations occur sporadically in an individual in whom neither parent carries the mutated gene. If the mutation occurs later in development, it may be present in only some of the cells in the body (mosaicism). If the mutation occurs in germline cells (eggs or sperm), it can still be passed on to that individual's offspring. However, *PTEN* mutations generally affect every cell in the body. Genetic screening can detect *PTEN* mutations.

Demographics

Cowden syndrome is extremely rare, occurring in approximately 1 in every 200,000 people. Because Cowden syndrome is not easily diagnosed, its true prevalence may be higher. The characteristic growths of Cowden syndrome usually appear before the age of 30. The disorder affects males and females equally.

Signs and symptoms

Symptoms of Cowden syndrome include hamartomas and cancers of the breast, thyroid, and uterine lining. Other symptoms may include:

- macrocephaly, a larger-than-normal head
- Lhermitte-Duclos disease, a rare benign brain tumor
- intellectual deficiencies

Diagnosis

Diagnosis of Cowden syndrome is very important because of the heightened risk of cancer and because symptoms may not appear until adulthood. Diagnosis allows for regular screenings to detect cancers early when they are more likely to be cured. Diagnosis may also alert other family members to the need to be screened for Cowden syndrome and cancers.

Examination

Clinical diagnosis may be based on presence of the characteristic skin lesions, the most notable being those on the face and mucous membranes. Facial papules (known as trichilemmomas) and keratoses (overgrowths of horny tissue) on the hands—including the palms—and mucous membranes affect 90% of people with Cowden syndrome. The healthcare practitioner notes the type of lesions, number of lesions, and their locations. Because thyroid disease occurs in approximately two-thirds of patients with Cowden syndrome, the thyroid is carefully examined. Inside the mouth, a characteristic pattern of cobblestone-like growths is apparent in approximately 40% of patients with this disorder.

Genetic testing

Genetic testing involves a blood test to detect known mutations in the *PTEN* gene. Because some mutations may not be detected by genetic testing, a negative test does not necessarily rule out Cowden syndrome. If a gene mutation is identified, other family members may have predictive testing to determine if they are at risk for developing tumors.

QUESTIONS TO ASK YOUR DOCTOR

- Should I have genetic testing for Cowden syndrome?
- Should my family members have genetic testing?
- What is my risk of having a child with Cowden syndrome?
- What cancer screenings do you recommend, and how often?
- Do you recommend annual mammography or MRI for breast cancer screening?

Treatment and management

Traditional

While there is no cure for Cowden syndrome, diligent management can help ensure that cancers are detected at an early stage. Even in the absence of symptoms, people with Cowden syndrome are advised to undergo regular cancer screenings.

- Breast cancer screenings include a monthly breast self-exam for men and women, yearly clinical breast exams for women aged 25 and over, and yearly mammograms for women beginning at ages 30 to 35 (or 5 to 10 years prior to the youngest diagnosis of breast cancer in the family). The American Cancer Society recommends that women with Cowden syndrome have annual breast screenings by magnetic resonance imaging (MRI).
- Men and women should have their first ultrasound screening for thyroid cancer at age 18 and possibly subsequent screenings on a yearly basis.
- Women should be screened for uterine cancer by uterine biopsy, beginning at age 35–40, and yearly uterine ultrasounds after menopause with biopsies of any suspicious growths.
- Men and women with a family history of kidney cancer should have annual urinalysis, urine cytology, and ultrasound of the kidney.

Treatment for skin lesions may include dermatological procedures such as chemical peels, laser resurfacing, or cryosurgery. In some cases, the lesions may be removed via surgery or shave excisions. Complications with keloid formation (scarring) may arise after surgery, so surgical intervention is avoided unless dermatological manifestations cause significant pain or deformity.

Drugs

Oral retinoids may offer temporary control of skin lesions; however, the growths usually reappear when the drug is discontinued.

Prognosis

People with Cowden syndrome have a significantly higher risk for developing cancers, particularly cancers of the breast, thyroid, and uterus. Breast cancer in women with Cowden syndrome develops, on average, between the ages of 38 and 46. Thus, a diligent schedule of cancer screenings is very important for a good prognosis. Individuals with Cowden syndrome and their siblings and offspring should undergo genetic counseling and testing, both for diagnosis and for family planning purposes, including preconception counseling and pre-implantation or prenatal diagnosis.

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ORGANIZATIONS

- American Cancer Society, 250 Williams St., N, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org>
- University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, (713) 792-2121 or (877) 632-6789, <http://www.mdanderson.org>

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CPT II deficiency see **Carnitine palmitoyl-transferase deficiency**

Crane-Heise syndrome

Definition

Crane-Heise syndrome is a lethal genetic disorder first defined in 1981. Some of the features of Crane-Heise syndrome are similar to those of another genetic disorder called aminopterin syndrome sine aminopterin (or pseudoaminopterin syndrome), indicating that the two conditions may be part of a spectrum of symptoms.

Description

Aminopterin syndrome is an established disorder resulting from the use of aminopterin as an abortifacient. Surviving infants who had been exposed to this chemical had severe developmental abnormalities, especially those of the skull. Crane-Heise is distinct from aminopterin syndrome in that the mothers of infants with Crane-Heise syndrome were not exposed to aminopterin.

Genetic profile

There are only nine documented cases of Crane-Heise syndrome, and therefore little is known about the genetic basis of the disorder. One candidate gene that may be associated with the syndrome is *FGDI*, located on the X chromosome at p11.21.

Since Crane-Heise syndrome has affected more than one sibling in a family and has been seen in both males and females, it is most likely transmitted through autosomal recessive inheritance. This means that two copies of the abnormal gene would have to be inherited, one from each parent, in order for the disorder to occur.

Demographics

Males and females are at equal risk for inheriting Crane-Heise syndrome since it is assumed to be an autosomal trait, meaning it is not inherited on one of the sex-determining chromosomes. No one ethnic group has been shown to be at higher risk, primarily due to the low number of reported cases. Of the cases reported, there tends to be a frequent recurrence of the disease with each pregnancy.

Signs and symptoms

Many distinct characteristics are seen in infants with Crane-Heise syndrome. Some of these include the following:

- large head with a relatively small face
- depressed nose with nasal openings turned forward
- underdeveloped jaw
- a narrow nose bridge with eyes close together

KEY TERM

Autosomal recessive—A pattern of genetic inheritance in which two copies of an abnormal gene are needed to display the trait or disease.

QUESTIONS TO ASK YOUR DOCTOR

- What is the likelihood of survival for a fetus with Crane-Heise syndrome?
- What information can a genetic counselor provide about the possibility of my having a child born with Crane-Heise syndrome?
- What treatments are available for a child born with this disorder?

- low-set ears that are turned to the back
- short neck
- partially fused fingers or toes
- clubfoot

The most definitive features of Crane-Heise syndrome and aminopterin syndrome are the cranial and bone abnormalities. Infants born with these syndromes typically have absent or underdeveloped brains (anencephaly), underdeveloped shoulder blades, and absent collarbones and vertebrae.

Diagnosis

Since the signs of Crane-Heise syndrome are nearly identical to those observed in infants with aminopterin syndrome, it is important to identify whether the mother was exposed to aminopterin for differential diagnosis. Some fetuses have been diagnosed with Crane-Heise syndrome in the uterus via ultrasonography; however, most diagnoses are based on physical examination at the time of birth.

Treatment and management

As of 2021, no treatment had been developed. Further research to better understand the cause and genetic basis of this disorder is necessary.

Prognosis

Crane-Heise syndrome is a lethal disorder, and infants are usually stillborn or survive only a few days

after birth. Malformations of the brain and vertebrae are usually severe and cannot be corrected surgically.

Resources

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- Griffiths, Anthony J. F., et al., eds. *Introduction to Genetic Analysis*. 12th ed. New York: Macmillan, 2020.
- Jones, Kenneth Lyons, et al., eds. *Smith's Recognizable Patterns of Human Malformation*. 8th ed. Philadelphia: Elsevier, 2021.

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ORGANIZATIONS

- Genetic Disease Foundation, Mount Sinai School of Medicine, One Gustavo L. Levy Place, Box 1497, New York, NY 10029, <http://www.geneticdiseasefoundation.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Sonya Kunkle
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Craniofacial microsomia

Definition

Craniofacial microsomia is a general diagnosis used to describe facial birth defects of varying severity that may involve certain differences in the eyes, ears, facial bones, jaw, mouth, neck, or spine. These defects often affect only one side of the face, with that side appearing smaller than the other.

Description

Individuals with craniofacial microsomia have physical differences that are present at birth (congenital). These abnormalities are typically limited to the head and bones of the spinal column (vertebrae) and may be severe or mild. In some cases, the changes are seen on both sides of the face (bilateral). In other cases, they are limited to one side of the face (unilateral).

Different terms may be used for this pattern of differences. Craniofacial microsomia may also be called hemifacial microsomia, first and second branchial arch syndrome, Goldenhar syndrome, otomandibular dysostosis, facioauriculovertebral sequence, or oculo-auriculo-vertebral spectrum (OAVS). This final name describes

the common birth defects seen in persons with craniofacial microsomia. “Oculo” refers to the eye, and “auriculo” refers to the ear. Finally, “vertebral” refers to the physical problems present in the vertebrae.

Genetic profile

Craniofacial microsomia is caused by a disruption of normal facial development. A baby’s face forms very early, normally between the eighth and twelfth weeks of pregnancy. Normal facial development depends on many different tissues growing together in the correct order. When the movement and development of these tissues is disrupted, the face may have abnormal openings, underdevelopment of some facial features, and/or excess skin. In craniofacial microsomia, some unknown event disrupts normal development of the first and second branchial arches, the embryonic structures that later develop into the sides of the face, the jaw, and the upper neck.

There are most likely many different factors that may lead to the abnormal development of the facial tissues. In some cases, these factors may be environmental. For example, there are certain medications a woman can take while pregnant that can cause the baby to have the symptoms of craniofacial microsomia. However, in the vast majority of cases, craniofacial microsomia is not caused by a medication or drug of abuse consumed during pregnancy.

In other cases, normal development of the facial tissues may be disrupted by genetic factors. Unlike some other syndromes, there has been no single gene mutation identified that causes craniofacial microsomia. Studies in a few persons with craniofacial microsomia point to a possible candidate gene located on the long arm of chromosome 14 at 14q32; however, this finding requires further study and characterization. Another group of researchers in Italy reported in 2015 on a patient with OAVS found to have a microduplication on the long arm of chromosome 3 at 3q29. This microduplication, however, involved nine separate genes, any of which might be identified in the future as associated with craniofacial microsomia. In addition, further research is required to determine whether this specific genetic abnormality can be identified in a larger population than a single patient.

A few families in which craniofacial microsomia occurs show an autosomal recessive inheritance pattern, while other families show an autosomal dominant pattern of inheritance. Most cases of craniofacial microsomia are not inherited.

Craniofacial microsomia typically occurs sporadically (at random). Doctors are often unable to explain why it occurs. Since it is sporadic in nature, if a child is diagnosed with craniofacial microsomia, the risk for the parents to have another child with the disorder is low,

KEY TERMS

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a non-sex chromosome is required for a disease or inherited trait to develop in an individual.

Autosomal recessive—A pattern of genetic inheritance in which two copies of an abnormal gene are needed to display the trait or disease.

Branchial arches—Structures that form during the development of the human embryo as outpouchings of the developing pharynx. The first and second branchial arches in humans give rise to the bony and muscular structures of the face, jaw, and upper neck.

Coloboma—A birth defect in which part of the eye does not form completely and appears to be cleft or notched.

Congenital—Refers to a disorder that is present at birth.

Dysostosis—A general term for a disorder of bone development.

Mandible—The lower jaw bone.

Maxillae—The two facial bones that fuse to form the upper jaw and the roof of the mouth in humans.

Microduplication—A condition in which a small amount of genetic material is abnormally copied in a chromosome, usually a dozen genes or fewer.

Microphthalmia—A developmental disorder of the eye in which one or both eyes are smaller than normal and have other structural defects.

Microsomia—A general term for an abnormally small body or body part.

Scoliosis—Abnormal curvature of the spine, usually defined as greater than ten degrees to the right or left as the doctor faces the patient.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

about 3%. In rare cases, one parent or another family member may have some of the physical symptoms of craniofacial microsomia. If this is the case, then the risk of having a child with the disorder may be higher, and the parents should consult a genetic counselor.

Demographics

Craniofacial microsomia is a relatively common congenital disorder; it occurs once in every 3,000–5,000 live

births. Other researchers estimate that the disorder is much less common, affecting only one child in 26,550. One reason for this discrepancy is that doctors do not agree on the criteria for diagnosing craniofacial microsomia. Another reason is that mild cases might not come to a doctor's attention. Males are affected more frequently than females: some researchers give a sex ratio of two males to one female. Craniofacial microsomia is seen in all ethnic groups and cultures.

Signs and symptoms

The symptoms associated with craniofacial microsomia are highly variable. Some individuals have many severe abnormalities, while others have only a few minor birth defects.

The abnormalities seen in craniofacial microsomia are typically limited to the face and vertebrae. Thirty percent of patients have bilateral facial abnormalities. In those patients, the right side is usually affected more severely. The facial asymmetry commonly observed in persons with craniofacial microsomia is caused by hypoplasia (underdevelopment) of the upper and lower jaw. These bones are called the mandible (lower jaw) and the maxillae (two bones in humans that fuse to form the upper jaw and the roof of the mouth). In addition to the bones of the face, the muscles of the face can also be underdeveloped. Cleft lip and cleft palate are other facial differences associated with craniofacial microsomia. Cleft lip is an abnormal split or opening in the lip that can extend toward the nose or toward the cheek. Cleft palate is an opening in the roof of the mouth. Individuals with craniofacial microsomia can also have an unusually wide mouth (macrostomia).

Birth defects of the eye are common in craniofacial microsomia. Cysts on the eyeball (epibulbar dermoids) are common, as is microphthalmia (small eye). Some individuals with Goldenhar syndrome have a notch of tissue missing from the upper eyelid (coloboma). Strabismus (crossing of the eyes) is also prevalent.

Abnormal development of the ears is another characteristic of the craniofacial microsomia spectrum. The ears may be smaller than normal (microtia), or absent (anotia). Ear tags (excess pieces of skin) may be seen on the cheek next to the ear and may extend to the corner of the mouth. The shape of the ears may also be unusual. Hearing loss is common in individuals with craniofacial microsomia.

The vertebral anomalies seen in many persons with craniofacial microsomia result from improper development of the vertebrae. Vertebrae can be incompletely developed (hemivertebrae), absent, or fused. Ribs can also be abnormal. Approximately 50% of individuals

QUESTIONS TO ASK YOUR DOCTOR

- Do you think that the gene or genes associated with craniofacial microsomia will be identified in the near future?
- Can you recommend a children's hospital with experienced specialists who can treat my child's craniofacial microsomia?
- How can we help our child cope with the outward signs of his disorder as he or she grows older?
- What are the chances that we or other family members will have another child with craniofacial microsomia?

with craniofacial microsomia will have side-to-side curvature of the spine (scoliosis).

Other differences outside the face and vertebrae can occasionally be seen in craniofacial microsomia. Approximately 15% of individuals with craniofacial microsomia have developmental delays or intellectual disability. The likelihood of intellectual disability increases if the individual has microphthalmia (abnormally small eyes). Heart defects and kidney defects can occur. Arm defects, though rare, may also occur.

Diagnosis

The diagnosis is made when an individual has the common symptoms associated with the condition. It can be made before birth by a physician using ultrasound imaging, or after birth on the basis of the observed physical features. Although it is not universally accepted, one scale used by many doctors in the United States for evaluating the severity of craniofacial microsomia is the OMENS scale (Orbital distortion, Mandibular hypoplasia, Ear anomaly, Nerve involvement, and Soft tissue deficiency). The scale was introduced in 1991 by a team of doctors at Harvard Medical School.

Treatment and management

Once a child is diagnosed with craniofacial microsomia, additional tests should be performed. The parents should consider having their child evaluated and treated at a specialized children's hospital with a craniofacial center. A hearing evaluation is necessary to determine whether there is hearing loss. If hearing loss is evident, the child should be referred to a hearing specialist. Speech therapy may be helpful. X-rays of the spine are

recommended to determine whether there are vertebral problems. Individuals with craniofacial microsomia may be followed regularly to check for scoliosis. Ultrasounds of the kidneys and heart may be recommended, due to the increased risk of birth defects in those organs. A doctor would make this recommendation. Finally, individuals with craniofacial microsomia should be evaluated by an eye specialist (ophthalmologist).

Surgery may be necessary to correct the birth defects seen in craniofacial microsomia. Surgery to correct the facial birth defects can improve the child's appearance and function. As the child approaches school age, psychological counseling may be beneficial to assist him or her in coping with the social challenges presented by abnormal facial features or postural problems.

Prognosis

The prognosis for individuals with craniofacial microsomia is very good. These individuals typically have a normal lifespan and normal intelligence.

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Association. <https://www.faces-cranio.org/what-is-hemifacial-microsomia> (accessed May 14, 2021).

ORGANIZATIONS

- Children's Craniofacial Association, 13140 Coit Road, Suite 517, Dallas, TX 75240, (214) 570-9099 or (800) 535-3643, (214) 570-8811, contactCCA@ccakids.com, <http://www.ccakids.com>
- FACES: The National Craniofacial Association, P.O. Box 11082, Chattanooga, TN 37401, (800) 332-2373, info@faces-cranio.org, <http://www.faces-cranio.org>
- Genetic Alliance, 26400 Woodfield Road, #189, Damascus, MD 20872, (202) 966-5557, (202) 966-8553, info@geneticalliance.org, <http://www.geneticalliance.org>
- Hearing Loss Association of America, 6116 Executive Boulevard, Suite 320, Rockville, MD 20852, (301) 657-2248, (301) 913-9413, <http://www.hearingloss.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 263-9938, <http://www.rarediseases.org>

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Revised by Bharati K. Hegde, BE, MS, PhD

Craniofrontonasal dysplasia see **Otopalatodigital syndrome**

Craniostenosis see **Craniosynostosis**

Craniosynostosis

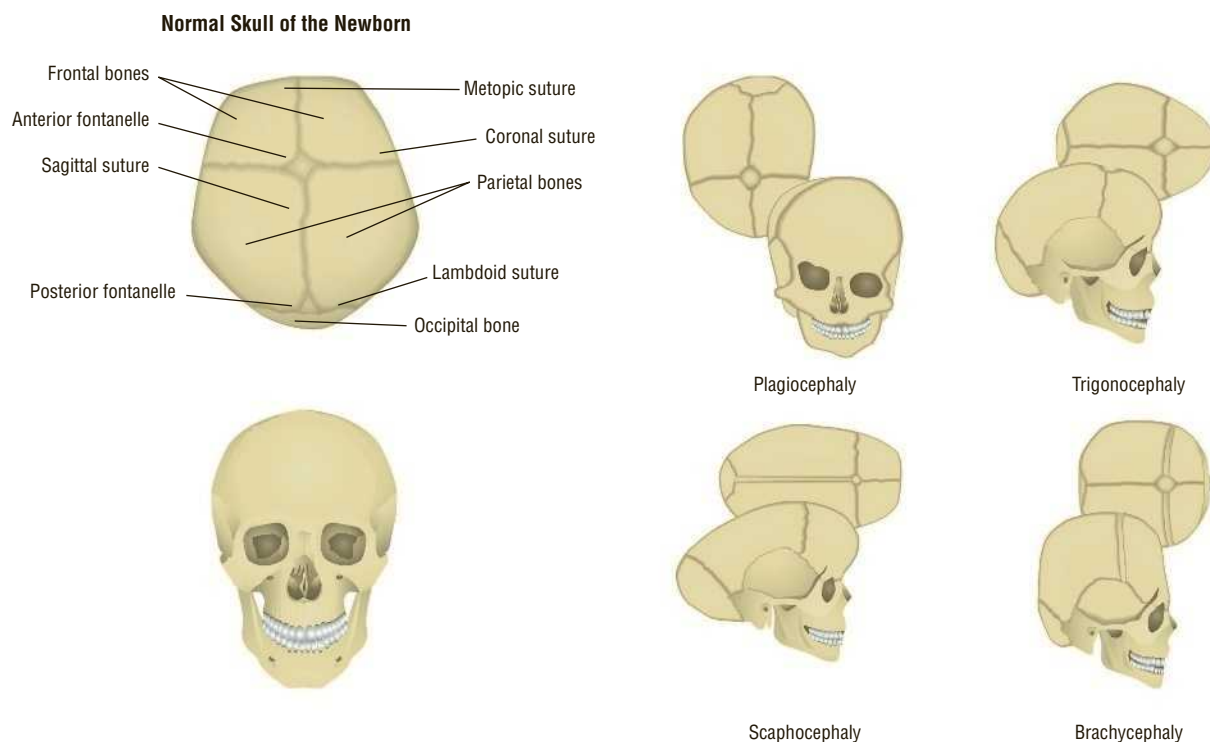
Definition

Craniosynostosis is a congenital abnormality of the central nervous system that involves the premature closing of one or more of the fibrous joints between the bones of the skull (cranial sutures).

Description

Craniosynostosis is a birth defect that affects the shape of the skull. Because there are several different types of this defect, some doctors refer to them in the plural as the craniosynostoses. Individuals born with craniosynostosis have abnormally shaped heads and a prominent bony ridge over the affected suture or sutures. All affected individuals also are likely to experience water on the brain (hydrocephalus), which can cause enlargement of the head and increased pressure inside the skull. Developmental delay is commonly experienced by those individuals affected by craniosynostosis.

Craniosynostosis



Different types of craniosynostosis (Gale)

There are two major classifications of the craniosynostoses: primary and secondary. There are multiple causes of primary craniosynostosis, which involves abnormal cranial suture development. The premature closure of one or more of the sutures causes the skull bones to grow parallel to the affected suture but not perpendicular to it. At other sutures there may be too much growth. The disrupted growth patterns cause a misshapen skull. The cause of secondary craniosynostosis is failure of the brain to grow and expand. This failure results in uniform premature suture closure so that the head is symmetric and abnormally small (microcephalic).

The human skull consists of several bony plates separated by a narrow gap that contains stem cells. These fibrous joints are referred to as cranial sutures. There are six cranial sutures: the sagittal, which runs from front to back across the top of the head; the two coronal sutures, which run across the skull parallel to and just above the hairline; the metopic, which runs from front to back in front of the sagittal suture; and the two lambdoid sutures, which run from side to side across the back of the head. There are seven types of primary craniosynostosis classified according to the cranial suture or sutures that are

affected: sagittal; bicoronal (both coronal sutures); unicoronal (one coronal suture); coronal and sagittal; metopic; lambdoid and sagittal; and total, in which all the cranial sutures are affected. Approximately 40% of all cases of craniosynostosis are sagittal; 20% are bicoronal; 15% are unicoronal; 10% are coronal and sagittal; 4% are metopic; 1% are lambdoid and sagittal; and 10% are total.

Genetic profile

Craniosynostosis does not have a single genetic cause, but it is sometimes passed from one generation to another. It has been associated with over 150 different genetic syndromes. Genetic inheritance of craniosynostosis is not sex-linked (it is autosomal), and it has been tied to both dominant and recessive patterns of inheritance. The overall occurrence rates are equivalent between males and females, but sagittal craniosynostosis is seen four times as often in males as in females, while coronal craniosynostosis is observed twice as often in females as in males.

Craniosynostosis is known to be marked by genetic heterogeneity, which means that more than one gene or

genetic mechanism can produce the disorder. Three of the genes associated with craniosynostosis—at chromosome locations 8p11.23-p11.22 (*FGFR1*), 10q26 (*FGFR2*), and 4p16.3 (*FGFR3*)—are related to fibroblast growth factor receptors (*FGFRs*), which are molecules that control cell growth. Mutations in these genes are linked to such syndromes as Muenke syndrome, Apert syndrome, Crouzon syndrome, and others in which craniosynostosis is one feature among others (limb defects, hearing loss, developmental delays, deformed facial features, etc.) These known genetic syndromes account for about 10% to 20% of reported cases of craniosynostosis.

In addition to the *FGFR*-related genes, four other genes had been linked to craniosynostosis as of 2021. These forms of the disorder are presently classified as types 1 through 4; all are relatively rare:

- Craniosynostosis type 1 (CRS1) is caused by a mutation in the *TWIST1* gene on the short arm of chromosome 7 at 7p21 and is inherited in an autosomal dominant pattern. The mutation causes coronal and sagittal forms of the disorder.
- Craniosynostosis type 2 (CRS2) is caused by mutations in the *MSX2* gene on the long arm of chromosome 5 at 5q35.2. This mutation also is inherited in an autosomal dominant fashion.
- Craniosynostosis type 3 (CRS3) is caused by mutations in the *TCF12* gene on the long arm of chromosome 15 at 15q21.3. Type 3 craniosynostosis occurs in several different forms, including coronal, sagittal, and multi-suture presentations.
- Craniosynostosis type 4 (CRS4) is caused by mutations in the *ERF* gene on the long arm of chromosome 19 at 19q13.2. Type 4 craniosynostosis has the widest variety of presentations, with sagittal, metopic, lambdoid, coronal, and multisuture craniosynostoses being reported in different families with the mutations.

Not all instances of craniosynostosis appear to have a genetic origin. The most common cause of nongenetic craniosynostosis is constraint of the fetal head during pregnancy. This condition is believed to account for between 50% and 60% of all cases of craniosynostosis.

Demographics

Craniosynostosis has an incidence of approximately 1 in every 2,200 live births. Genetic-based craniosynostosis is most commonly a dominant trait, but in some cases it has also been shown to be recessive. Therefore, while it is more likely to occur in children with a family history of craniosynostosis, it may not occur in the children of such families and it may also occur in children with no family history of the disorder. Nongenetic craniosynostosis has a higher occurrence among the children of malnourished or

KEY TERMS

Acrocephalopolysyndactyly syndromes—A collection of genetic disorders characterized by a cone-shaped abnormality of the skull and partial fusing of adjacent fingers or toes.

Acrocephaly—An abnormal cone shape of the head.

Anterior fontanelle—The soft spot on the skull of an infant that is located in the center of the head just behind the hairline.

Brachycephaly—An abnormal thickening and widening of the skull.

Congenital—Refers to a disorder that is present at birth.

Cranial suture—Any one of the seven fibrous joints between the bones of the skull.

Frontal plagiocephaly—An abnormal condition of the skull in which the front is more developed on one side than it is on the other side.

Hydrocephalus—The excess accumulation of cerebrospinal fluid around the brain, often causing enlargement of the head.

Microcephalic—Having an abnormally small head.

Primary craniosynostosis—Abnormal closure of the cranial sutures caused by an abnormality in the sutures themselves.

Proptosis—Bulging or protruding eyeballs.

Scaphocephaly—An abnormally long and narrow skull.

Secondary craniosynostosis—Abnormal closure of the cranial sutures caused by a failure of the brain to grow and expand.

Trigonocephaly—An abnormal development of the skull characterized by a triangle-shaped forehead.

drug-abusing mothers. It is also more likely to occur in the children of teenage mothers because of the lack of development of an appropriately sized uterus for fetal growth in many of these cases.

Signs and symptoms

The most obvious symptom of craniosynostosis is an abnormally shaped head that is not the result of the birth process. Craniosynostosis may be confirmed by the presence of a bony ridge over the affected cranial suture. Associated symptoms include such unusual facial

features as wide-set, down-slanting, or protruding eyes and a prominent jaw; visual impairment; hearing loss; breathing problems; water on the brain (hydrocephalus); and developmental delay.

Each type of craniosynostosis has different physically observable symptoms and results in a different head shape. Sagittal craniosynostosis is characterized by a long and narrow skull (scaphocephaly). This is referred to as an increase in the A-P, or anterior-to-posterior, diameter. Thus an observer looking down on the top of the skull would see that the diameter of the head is greater than normal in the front-to-back direction. Individuals born with sagittal craniosynostosis have broad foreheads and a larger-than-normal back of the head. The so-called soft spot found just beyond the hairline in a normal baby (the anterior fontanelle) is missing or very small in a baby affected with sagittal craniosynostosis. The result of neurological testing is generally normal for individuals with sagittal craniosynostosis.

Bicoronal craniosynostosis is characterized by a wide and short skull (brachycephaly) or by a cloverleaf-shaped skull. This feature is referred to as a decrease in the A-P diameter. Individuals affected with bicoronal craniosynostosis have poorly formed eye sockets and foreheads. This characteristic causes a smaller-than-normal eye socket that can lead to visual complications. These complications include damage to the optic nerve, which can cause a loss of visual clarity; bulging eyeballs (a condition called proptosis), which usually results in damage to the cornea; widely spaced eyes; and a narrowing of the sinuses and tear ducts that can cause inflammation of the mucous membranes lining the exposed portion of the eyeball (conjunctivitis). Bicoronal craniosynostosis can be further complicated by water on the brain (hydrocephalus) and increased intracranial pressure. Most individuals affected with bicoronal craniosynostosis also have an abnormally high and arched palate that can cause dental problems and protrusion of the lower jaw. Bicoronal craniosynostosis is associated with several acrocephalosyndactyly syndromes (genetic syndromes that involve abnormalities of the head and webbed fingers or toes), which include Apert syndrome, Apert-Crouzon syndrome, Saethre-Chotzen syndrome, and Pfeiffer syndrome.

Unicoronal craniosynostosis is characterized by a skull that is more developed in the front on one side than it is on the other side (frontal plagiocephaly). This characteristic leads to a distinct asymmetry between the sides of the face, a flattening of the forehead on the side affected by the premature suture closure, and a misalignment of the eyes such that the eye on the affected side is higher than the eye on the unaffected side.

QUESTIONS TO ASK YOUR DOCTOR

- What does the term “craniosynostosis” mean?
- How do the primary and secondary craniosynostoses differ from each other?
- Can craniosynostosis be diagnosed with prenatal imaging and genetic tests?
- What kind of surgical procedures are available for dealing with craniosynostosis in an infant, and how successful are those procedures at present?

Coronal and sagittal craniosynostosis is characterized by a cone-shaped head (acrocephaly). The front soft spot (the anterior fontanelle) is generally much larger than normal, and it may never close without surgical intervention. Individuals affected with coronal and sagittal craniosynostosis may have higher than normal intracranial pressure. Pfeiffer syndrome is closely associated with coronal and sagittal craniosynostosis.

Total craniosynostosis is characterized by a normally shaped but small skull (microcephaly). Individuals affected with total craniosynostosis have higher than normal intracranial pressure, and they are the most likely of all craniosynostosis-affected individuals to suffer from developmental delay.

Metopic craniosynostosis is characterized by a triangle-shaped forehead (trigonocephaly), thickened bones in the forehead, and narrowly spaced eyes. Individuals affected with metopic craniosynostosis tend to have developmental abnormalities associated with processes that are known to be controlled by the front of the brain (the forebrain).

Lambdoid and sagittal craniosynostosis is the rarest type of craniosynostosis. It is characterized by a flattening of the back of the skull (the occipital bone) and a bulging of the front of the skull (the frontal bone). This condition may occur symmetrically or asymmetrically.

Diagnosis

Prenatal, transabdominal, or traditional ultrasound can be used to assess fetal skull development in the second and third trimesters of pregnancy; however, a CT scan is considered the most accurate diagnostic imaging test for prenatal diagnosis of craniosynostosis. Plain radiographic studies may also be performed. Bicoronal

and unicoronal craniosynostosis associated with one of the acrocephalosyndactyly syndromes may be detected via several different genetic tests. These tests are able to identify the underlying mutations in all three *FGFR* genes and the genes that are linked to craniosynostosis types 1, 2, and 4. In 2019, Fulgent Genetics in California introduced a single gene test for the gene associated with craniosynostosis type 3.

Almost all cases of craniosynostosis are evident at birth; however, the cranial sutures are not fully closed at this time, so instances of craniosynostosis have been diagnosed later in infancy as well. Skull x-rays and/or a CT scan may also be used after birth to diagnose craniosynostosis.

Treatment and management

Because craniosynostosis is associated with other conditions and may require multiple treatments of the skull, face, eyes, and ears, a multidisciplinary team of doctors and specialists is often required. The skull abnormalities of craniosynostosis should be surgically corrected within the first year of life. In the first year of life, changing the elevation and contours of the skull bones is much easier, and new bone growth and reshaping occur rapidly. Also, at this point the facial features are still highly undeveloped, so significant improvement in appearance can be achieved.

Multiple surgeries may be required over the patient's lifetime, depending on the circumstances of the case. Follow-up support by pediatric, dental, psychological, neurological, surgical, and genetic specialists may be necessary.

In the types of craniosynostosis that involve the eyes, consultation with an ophthalmologist is often recommended, and eye surgery may also be necessary. Speech and hearing therapy may also be needed when the ears and the frontal lobe have been affected. In the case of bicoronal craniosynostosis in which the palate is severely malformed, dental consultation may also be required. In the most severe cases of coronal craniosynostosis, it will be necessary to address feeding and respiratory problems that are associated with the abnormally formed palate and sinuses.

Families with a history of craniosynostosis can participate in genetic counseling in order to learn whether genetic testing can identify the likelihood that their children might be affected.

Prognosis

In all but the most severe and inoperable cases of craniosynostosis, it is possible that considerable

improvement in physical appearance can be achieved via surgery. Depending on the neurological damage resulting from certain types of craniosynostosis versus the rapidity of treatment, certain affected individuals may suffer developmental disabilities ranging from the extremely mild to very severe. Most individuals with craniosynostosis that involves coronal sutures will continue to have vision problems throughout life. These problems vary in severity, but many are now amenable to fully corrective treatments.

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ORGANIZATIONS

Children's Craniofacial Association, 13140 Coit Rd., Suite 517, Dallas, TX 75240, (214) 570-9099 or (800) 535-3643, contactCCA@ccakids.com, <http://www.ccakids.com>

FACES: The National Craniofacial Association, PO Box 11082, Chattanooga, TN 37401, (800) 332-2373, faces@faces-cranio.org, <http://www.faces-cranio.org/index.htm>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Paul A. Johnson
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Creutzfeldt-Jakob disease

Creutzfeldt-Jakob (pronounced KROYTZ-felt YAH-kob) disease (CJD) is a rapidly progressive neurodegenerative disorder that has no cure and ends in death, often within a matter of months. It is named for Hans Gerhard Creutzfeldt and Alfons Maria Jakob, two German neuropathologists who first reported it in a series of four patients in 1920 and 1921.

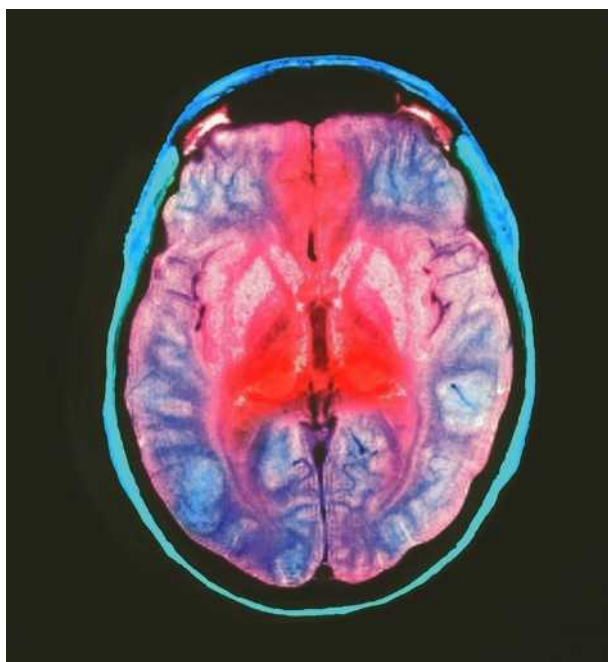
CJD is a very rare disease of the central nervous system caused by a prion, or a misfolded protein that can convert normal proteins to its abnormal shape. The term “prion” was coined in 1982 by Stanley Prusiner, an American neurologist, to describe these unusual disease agents that can replicate and cause transmissible disease, even though they lack the nucleic acids found in bacteria, viruses, and parasites. The word “prion” is derived from a combination of “protein” and “infection.”

CJD Pathology

CJD develops when a prion induces normally folded copies of proteins to conform to its misfolded structure, resulting in a chain reaction in which each new prion spreads its abnormal structure to other normal protein molecules. The misfolded proteins cannot be utilized by cells in the normal process of protein breakdown known as proteolysis; they then accumulate on the outside of the cells, eventually causing cell death. In the brain, the death of nerve cells results in vacuoles (small cavities) in the brain tissue resembling those of sponges, which can be seen on autopsy, giving the disease the spongiform description. CJD is grouped together with kuru, Gerstmann-Sträussler-Scheinker syndrome, fatal familial insomnia, and bovine spongiform encephalopathy (Mad Cow Disease) as a transmissible spongiform encephalopathy (TSE). TSEs are contagious (transmissible) and cause a sponge-like series of holes in the brain.

CJD is classified into several subtypes:

- **Sporadic:** Sporadic CJD occurs randomly within the general population and accounts for about 85% of cases. There is no recognizable pattern of transmission or set of risk factors in sporadic CJD.
- **Familial CJD (fCJD):** Familial CJD is caused by a mutation in the *PRNP* gene, which codes for the normal protein that is eventually converted to a prion, or PrPC. The mutated gene codes for the disease-causing misfolded protein, or PrPSc. The Sc in the name of the misfolded protein is derived from scrapie, a disease of sheep that is also a TSE. Familial CJD accounts for 10% to 15% of cases of CJD.



Colored magnetic resonance imaging (MRI) scan of the brain of a 17-year-old male suffering from Creutzfeldt-Jakob disease. The front of the head is at the top. In this axial view through the brain, the folded cerebrum is seen forming two hemispheres. At lower center are two red areas of the thalamus diseased with CJD, which destroys nerve cells and causes brain tissue to become spongy. Symptoms include dementia, muscle contractions, and sometimes death. (Simon Fraser/Royal Victoria Infirmary, Newcastle Upon Tyne/Science Source)

- **Iatrogenic, or hospital-acquired, CJD:** Iatrogenic CJD is a form of the disease caused by contaminated surgical instruments, blood transfusions, human-derived growth hormone, or the use of transplanted tissue taken from the dura mater of an infected patient. About 250 cases of iatrogenic CJD were reported before strict sterilization protocols were made mandatory for the reuse of surgical instruments or the use of human-derived biological materials. There have been no cases of iatrogenic CJD reported since 1976.
- **Variant CJD (vCJD):** Variant CJD is another acquired form of CJD that develops when a person eats beef from a cow infected with bovine spongiform encephalopathy. The number of cases of vCJD peaked in 2000 and declined to about two cases per year by 2008. There have been about 229 cases of vCJD reported worldwide since 1996.

Genetic Susceptibility

Familial CJD is the only form of the disease that has a known genetic profile. It is caused by a mutation in the

PRNP gene on the short arm of chromosome 20 at 20p13. About 30 different mutations of the *PRNP* gene have been identified as causing fCJD. Some of these mutations replace single amino acids in the normal prion protein (PrPC), while other mutations add extra amino acids or remove portions of the normal protein, resulting in an unusually short form of it. These changes in the structure of the normal protein result in the disease-causing form PrPSc. This abnormal form binds to the normal PrPC, changing it into PrPSc. The abnormal PrPSc builds up in the tissues of the brain, because it cannot be broken down in the normal process of proteolysis. The clumps of PrPSc eventually destroy the neurons (nerve cells), producing the small vacuoles that give the diseased brain tissue a sponge-like appearance.

Familial CJD is transmitted in an autosomal dominant pattern, which means that only one copy of the mutated *PRNP* gene is necessary for the disease to appear in a patient.

Researchers have discovered that a person's risk of developing fCJD is influenced by a mutation in the *PRNP* gene at position 129 in the normal PrPC protein. People who inherit the same mutation from both parents at that spot are more likely to develop fCJD. In addition, they will usually develop symptoms of CJD at an earlier age and have a more rapid progression of the disease.

Epidemiology

All forms of CJD are very rare, affecting about one person per million. There are about 300 cases reported each year in the United States; of these, between 30 and 45 cases are fCJD.

Sporadic and familial CJD (sometimes grouped together as classic CJD) are almost entirely diseases of middle-aged or older adults. The average age at the time of symptom onset is 60. Persons with the familial form of CJD may develop symptoms as early as age 40. Males and females are equally affected. CJD occurs at the same rate worldwide in all races and ethnic groups.

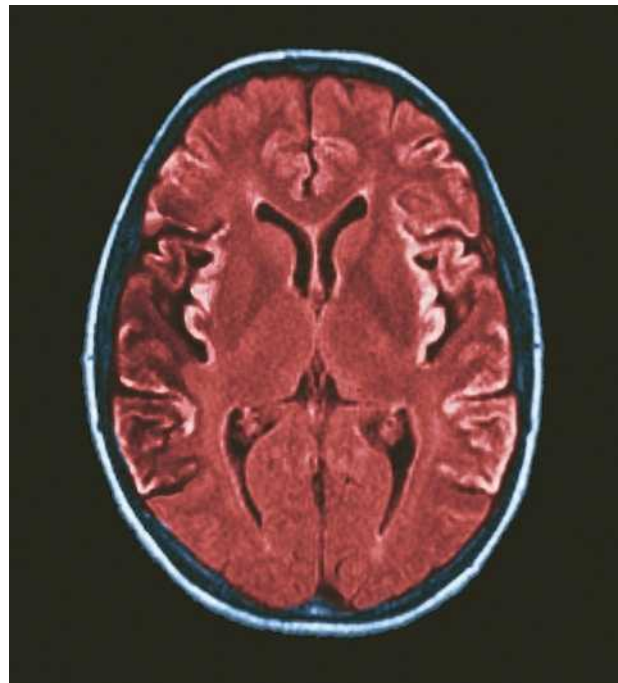
vCJD affects younger adults, with an average age of 25 at the time of symptom onset. As with classic CJD, males and females are equally affected. Variant CJD has become increasingly rare since preventive measures related to the feeding and slaughter of cattle were introduced in the 1990s.

Signs and Symptoms

The signs and symptoms of classic CJD typically begin with dementia, a condition characterized by the loss

of not only memory but also judgment, reasoning ability, and the ability to carry out activities of daily life (ADLs). In contrast to such other dementing disorders as Alzheimer's disease, frontotemporal dementia, Lewy body disease, and others, the dementia associated with CJD progresses very rapidly; family members of patients with CJD often say that they can see the patient's mental functions decline from one day to the next. Other common symptoms of CJD include difficulties with speech or swallowing, visual problems, personality changes, insomnia, or depression. Some patients also have auditory or visual hallucinations and may go completely blind.

Another major symptom of CJD is myoclonus, which is the involuntary twitching or jerking of muscles or muscle groups. Fairly quickly in the course of the disease, the patient will usually have problems with walking and muscular coordination (ataxia), and they may become completely bedridden. Other neuromuscular symptoms of CJD include athetosis (slow, involuntary writhing movements of the hands, arms, or feet) and akinetic mutism, a condition in which the patient can neither move nor speak. Deterioration of the breathing muscles makes patients with CJD susceptible to pneumonia, which often hastens their death.



Colored magnetic resonance imaging scan of the brain of a 35-year-old patient, showing hyperintensity in the region of the putamen and cerebral cortex. These are typical signs indicative of the presence of Creutzfeldt-Jakob disease. (Zephyr/Science Source)

KEY TERMS

Akinetic mutism—A medical condition in which the patient is unable to move (akinetik) or speak (mutism).

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Athetosis—A condition marked by slow, writhing, involuntary muscle movements.

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a non-sex chromosome is necessary for a disease or inherited trait to develop in an individual.

Dementia—A condition of deteriorated mental ability characterized by a marked decline of intellect and often by emotional apathy.

Dura mater—A thick membrane that is the outermost of the three layers of tissue (meninges) covering the brain and spinal cord. Tissue from this membrane has been used for transplantation in cases of head trauma but is now considered a risk factor for iatrogenic CJD.

Encephalopathy—The medical term for any global dysfunction of the brain. It is not a single disease but rather a syndrome that has many different causes and prognoses.

Iatrogenic—Referring to a symptom or disorder caused inadvertently by a medical intervention or diagnostic procedure.

Kuru—An incurable neurodegenerative disease that is classified as a transmissible spongiform encephalopathy. It is transmitted among humans by cannibalism.

Myoclonus—Twitching or spasms of a muscle or an interrelated group of muscles.

Polymorphism—A change in the base pair sequence of DNA that may or may not be associated with a disease.

Prion—A protein that can fold in several different and distinctive ways, one of which can be transmitted to other proteins.

Proteolysis—The breakdown of proteins into smaller units, usually polypeptides or amino acids.

Scrapie—A fatal disease of sheep and goats that is classified as a transmissible spongiform encephalopathy. Although scrapie is caused by a prion, it is not transmissible to humans.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

Vacuole—A small cavity found within organic tissue.

Diagnosis

The diagnosis of CJD is complicated by the fact that the condition is so rare that most doctors will never see a case of it in their entire careers. In addition, the early symptoms of CJD are not unique to the disease and can be easily confused with the symptoms of Parkinson's disease, Huntington's disease, Alzheimer's disease, tertiary syphilis, or major depression (if the initial symptoms are personality changes). There is at present no blood or urine test that can be used to screen for CJD.

Because CJD is incurable and invariably fatal, doctors begin the diagnostic process by attempting to determine whether the patient has a disease that can be treated, such as encephalitis (inflammation of the brain), neurosyphilis, or meningitis. Common tests include an electroencephalogram (EEG), which is often valuable because CJD produces distinctive sharp brain wave patterns. A spinal tap may be done to rule out infections of the central nervous system. The patient's cerebrospinal fluid may also be tested for 14-3-3 protein, a regulatory molecule that is found in elevated amounts in the CSF

of patients with CJD. Imaging studies may include a CT scan and an MRI. CT scans are useful in ruling out stroke or a brain tumor as the cause of the patient's symptoms. MRIs in particular will reveal patterns of deterioration in the brain tissue that point to CJD.

The next step in diagnosis is to evaluate the patient's clinical symptoms together with the results of the various imaging and other tests. According to the Centers for Disease Control and Prevention (CDC), the following criteria are used to determine the possibility or probability of a diagnosis of CJD:

- **Probable:** The patient has rapidly progressing dementia plus at least two of four other signs (myoclonus, akinetic mutism, visual disorders or ataxia, or abnormal reflexes) plus a positive result on at least one test (EEG, MRI, CT, or 14-3-3 protein), combined with the absence of an alternative diagnosis.
- **Possible:** The patient has progressive dementia plus two of the four signs (myoclonus, akinetic mutism, visual disorders or ataxia, or abnormal reflexes) plus the absence of a positive result on any of the tests (EEG,

MRI, CT, or 14-3-3 protein). The patient has also had the illness less than two years and does not have an alternative diagnosis.

A definite diagnosis requires examination of a sample of the patient's brain tissue. Although such a sample can be taken while the patient is alive, there is a considerable risk of missing the portion of the brain that is directly affected by the disease and thus obtaining a false negative. In addition, the biopsy risks exposing the surgeon and other healthcare personnel to contaminated body fluids and tissue. In most cases, the definite diagnosis of CJD is obtained only at autopsy.

Criteria for a diagnosis of fCJD include a diagnosis of probable or possible CJD in the patient, plus a diagnosis of probable or possible CJD in a first-degree relative (parent, child, or sibling), plus detection of a mutation in the *PRNP* gene on molecular genetic testing. Genetic counseling should be offered to other family members when a patient is diagnosed with fCJD.

In 2014, an international team of researchers reported that they had developed a technique for detecting the form of the prion protein implicated in sporadic CJD in nasal brushings taken from living patients diagnosed with CJD. The method proved to be more accurate than analysis of samples of cerebrospinal fluid, and it may offer a minimally invasive laboratory test for detecting sporadic CJD. Also in 2014, another group of researchers reported that they had developed a urine test that appears to be effective in detecting very small amounts of the abnormal PrP^{Sc} protein in patients with variant CJD.

Treatment and Management

There is no specific treatment for CJD, as the disease is incurable. Care is supportive. The patient may be helped by antidepressants for depression or anxiety, or clonazepam or an anticonvulsant drug to relieve severe myoclonus. Quetiapine has been found to be helpful in treating hallucinations. In general, patients with classic CJD will require skilled nursing care as the disease progresses, and they may prefer referral to a hospice for end-of-life care.

Although CJD is defined as transmissible, it is not contagious in the usual sense. People cannot contract CJD from touching or holding their loved one; it is not necessary to quarantine or isolate patients diagnosed with CJD or to restrict visits from friends and family members. Healthcare workers should, however, avoid exposure to cerebrospinal fluid and brain tissue from CJD patients.

Prognosis

The prognosis of all forms of CJD is uniformly grim, as there is no cure for the disease right now. The time

QUESTIONS TO ASK YOUR DOCTOR

- Have you ever cared for a patient who turned out to have CJD?
- Do you think a cure will be developed someday for this disease?
- What advice would you give to a family with a member with possible or probable CJD?
- Would you recommend genetic testing to such a family?

from symptom onset to death ranges from a few months to five years.

Methods to Characterize the Misfolded Protein and Potential Treatments

Scientists have come a long way in characterizing the misfolding of mutant PRPC protein. With advanced imaging techniques, they have been able to locate the origin of misfolding on the protein and view the changes in shape as the protein misfolds. Scientists have also generated antibodies that bind to the location that initiates misfolding of the protein and prevent misfolding due to mutations. This work has pointed to an avenue of research around preventing misfolding.

Live human brain tissue may help screen potential treatments for CJD. Human cerebral organoids are small balls of human brain cells whose organization, structure, and electrical signaling mimic human brain tissue. Because studies in mice have failed to identify effective treatment in patients, human cerebral organoids are necessary to study potential treatments for CJD. Skin cells from patients are genetically engineered and manipulated to become brain cells for use in organoid research on CJD transmissibility and its inhibition.

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ORGANIZATIONS

Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, Atlanta, GA 30329-4027, (800) 232-4636, <http://www.cdc.gov>

Creutzfeldt-Jakob Disease Foundation, 3634 W. Market St., Suite 110, Akron, OH 44333, (800) 659-1991, help@cjd.foundation.org, <http://www.cjd.foundation.org>

National Institute of Neurological Disorders and Stroke (NINDS), P.O. Box 5801, Bethesda, MD 20824, (301) 496-5751 or (800) 352-9424, <http://www.ninds.nih.gov/index.htm>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Rebecca J. Frey, PhD
Revised by Kimberly Napoli

Cri du chat syndrome

Definition

Cri du chat syndrome occurs when a piece of chromosomal material is missing from a particular region on chromosome 5. Individuals with this syndrome have unusual facial features, poor muscle tone (hypotonia), small head size (microcephaly), and intellectual disability. A classic feature of the syndrome is the cat-like cry made by infants with this disorder.

Description

Dr. Jerome Lejeune first described cri du chat syndrome in 1963. The syndrome is named for the cat-like cry made by infants with this genetic disorder. *Cri du chat* means "cry of the cat" in French. This unusual

cry is caused by abnormal development of the larynx (the organ in the throat responsible for voice production). Cri du chat syndrome is also called 5p minus syndrome because it is caused by a deletion, or removal, of genetic material from chromosome 5. The deletion that causes cri du chat syndrome occurs on the short or "p" arm of chromosome 5. This deleted genetic material is vital for normal development. Absence of this material results in the features associated with cri du chat syndrome.

A high-pitched mewing cry during infancy is a classic feature of cri du chat. Infants with cri du chat typically have low birth weight, slow growth, a small head (microcephaly), and poor muscle tone (hypotonia). They also may have congenital heart defects. Individuals with cri du chat syndrome have language difficulties, delayed motor skill development, and intellectual disability. Behavioral problems may also develop as the child matures.

Genetic profile

Cri du chat is the result of a chromosome abnormality. Human beings have 46 chromosomes in the cells of their body. Chromosomes contain genes, which regulate the function and development of the body. An individual's chromosomes are inherited from their parents, 23 chromosomes from the egg and 23 chromosomes from the sperm. The 46 chromosomes in the human body are divided into pairs based on their physical characteristics. Chromosomes can only be seen when viewed under a microscope.

Most chromosomes have a constriction near the center called the centromere. The centromere separates the chromosome into long and short arms. The short arm of a chromosome is called the "p arm." The long arm of a chromosome is called the "q arm."

Individuals usually have two copies of chromosome 5. Cri du chat is caused when the end of the short arm of the chromosome is deleted, or erased, from the "p" arm of one chromosome 5. The piece of chromosomal material deleted contains many genes necessary for normal development. One gene specifically known to be affected by this deletion is the *CTNND2* gene, which codes for a protein known as delta-catenin. Since delta-catenin is essential in the nervous system and muscular system, a deletion of this gene results in abnormal structure and function of the brain, nerves, and muscles of the human body. When these genes are missing, the larynx, brain, and other parts of the body do not develop as expected. This is what causes the symptoms associated with cri du chat.

In 90% of patients with cri du chat syndrome, the deletion is sporadic. This means that it happens randomly

and is not hereditary. If a child has cri du chat due to a sporadic deletion, the chance the parents could have another child with cri du chat is 1%. In approximately 10% of patients with cri du chat, there is a hereditary chromosomal rearrangement that causes the deletion. If a parent has this rearrangement, the risk of having another child with cri du chat is greater than 1%.

Demographics

It has been estimated that cri du chat syndrome occurs in 1 of every 50,000 live births. According to the 5p Minus Society, approximately 50–60 children are born with cri du chat syndrome in the United States each year. It can occur in all races and in both sexes.

Signs and symptoms

An abnormal larynx causes the unusual cat-like cry made by infants that is a hallmark feature of the syndrome. As children with cri du chat get older, the cat-like cry becomes less noticeable. This can make the diagnosis more difficult in older patients. In addition to the cat-like cry, individuals with cri du chat also have unusual facial features. These facial differences can be very subtle or more obvious. Microcephaly (small head size) is common. During infancy, many patients with cri du chat do not gain weight or grow normally. Approximately 30% of infants with cri du chat have a congenital heart defect. Hypotonia (poor muscle tone) is also common, leading to problems with eating, and slowing normal development. Intellectual disability and psychomotor retardation is present in all patients with cri du chat, but the degree of intellectual disability and physical retardation varies between patients.

Diagnosis

During infancy the diagnosis of cri du chat syndrome is strongly suspected if the characteristic cat-like cry is heard. If a child has this unusual cry or other features seen in cri du chat syndrome, chromosome testing should be performed. Chromosome analysis provides the definitive diagnosis of cri du chat syndrome and can be performed from a blood test. Chromosome analysis, also called karyotyping, involves staining the chromosomes and examining them under a microscope. In some cases, the deletion of material from chromosome 5 can be easily seen. In other cases, further testing must be performed. FISH (fluorescence in-situ hybridization) is a special technique that detects very small deletions. The majority of the deletions that

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Centromere—The constricted region of a chromosome. It performs certain functions during cell division.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted through either the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome—A microscopic thread-like structure found within each cell of the body consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Congenital—Refers to a disorder that is present at birth.

Deletion—The loss of genetic material that is normally found in a chromosome. Often, the genetic material is missing due to an error in replication of an egg or sperm cell.

Hypotonia—Reduced or diminished muscle tone.

Karyotyping—A laboratory procedure in which chromosomes are separated from cells, stained, and arranged so that their structure can be studied under the microscope.

Microcephaly—An abnormally small head.

cause cri du chat syndrome can be identified using the FISH technique.

Cri du chat syndrome can be detected before birth if the mother undergoes amniocentesis or chorionic villus sampling (CVS). This testing would only be recommended if the mother or father is known to have a chromosome rearrangement or if they already have a child with cri du chat syndrome. Other high-accuracy

QUESTIONS TO ASK YOUR DOCTOR

- How did cri du chat syndrome get its name, and what relevance does it have today?
- Can you explain the genetic basis for this disorder?
- What are the most common health risks faced by an infant born with cri du chat syndrome?
- Are there support groups available for parents of children born with cri du chat syndrome?
- How much support and attention will my child need for activities of daily life?
- Is there testing that can be done prior to giving birth to our next child to know whether or not he or she will have a genetic disorder as well?

prenatal genetic screening for cri du chat syndrome includes single-nucleotide polymorphism (SNP)-based microdeletion testing and noninvasive prenatal genetic testing (NIGT). Both are noninvasive tests with high accuracy for detecting a deletion in genes such as *CTNND2* associated with cri du chat syndrome. All genetic testing should be done in conjunction with genetic counseling for making informed decisions if genetic testing is positive for any disorder.

Diagnostic imaging can also be helpful for diagnosing an infant with cri du chat syndrome. On MRI, hypoplasia of the brainstem, pons, and cerebellum is largely associated with prenatal congenital disorders like cri du chat syndrome.

Treatment and management

Currently, there is no cure for cri du chat syndrome. Treatment consists of supportive care and developmental therapy.

Prognosis

Individuals with cri du chat have a 10% mortality during infancy due to complications associated with congenital heart defects, hypotonia, and feeding difficulties. Once these problems are controlled, most individuals with cri du chat syndrome have a normal lifespan. The degree of intellectual disability can be severe. However, a recent study suggested that the severity is somewhat affected by the amount of therapy received.

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- Chromosome Deletion Outreach, PO Box 724, Boca Raton, FL 33429-0724, (561) 395-4252, info@chromodisorder.org, <http://www.chromodisorder.org>
- 5p- Society, PO Box 268, Lakewood, CA 90714-0268, (888) 970-0777, (562) 920-5240, <http://www.fivepminus.org>
- Genetic Alliance, 26400 Woodfield Road #189, Damascus, MD 20872, (202) 966-5557, info@geneticalliance.org, <http://www.geneticalliance.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 798-2291, (203) 798-2291, <http://www.rarediseases.org>

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CRISPR/Cas

Definition

CRISPR/Cas is a tool that is used by researchers to examine and change DNA. It is part of the immune system of bacteria and some other micro-organisms. Researchers are exploring its use for diagnosing and treating diseases and for agricultural applications. CRISPR/Cas is often shortened to CRISPR, pronounced "crisper."

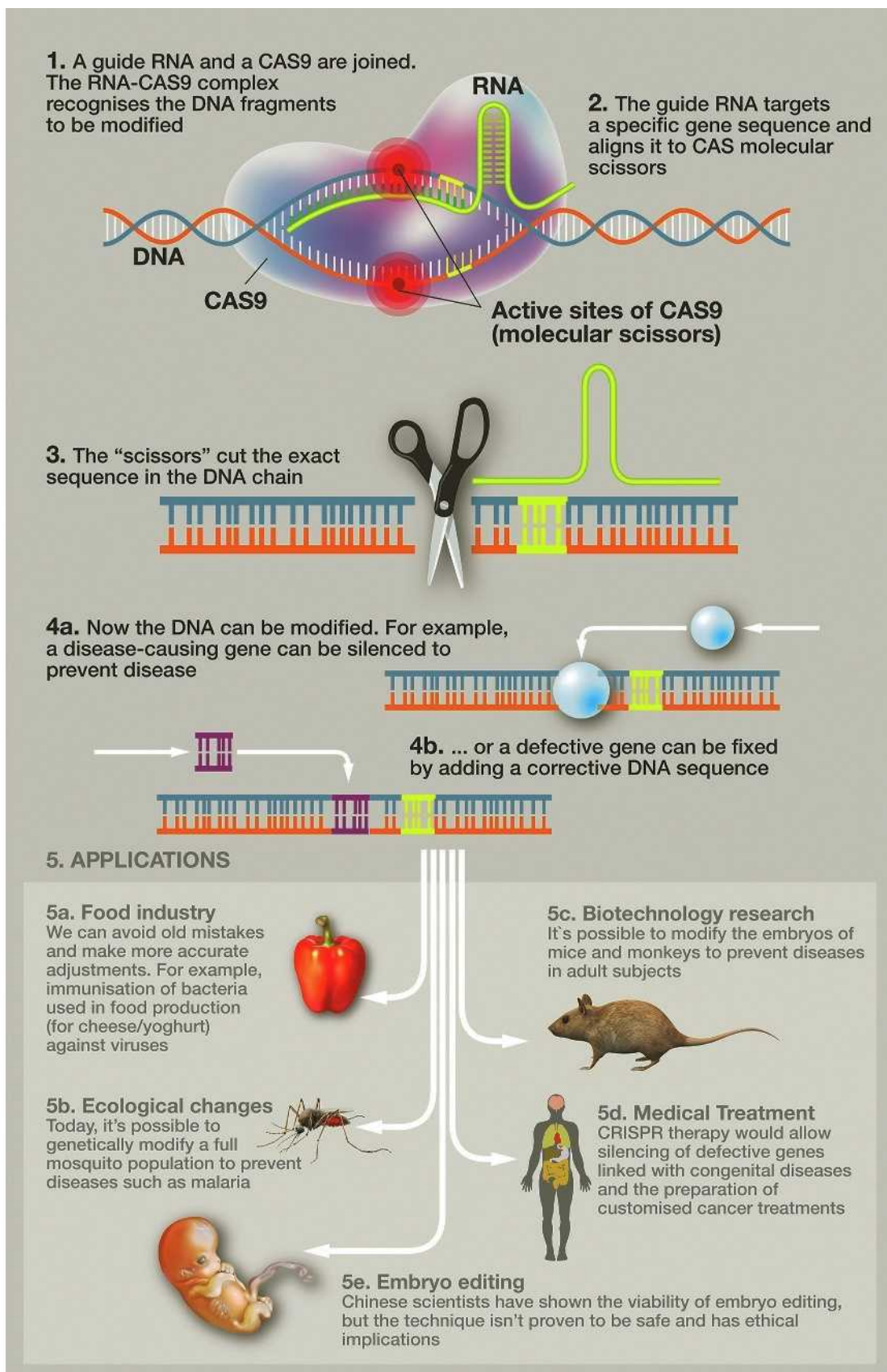


Diagram of the process that occurs in CRISPR-Cas9 gene editing. A protein (purple) is used in genome engineering to cut DNA (deoxyribonucleic acid). It uses a guide RNA (ribonucleic acid) sequence (yellow) to cut DNA (orange and blue) at a complementary site. The cut area of DNA is also shown in yellow. The process of silencing a gene or inserting a fragment of donor DNA (purple) is shown at center, with examples of genetically modified organisms at bottom. (Jose Antonio Penas/Science Source)

Description

CRISPR and Cas are part of the immune system of micro-organisms like bacteria. CRISPR stands for clustered, regularly interspaced, short palindromic repeats. It is made up of segments of repeating DNA sequences and short segments of spacer DNA (spacers). The spacers are bits of DNA taken from viruses that have previously infected the bacteria. These spacers help bacteria to recognize and fight off future infections. Cas is a CRISPR-associated protein. It is like a pair of molecular scissors that can cut DNA. When the virus attacks the bacteria again, the CRISPR DNA creates RNA, which contains the viral sequence. This RNA then guides the Cas to a spot in the virus that has a complementary DNA sequence. Cas then cuts the viral DNA in this spot and destroys it. This helps to protect bacteria from other organisms like viruses.

CRISPR repeats were first identified in *E. coli* bacteria in the 1980s, but major CRISPR/CAD development did not begin until 2005. By 2012, researchers were able to make CRISPR RNAs that could guide a Cas protein to target any DNA sequence. They were able to apply it to several species, including yeast, fish, flies, nematodes, plants, mice, monkeys, and humans. Since then, researchers have rushed to obtain patents on this technology. As of 2020, the Broad Institute appears to be winning this battle in the United States as it relates to animal and plant cells.

There are two different classes of CRISPR-Cas systems (I and II), which are subdivided into six types (I, II, III, IV, V, VI). The different classes and types are based on the structure and function of the Cas protein involved. The most commonly used systems by researchers are type II (Cas9), Type V (Cas12a) and Type VI (Cas13). CrisprGE (<http://crdd.osdd.net/servers/crisprge>) is a central online data base with a catalogue of more than 200 unique published CRISPR genes from more than 30 different model/animal systems. The website provides free tools for researchers who are interested in working with CRISPR/Cas systems.

Applications for CRISPR-Cas

There are many potential applications for CRISPR-Cas, such as diagnosing and treating genetic conditions, combating infectious diseases like COVID-19 and HIV, and genetically modifying crops. The two major areas where CRISPR-Cas has been used are gene editing and diagnosing disease.

CRISPR-Cas gene editing

CRISPR-Cas can be used to change an organism's DNA by making a cut in the DNA at a specific location and tricking the body's DNA repair mechanism to make

KEY TERMS

Endonucleases—Enzymes that recognize short pieces of DNA (often palindromic) and cleave either within or near the recognized sequence.

Gene editing—A process that involves changing an organism's DNA by removing, adding, or changing it.

Guide RNA (gRNA)—A combined tracer RNA and spacer RNA (pre-crRNA) that, when used in conjunction with a Cas9 nuclease (crRNA), can target and cut specific DNA sequences.

Leader sequence/leader RNA—Also known as the 5' untranslated region (5' UTR), the section of mRNA found immediately before the initiation codon for translation of a transcript.

Locus—The position occupied by a gene on a chromosome.

Operon—A functional unit of genomic DNA containing several genes under the control of one promoter.

Protospacer—A regularly sized piece of phage DNA that has been excised and incorporated into the CRISPR array.

Protospacer-adjacent motifs (PAMs)—Highly conserved short DNA sequences (2bp–5bp) that are necessary for the excision of adjacent protospacers.

the desired change. This technique has been used extensively in food production and agriculture. For example, CRISPR/Cas can be used in yogurt production to help prevent the good bacteria in yogurt from being destroyed by viruses. CRISPR/Cas has also been used to change the DNA of certain crops to improve their nutrition, drought tolerance, and pest resistance.

A significant amount of research is being done to use CRISPR-Cas to treat genetic diseases such as sickle cell disease and cystic fibrosis and infectious diseases such as COVID-19 and HIV. CRISPR/Cas is currently only being used on humans in clinical trials. It can be used to treat genetic conditions both outside the body (ex vivo) and inside the body (in vivo). For example, CRISPR/Cas was used to treat sickle cell disease ex vivo. Sickle cell disease is a genetic disease that causes abnormal red blood cells that cannot properly carry oxygen throughout the body. A woman with sickle cell disease was successfully treated by removing cells from her bone marrow, using CRISPR/Cas to edit the DNA of these cells, and infusing the repaired cells back into

QUESTIONS TO ASK YOUR DOCTOR

- Are there currently clinical trials for CRISPR/Cas-based therapies that are pertinent to my illness/disease?
- What are the risks associated with gene-editing therapies, and are there other alternatives?
- How does CRISPR/Cas gene editing work?
- What prognosis can you offer with this type of treatment?

her body. Another clinical trial is testing CRISPR/Cas in vivo to treat a genetic cause of blindness called Leber's congenital amaurosis. The CRISPR/Cas components are injected directly into the eye to repair the DNA variation causing the blindness. Researchers are also investigating using CRISPR/Cas to treat COVID-19 by targeting and cutting the viral DNA. They are also testing using CRISPR/Cas for treating other diseases such as hepatitis C, cancer, muscular degenerative diseases, and cystic fibrosis.

Diagnosing disease using CRISPR-Cas

CRISPR/Cas can be used for diagnosing infectious and genetic diseases. For example, a custom CRISPR/Cas can be created that will recognize and make a cut only if a specific genetic sequence associated with the COVID-19 virus is present. In one type of test, called SHERLOCK, the virus is present if a line appears on a special paper strip that is dipped into the sample.

CRISPR/Cas can also be used to diagnose mutations in DNA that can cause genetic diseases. For example, researchers in California have created a device with a CRISPR-Chip, which identifies specific mutations. The researchers were able to use the device to identify genetic mutations associated with Duchenne muscular dystrophy.

Limitations and ethical issues

Although CRISPR/Cas is powerful, it has a number of limitations:

1. It is hard to deliver CRISPR/Cas to cells in large numbers.
2. Not all cells that take in CRISPR/Cas are able to edit the DNA.
3. Sometimes CRISPR/Cas can cause unintended variations (mutations) in other parts of the DNA.

It is possible to change the DNA of eggs and sperm and early embryos using CRISPR/Cas. This technique is called germline editing. These types of changes will cause permanent changes in the individual and their offspring. Germline editing also allows CRISPR/Cas to be used to improve desirable traits rather than curing disease. It could also result in unintended changes to other parts of the DNA that could cause cancer, genetic disease, and other problems. Most scientists support a moratorium on using CRISPR/Cas for germline editing until more research is done and global ethical guidelines are developed. Germline editing has been banned in many countries. One example of how this experimentation can go wrong occurred in 2018. Chinese scientists performed germline editing using CRISPR/Cas on twin girls to make them more resistant to HIV. Unfortunately, the gene variation introduced into these babies may also make them and future generations more susceptible to other infections, such as influenza. This germline editing using CRISPR/Cas may also have introduced other unintended mutations. This experiment received international condemnation and renewed calls for an international moratorium on germline editing. The scientists involved were sent to prison and fined as a result.

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Crohn's disease

Definition

Crohn's disease is a common form of inflammatory bowel disease (IBS). It is an often serious condition that leads to inflammation and thickening of the walls of the bowel. In some cases, painful sores or ulcers of the digestive tract may develop. The most common features of Crohn's disease include chronic diarrhea, abdominal pain, decreased appetite, weight loss, fatigue, and fever.

Description

The inflammation of Crohn's disease primarily affects the large intestine and lower parts of the small intestine. The chronic swelling and thickening of intestinal lining lead to ulcers and open sores that cause the symptoms of diarrhea, abdominal cramping, loss of appetite, and weight loss experienced by those with Crohn's.

In addition to intestinal discomfort and symptoms, individuals with Crohn's disease may also experience persistent intestinal bleeding that may lead to anemia, a reduced number of red blood cells in the body; medical conditions that affect other parts of the body such as the eyes, joints, and skin; and intestinal blockage. A serious complication of this disease, intestinal blockage, may become life-threatening.

Genetic profile

Crohn's disease is caused by abnormalities of chromosome 5 and 10 and mutations in the *ATG16L1*, *IL23R*, *IRGM*, and *NOD2* genes. These chromosomal and genetic changes are associated with an increased risk of developing Crohn's disease.

The causes of Crohn's disease are complex and varied, involving behavioral, environmental, and genetic factors. Cigarette smoking is believed to increase the risk of developing the disease and may increase the number of flare-ups in individuals who have been diagnosed. Changes in an individual's immune system and the presence of certain bacteria in the digestive tract may also contribute to the development of Crohn's disease.

Specific genetic factors that lead to Crohn's disease include mutations in the *ATG16L1*, *IL23R*, *IRGM*, and *NOD2* genes. Each of these genes is significant in the formation of proteins important in developing and maintaining a healthy immune system. Mutations in any of these genes may cause the cells of the intestinal system to respond abnormally to bacteria and may lead to inflammation and the symptoms of Crohn's disease.

Abnormalities in specific regions of chromosomes 5 and 10 are associated with an increased risk of developing Crohn's disease. Specifically, abnormalities of the IBD5 locus of chromosome 5 have been found in individuals with Crohn's disease. Additionally, regions of chromosome 5 and 10 have large areas known as "gene deserts" that do not contain individual genes. Researchers believe that these regions may be important in regulating nearby genes, and suspect that these areas may be important in determining the genetic causes of Crohn's disease.

It is likely that there is an inheritance pattern for Crohn's disease because the disease does appear to run in families; however, the exact mechanism of inheritance has not been discovered.

Demographics

More than 780,000 Americans are affected by Crohn's disease. The condition is more common in Western Europe and North America, and occurs more frequently in whites and descendants of Ashkenazi Jews.

Signs and symptoms

The most common symptoms of Crohn's disease are chronic diarrhea, abdominal pain, decreased appetite, weight loss, fatigue, and fever. In addition to these symptoms, individuals with Crohn's may also have chronic anemia due to internal bleeding caused by open sores along the intestinal lining. This disease may also cause inflammation throughout the body. That systemic inflammation may cause abnormalities of the eyes, skin, and joints. A serious complication of Crohn's disease is intestinal blockage. Layers of thickened scar tissue may accumulate in the large and/or small intestine. This thickened tissue may completely block the bowel and prevent waste from exiting the body. If this occurs, immediate medical treatment is required.



Intestine displaying signs of Crohn's disease. (Juan Gaertner/Shutterstock)

Another condition caused by Crohn's disease is the formation of a fistula. A fistula is an abnormal opening in the bowel wall that connects to other tissue or another organ. These openings may connect to other abdominal organs such as the bladder or the vagina, and must be surgically repaired to prevent solid waste from entering these organs.

Diagnosis

Before a diagnosis of Crohn's disease is made, other causes for symptoms must be ruled out. In order to make an accurate diagnosis, doctors will record a complete medical and family history, and will compile a list of the patient's symptoms. Once other conditions and diseases are excluded, medical tests will be performed to diagnose Crohn's.

Laboratory tests that may be performed include the following:

- **Complete blood count (CBC)**—A blood test that counts blood cells and can determine if anemia or infection is present.

- **Fecal occult blood test**—A test in which a stool sample is examined to look for blood cells.

Imaging and scoping tests that may be used to diagnose Crohn's disease include the following:

- **Endoscopy**—A thin, flexible, lighted tube with an attached camera is inserted through the mouth into the upper portion of the digestive tract. Doctors are able to view the upper digestive tract for signs of sores or other symptoms of Crohn's disease.
- **Colonoscopy**—A thin, flexible, lighted tube with an attached camera is inserted into the rectum and guided through the colon. This test provides images of the entire colon. The doctor may also take small samples of tissue (biopsy) for testing to help confirm a diagnosis. The presence of granulomas, clusters of inflammatory cells, in the colon will help confirm the diagnosis of Crohn's.
- **Flexible sigmoidoscopy**—A thin, flexible, lighted tube is inserted in the colon and moved to the sigmoid, the section of the colon closest to the rectum.

- Computerized tomography (CT) scan—An imaging test that uses x-rays and computers to provide detailed images of the entire bowel as well as tissues outside the bowel.
- CT enterography—A specialized type of CT scan used to provide detailed images of the small intestine. This test has replaced barium x-ray tests in some circumstances.
- Magnetic resonance imaging (MRI)—An imaging test that uses a magnetic field and radio waves to create detailed images of organs and tissues. MRI is particularly useful for evaluating fistulae in the bowels.
- Capsule endoscopy—This test uses a small camera inside a capsule that is swallowed. Images from the camera are transmitted to a computer worn on the patient's waist. The images are then downloaded to a computer and examined by a doctor for signs of Crohn's disease. The camera is shed painlessly from the body when stool is passed.
- Double-balloon endoscopy—For this test, a longer scope is used to look farther into the small bowel where standard endoscopes do not reach. This technique is useful to help confirm a diagnosis when capsule endoscopy shows abnormalities.
- Small bowel imaging—This test looks at the part of the small bowel that can't be seen by colonoscopy. The patient swallows a liquid containing barium; and x-ray, CT, or MRI images of the small intestine are taken. The images are used to confirm diagnosis.

Treatment and management

There is currently no cure for Crohn's disease. Treatment is designed to lessen the severity of the symptoms and increase the comfort of the individual. Effective treatment will decrease symptoms, improve long-term prognosis, and possibly lead to remission.

There is no one general treatment for all people with Crohn's disease. Treatment is individualized and tailored to meet the needs of each patient. The primary treatment involves drug therapy and medication with the goal of reducing the inflammation that is the main cause of symptoms.

Categories of drug therapy for Crohn's disease include the following:

- Anti-inflammatory drugs—Anti-inflammatory drugs are often the first step in the treatment of inflammatory bowel disease. Some anti-inflammatory drugs used to treat Crohn's disease include oral 5-aminosalicylates, sulfasalazine (Azulfidine), and mesalamine (Asacol, Delzicol, Pentasa, Lialda, Apriso). These drugs, especially sulfasalazine, have numerous side effects, including nausea,

KEY TERMS

Barium—A chemical swallowed to help with outlining the gastrointestinal system during an x-ray study.

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light, resulting in blurry vision.

Glaucoma—An increase in the fluid pressure within the eye, eventually leading to damage of the optic nerve and ongoing visual loss.

Granuloma—A group of noncancerous nodular cells that form as a result of inflammation in the tissue.

Hypertension—The medical term for high blood pressure.

Inflammation—Swelling and reddening of tissue; usually caused by the immune system's response to the body's contact with an allergen.

Locus—The position occupied by a gene on a chromosome.

Lymphoma—Cancer of the lymphatic system, the system in the body that controls the immune system.

Osteoporosis—Loss of bone density that can increase the risk of fractures.

Remission—The time during which symptoms of a disease or condition are reduced or not present.

Strictureplasty—A surgical procedure in which a narrowed portion of the intestine is removed and the remaining section is reconnected to a healthy section of bowel.

diarrhea, vomiting, heartburn, and headache and are used less frequently than they once were.

- Corticosteroids—These medications, such as prednisone, help reduce inflammation in the entire body. They have many side effects, including facial swelling, excessive facial hair growth (in men and women), night sweats, insomnia, and hyperactivity. More serious side effects include hypertension, diabetes, osteoporosis, bone fractures, cataracts, glaucoma, and an increased chance of infection. Budesonide (Entocort EC), a newer type of corticosteroid, appears to work better with fewer side effects. However, its effectiveness is limited to reducing inflammation in specific areas of the colon. Corticosteroids may not be used for long term treatment; however, they may lead to remission when they are combined with immune suppressor medications.

- **Immunomodulators**—There are two types of immunomodulator medications: immune system suppressors and immune system stimulants. Immune system suppressors lessen the effect of the body's natural defenses in an attempt to reduce inflammation. These medications may increase the risk of developing certain infections and cancers. Immune stimulant medications increase the body's natural defenses so that those defenses can help fight inflammation. Azathioprine, mercaptopurine, methotrexate, and levamisole are the most frequently prescribed immunomodulators. The BCG vaccine, a vaccine for tuberculosis, has been shown to be an effective treatment for Crohn's. A combination of these drugs, rather than a single drug, may work better for some people.

There are many side effects to immunomodulator treatment, such as nausea and vomiting. In the short term these medications may be associated with inflammation of internal organs such as the liver or pancreas and may affect the functioning of bone marrow. Side effects of long-term treatment, though rare, include an increased risk of significant infection and cancers such as lymphoma and skin cancer.

- **Tumor necrosis factor (TNF) inhibitors**—These drugs work by neutralizing an immune system protein known as tumor necrosis factor (TNF). They are prescribed to both adults and children who have moderate to severe symptoms of Crohn's disease to help reduce signs and symptoms. Examples of TNF inhibitors include infliximab (Remicade), adalimumab (Humira), and certolizumab pegol (Cimzia). TNF inhibitors may be prescribed soon after diagnosis, especially if there is a family history of serious complications from Crohn's disease or if a fistula is present. TNF inhibitors may be combined with other medications or be used when other medications have been ineffective. In some cases, TNF inhibitor therapy may lead to remission. Side effects of TNF inhibitors include an increased risk of developing serious infections and some cancers such as lymphoma and skin cancers.

Other medications that may be prescribed to treat Crohn's disease include the following:

- **Methotrexate (Rheumatrex)**—This drug, often used to treat cancer, psoriasis, and rheumatoid arthritis, may be prescribed to people with Crohn's disease for whom other medications have been ineffective. Short-term side effects include fatigue, nausea, diarrhea, and rarely, potentially life-threatening pneumonia. Long-term use may lead to bone marrow suppression, scarring of the liver, or cancer.
- **Cyclosporine (Gengraf, Neoral, Sandimmune) and tacrolimus (Astagraf XL, Hecoria)**—These are extremely powerful medications generally prescribed to patients

QUESTIONS TO ASK YOUR DOCTOR

- Is there another disease that could be causing my symptoms?
- What happens if I stop taking my medications?
- What over-the-counter drugs can I take?
- What type of diet should I eat?
- May I crush my medication to take it orally?
- What other lifestyle changes should I make?

with Crohn's-related fistulas and those for whom other medications have been ineffective. Not suitable for long-term use, cyclosporine may cause serious side effects including organ damage (specifically kidney and liver damage), seizures, and fatal infections.

- **Vedolizumab (Entyvio) and natalizumab (Tysabri)**—These drugs work by stopping immune cells called integrins from binding to other cells in the intestinal lining. They are used to fight inflammation in patients for whom other medications have been ineffective. Natalizumab is only approved for experimental treatment because it has been associated with a serious side effect, leukoencephalopathy, a progressive brain disease that may lead to permanent disability or death. Vedolizumab works similarly to natalizumab but appears not to have the same risks.
- **Ustekinumab (Stelara)**—Used to treat psoriasis, this drug has been found to reduce symptoms of Crohn's disease. It may be prescribed when other medical treatments fail.
- **Antibiotics**—Antibiotics are used to treat infection, inflammation, and fistulas associated with Crohn's disease. Some researchers suspect antibiotics help reduce harmful intestinal bacteria that may play a role in overstimulating the intestinal immune system and may lead to inflammation. Antibiotics may be prescribed in addition to other medications when infection is a concern.
- **Over-the-counter medications**—In addition to controlling inflammation, some medications may help relieve signs and symptoms of Crohn's disease. Always talk to a doctor before taking any over-the-counter medications; however, depending on the severity of Crohn's disease, the doctor may recommend one or more of the following:
- **Antidiarrheals** like psyllium powder (Metamucil), methylcellulose (Citrucel), or loperamide (Imodium)

- Pain relievers such as acetaminophen (Tylenol, others). Other common pain relievers such as ibuprofen (Advil, Motrin IB, others) and naproxen sodium (Aleve, Anaprox) are not recommended because they are likely to make symptoms worse and can make the disease worse as well
- Iron supplements to help alleviate decreased iron caused by intestinal bleeding
- Supplements such as vitamin B, calcium, and vitamin D to help decrease the increased risk of osteoporosis that people with Crohn's disease may face

Other treatment options that may decrease the symptoms of Crohn's disease include the following:

- Nutrition therapy—A special diet including enteral nutrition (tube feeding with a highly nutritious liquid diet) or parenteral nutrition (nutrients injected directly into a vein). Either of these options may give the bowel time to rest and heal, which may reduce inflammation in the short term. These therapies may also be used with immune system suppressors. Enteral and parenteral nutrition are typically used to help people become more stable and healthier before surgery, or when symptoms do not respond to other medications. A low-residue or low-fiber diet designed to reduce the size and number of stools may be prescribed to reduce the risk of intestinal blockage.
- Surgery—If other treatment options are not effective, surgery may be required to help decrease or eliminate symptoms of Crohn's disease. Up to half of all individuals with Crohn's disease will require at least one surgery. During surgery, the damaged portion of intestine is removed and the intestine is reconnected to healthy sections. Strictureplasty, which widens a too-narrow segment of the intestine, is common for patients with Crohn's disease. The benefits of surgery for Crohn's disease are usually temporary, and surgery is not a cure for Crohn's disease. The disease often recurs frequently near the reconnected tissue. Surgery is generally followed by drug therapy to reduce the risk of recurrence.

Prognosis

Most individuals with Crohn's disease will have a normal life expectancy. Rarely, complications from the disease may lead to early death. There is no cure for Crohn's disease; however, the symptoms may be managed through medication, diet modification, and sometimes surgery. A characteristic of the disease is symptom flare-ups. The symptoms may disappear for periods of time only to recur.

Individuals with Crohn's may be at a greater risk of developing colon cancer, and doctors often recommend colon cancer screening on a regular basis.

Other conditions that may occur more frequently in individuals with Crohn's disease include the following:

- anemia
- fistulas in the bladder, skin, or vagina
- intestinal infection
- intestinal blockage
- delayed growth and development in children
- difficulty maintaining healthy body weight
- joint swelling and pain
- nutritional deficiencies

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American Autoimmune Related Diseases Association, 22100 Gratiot Ave., Eastpointe, MI 48021, (586) 776-3900, (586) 776-3903, <http://www.aarda.org>
 Crohn's & Colitis Foundation of America, 733 Third Ave., Suite 510, New York, NY 10017, (800) 932-2423, info@ccfa.org, <http://www.ccfa.org>

Deborah L. Nurmi, MS

Crouzon craniofacial dysostosis see **Crouzon syndrome**

Crouzon syndrome

Definition

Crouzon syndrome is a genetic condition that causes early closure of the bones in the skull. This event is called craniosynostosis and causes the skull to form abnormally.

Because of the craniosynostosis, individuals affected with Crouzon syndrome have characteristic facial features.

Description

Features of Crouzon syndrome include wide-set prominent eyes. Individuals with this syndrome may also have a condition called strabismus, which means that the eyes have difficulty focusing on objects. Other facial features may include an underdeveloped upper jaw, which causes tooth abnormalities. Individuals with Crouzon syndrome often have a beak-shaped nose and hearing loss. A skin condition called acanthosis nigricans occurs in approximately 5% of individuals with Crouzon syndrome. It is important to note that there is a wide range of severity in Crouzon syndrome. No two individuals with the condition will necessarily have all of the listed features.

Affected individuals often undergo several corrective surgeries, increasing the need for continual medical care throughout their lives. This can be very stressful and difficult for patients and their families. Additionally, since people with Crouzon syndrome have significant facial differences, it may be difficult for them (and their parents) to feel accepted by society. There may be psychological implications, ranging from feeling bad for “looking different” to parents who have trouble bonding with their child. The psychological impact may be less if there are others in the family with Crouzon syndrome. Having more than one family member with this syndrome may help those affected to feel less isolated and provide them with a stronger support system.

Genetic profile

Crouzon syndrome is caused by mutations in the *FGFR2* gene (on the long arm q of chromosome 10 at 10q25.3-q26) and the *FGFR3* gene (on the short arm p of chromosome 4 at 4p16.3). At least 40 different mutations in the *FGFR2* gene are known to cause Crouzon syndrome, which is inherited in an autosomal dominant manner. Affected individuals have one copy of a gene with the *FGFR* mutation as well as a normal copy of the *FGFR* gene, and thus have a 50% chance of passing the mutation on to each of their children, regardless of those children’s sex. About 75% of affected people have a family history of Crouzon syndrome—typically a parent with the condition. In the remaining 25% of people with Crouzon syndrome, the genetic mutation is new (*de novo*) in the affected individual and there is no family history of the disorder. One factor in the risk for these new mutations is advancing paternal age. However, with no family history of the condition, there is

KEY TERMS

Acanthosis nigricans—A skin condition characterized by darkly pigmented areas of velvety, wart-like growths. Acanthosis nigricans usually affects the skin of the armpits, neck, and groin.

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman’s abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a nonsex chromosome is necessary for a disease or inherited trait to develop in an individual.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted through either the mother’s vagina or abdominal wall, and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic disorders.

Coronal suture—The skull suture that lies behind the forehead area, across the head from the left side to the right side.

Craniosynostosis—Premature, delayed, or otherwise abnormal closure of the sutures of the skull.

FGFR2* and *FGFR3—The genes encoding fibroblast growth factor receptors 2 and 3; mutations in these genes can cause Crouzon syndrome.

Fibroblasts—Connective tissue cells.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as a disease, and that can be transmitted to offspring.

Otolaryngologist—A physician who specializes in the care of the ear, nose, and throat and their associated structures.

Strabismus—An improper muscle balance of the ocular muscles affecting binocular vision.

Suture—In anatomy, fibrous joints that hold the bones of the skull together.

no increased risk for Crouzon syndrome in the affected child’s siblings.

FGFR2 and *FGFR3* are responsible for the proper differentiation, growth, and movement of cells in the

body called fibroblasts. Fibroblasts are part of the bony structures of the body, including the skull, so problems with fibroblast growth and movement lead to skull/bone problems. About 95% of patients have an *FGFR2* mutation, and 5% have an *FGFR3* mutation. Almost all affected individuals who also have acanthosis nigricans appear to share a common *FGFR3* mutation.

Demographics

Crouzon syndrome occurs in about 1 per 25,000 live births. It affects all ethnic groups equally.

Signs and symptoms

The most common characteristic of Crouzon syndrome is bilateral (two-sided) coronal craniosynostosis. A cloverleaf skull may be present if the sagittal (long suture from the front to back of the head) and/or lambdoidal (short suture at the very back of the head) sutures are involved. This causes the skull shape to be taller than usual, often described as “tower-shaped.” The pattern looks like a cloverleaf because the skull is taller, and the sides of the skull and face bulge slightly from right to left. The eye orbits are always very shallow, causing the eyes to protrude significantly. Strabismus may be present, and eyes may be wide-set, making vision poor. Some individuals also have unexplained difficulties with vision. The nose can be narrow and beak-shaped, forcing people to breathe through their mouths.

The upper jaw may not be properly formed and can cause dentition problems, most commonly a missing tooth. The palate (upper ridge of the mouth) may be high and narrow, causing crowding of the existing teeth. Occasionally, clefting (improper closure) of the lip and palate occur. Mild to moderate conductive hearing loss (due to abnormal ear structure formation) occurs in some cases.

Intellectual development is typically within the normal range. Only rare cases of significant mental deficiency have been reported. Hydrocephalus, which is an accumulation of fluid in the brain and skull, occurs in about 30% of patients and may progress or worsen with time. It typically shows up as a general enlargement of the skull. Sometimes the fluid can put increased pressure on various structures in the brain, limiting their growth and development. Hydrocephalus may explain the few reported cases of Crouzon syndrome with learning problems. Occasionally, seizures occur with Crouzon syndrome.

Individuals with Crouzon syndrome may be shorter than normal height. This characteristic seems to affect females more than males.

Diagnosis

Historically, Crouzon syndrome has been diagnosed after careful physical examination and further studies. A diagnosis of Crouzon syndrome can be made by observing several of the following features. The abnormally shaped head is typically seen in newborns; sometimes it can be observed prenatally in an ultrasound examination. X-rays or physical examination of the skull can diagnose craniosynostosis. Once craniosynostosis is seen, it is important to determine whether it has occurred because of the abnormal formation of the cranial suture, possibly caused by an *FGFR* mutation. This is known as primary craniosynostosis and suggests Crouzon syndrome as a possibility. Craniosynostosis may also be caused by abnormal forces (secondary craniosynostosis) such as decreased brain growth or abnormal fetal head positioning. This can occur in the prenatal period, and in these cases, the abnormal head shape may correct itself with time. The next step in diagnosis is to determine the type of craniosynostosis. A cloverleaf skull makes Crouzon syndrome a possibility, but it is seen more commonly in other genetic craniosynostosis syndromes.

Some babies with Crouzon syndrome have breathing problems as newborns due to narrowed nasal passages. Protruding eyes are a hallmark feature for the condition and can be observed almost immediately after birth. The lack of abnormalities in the extremities (hands and feet) is also considered part of the diagnosis of Crouzon syndrome rather than another type of craniosynostosis.

Molecular (DNA-based) genetic testing is available for Crouzon and other *FGFR*-related syndromes. These tests are specific for Crouzon, distinguishing it from other craniosynostosis syndromes. A blood or other type of sample (such as fetal cells from amniotic fluid) from the affected individual is analyzed for *FGFR2* and *FGFR3* gene mutations. A negative result may indicate that the individual has a different condition or a previously unidentified mutation in an *FGFR* gene. Once a specific mutation is found in a family, other family members can be tested. Patients with features of Crouzon syndrome and acanthosis nigricans can be tested for the common *FGFR3* mutation.

Prenatal testing is available for both *FGFR2* and *FGFR3* mutations from samples obtained via amniocentesis or chorionic villus sampling (CVS). This is only offered when a parent has a *known* mutation. However, identifying a mutation by prenatal testing does not define the extent of the symptoms. The severity of Crouzon syndrome can only be determined after birth. A prenatal ultrasound can sometimes make a possible diagnosis of a syndrome involving craniosynostosis, but it is not as accurate as direct DNA testing. A cloverleaf skull seen on a prenatal ultrasound usually

QUESTIONS TO ASK YOUR DOCTOR

- How is Crouzon syndrome diagnosed in an infant?
- What types of treatment are available for my child with Crouzon syndrome?
- Are there side effects to these treatments?
- What are the short- and long-term prognoses for a child born with Crouzon syndrome?
- Should family members have genetic testing?

implies a more severe outcome for the baby than with other types of craniosynostosis.

Treatment and management

Treatment of Crouzon syndrome often involves the coordinated efforts of several medical specialists in a team setting. The specialists may include a pediatrician, plastic surgeon, neurosurgeon, geneticist, genetic counselor, dentist, social worker, audiologist, speech pathologist, psychologist, and otolaryngologist.

Craniosynostosis is typically repaired through a series of operations. There is a major surgery performed as early as the first three months of life, followed by several others that may extend over the lifespan. Each series of operations is tailored to the individual, but it is rare for the corrections to be perfect. Because the skull is continually growing in the early part of life, timing of these surgeries is critical for proper brain formation and better results. Surgeries after the skull has stopped growing rarely yield good results. Surgeries performed before various portions of the facial region have stopped growing also have a poor prognosis and will require additional follow-up procedures.

For individuals with hydrocephalus, sometimes a shunt, or tube, needs to be placed to allow the fluid to drain from the affected area(s) of the brain.

For babies with respiratory distress, oxygen and ventilation may be provided. Occasionally, a tracheostomy (opening in the windpipe) is created to help the baby breathe.

Because their eyes protrude so significantly, people with Crouzon syndrome sometimes have trouble closing their eyes. Surgical eye closure may be necessary; this allows the eye and its various structures (such as the cornea) to remain protected.

Occasionally, surgeries to correct structural ear abnormalities (resulting in hearing loss) are necessary.

Prognosis

The most problematic complication in Crouzon syndrome is the craniosynostosis. Prognosis primarily depends upon the severity and extent of this skull abnormality. Consequently, the success of corrective surgeries often determines prognosis.

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ORGANIZATIONS

- Children's Craniofacial Association, 13140 Coit Rd., Suite 517, Dallas, TX 75240 (214) 570-9099, (800) 535-3643, (214) 570-8811, contactCCA@ccakids.com, <http://www.cakids.com>

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Crouzonodermoskeletal syndrome

Definition

Crouzonodermoskeletal syndrome is a genetic disorder that is similar to Crouzon syndrome but with a skin condition called acanthosis nigricans. It is sometimes referred to as Crouzon syndrome with acanthosis

nigricans. A primary symptom of both Crouzonodermoskeletal and Crouzon syndromes is the premature fusion of the bones in the skull during development. Crouzonodermoskeletal syndrome results from a mutation in only one of the *FGFR* genes that are involved in Crouzon syndrome.

Description

Crouzonodermoskeletal syndrome is a genetic disorder that results from a mutation in a gene that carries the instructions for making fibroblast growth factor receptor 3 (*FGFR3*), a protein that participates in the development of cells, particularly those in bones and in the brain. Individuals need only inherit the altered gene from one parent to develop this disorder. More often than not, however, the genetic mutation arises spontaneously, so affected individuals have no family history of the disorder.

Premature fusion of certain skull bones (craniosynostosis) during development causes the skull to have an abnormal, noticeably asymmetric shape. Acanthosis nigricans is a skin condition distinguished by velvety, dark patches that may appear on the neck, under the arms, at finger joints, in the groin, or in other places where the skin is folded or creased. The color of the patches may vary from light brown to purplish brown to black.

Genetic profile

Located on chromosome 4, the *FGFR3* gene carries the blueprint for making fibroblast growth factor receptor 3, one of several fibroblast growth factor receptors in the body. These receptors bind with fibroblast growth factors, which are proteins that are important for functions such as the creation of new blood vessels (angiogenesis), wound healing, and growth of embryos. *FGFR3* participates in the development and maintenance of bone and brain tissue. In particular, it is believed to control the transformation of cartilage to bone during growth. Cartilage makes up much of the skeletons of embryos and infants, and gradually changes to bone with growth and development. Although the exact mechanism is unknown, mutations in the *FGFR3* gene cause the bones in the skull to fuse prematurely. Normally, the bones in a baby's skull fuse slowly over about the first two years of life, after which the baby's head has assumed its adult shape. In Crouzonodermoskeletal syndrome, the bones join together earlier than they should, resulting in the characteristic head and facial features of this disorder.

The *FGFR3* mutations that cause this disorder result in the substitution of single amino acids, the building blocks of proteins, in the *FGFR3* protein. In particular, the amino acid alanine is replaced with the amino acid glutamate. There are other *FGFR3* mutations that are

KEY TERMS

Acanthosis nigricans—A skin condition distinguished by velvety, dark patches where the skin is folded or creased.

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a nonsex chromosome is required for a disease or inherited trait to develop in an individual.

Cartilage—A tough elastic tissue that is a building block for bone.

Cementoma—A type of noncancerous tumor that contains a bony substance known as cementum.

Craniosynostosis—Premature, delayed, or otherwise abnormal closure of the sutures of the skull.

Crouzon syndrome—A genetic disorder that is similar to Crouzonodermoskeletal syndrome but without acanthosis nigricans.

Divergent strabismus—Eyes that point in different directions due to imbalanced eye muscles.

Fibroblast growth factors—Proteins that are important in such functions as the growth of new blood vessels (angiogenesis), wound healing, and embryonic growth.

Sleep apnea—A potentially life-threatening condition in which the individual has episodes during sleep in which breathing temporarily stops.

associated with other bone-growth disorders, including the following:

- achondroplasia
- hypochondroplasia
- Muenke syndrome
- thanatophoric dysplasia

Crouzonodermoskeletal syndrome is an autosomal dominant disorder, which means that an individual need have only one mutated *FGFR3* gene to develop the condition. The mutation may be inherited from a parent who has signs and symptoms of Crouzonodermoskeletal syndrome. Each of this parent's children has a 50% chance of inheriting the mutated gene. If both parents have the mutation, each of their children has a 75% chance of inheriting it. As noted, however, most cases of Crouzonodermoskeletal syndrome arise from spontaneous mutations, so the patient has no family history of the disorder. It is unknown why these spontaneous mutations occur.

QUESTIONS TO ASK YOUR DOCTOR

- Should my child have genetic testing for a mutation that causes Crouzonodermoskeletal syndrome?
- What are the risks of cranial surgery, and what surgical options are available?
- What improvements should be expected from cranial surgery?
- What is involved in the surgery to correct protruding eyes, and is there a possibility that my child's vision will be affected?
- Will lower jaw surgery affect speech?

Demographics

Crouzonodermoskeletal syndrome is an extremely rare genetic disorder that affects an estimated one in a million people. The incidence does not vary with sex, ethnicity, or geographic area.

Signs and symptoms

The appearance of various symptoms and their severity differ from one individual to the next. Crouzonodermoskeletal syndrome typically does not affect intelligence. Common symptoms include the following:

- premature joining of skull bones
- shallow eye sockets with eyes that are far apart and often protruding, sometimes in a very pronounced manner
- eyes that point in different directions (divergent strabismus)
- a small nose and upper jaw and comparatively large lower jaw
- flattened nasal passages, often externally evident as a so-called beaked nose
- sleep apnea (momentary halts in breathing during sleep)
- flattened temples
- acanthosis nigricans
- noncancerous tumors (cementomas) in the jaw that develop during young adulthood

Diagnosis

Crouzonodermoskeletal syndrome is sometimes evident in an ultrasound performed during pregnancy, but this is not always the case. Often, the skull abnormalities are only noted at or shortly after birth.

Examination

After obtaining a family history of the patient, including potential inherited disorders, the doctor will typically perform a neurological examination to determine the extent of movement problems.

Tests

Genetic tests are available for *FGFR3* gene mutations.

Procedures

The doctor may order magnetic resonance imaging (MRI). While MRI cannot positively diagnose Crouzonodermoskeletal syndrome, it can help the doctor eliminate other disorders as possibilities.

Treatment and management

The premature fusion of skull bones can result in too little room for the brain to grow, so corrective cranial surgery early in life may be necessary. This surgery is generally successful, although some skull malformation may remain. Additional surgery is sometimes employed to reduce the oversized lower jaw and to at least partially correct protruding eyes, although the severity of the eye bulge sometimes fades as the child grows. Depending on the specific malformations, other surgeries may be recommended.

Crouzonodermoskeletal syndrome is a genetic disorder that cannot be prevented. Adults who have the disorder may want to undergo genetic counseling before deciding to have children so that they understand both the risks of passing on the disorder and/or the availability of preimplantation diagnosis via assisted reproduction technologies to ensure that an implanted embryo does not carry the mutation.

Prognosis

Infants are born with symptoms of Crouzonodermoskeletal syndrome. With early surgery to provide for proper brain development, individuals with this disorder do very well and live long and productive lives.

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ORGANIZATIONS

Children's Craniofacial Association, 13140 Coit Rd., Suite 517, Dallas, TX 75240, (214) 570-9099, (800) 535-3643, (214) 570-8811, contactCCA@ccakids.com, <http://www.ccakids.com>

FACES: The National Craniofacial Association, PO Box 11082, Chattanooga, TN 37401, (800) 332-2373, faces@faces-cranio.org, <http://www.faces-cranio.org/index.htm>

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Cryptophthalmos syndactyly syndrome see
Fraser syndrome

Cutis-gyrata syndrome of Beare and Stevenson see
Beare-Stevenson cutis gyrata syndrome

Cystathionine beta-synthetase see
Homocystinuria

Cystic fibrosis

Definition

Cystic fibrosis (CF) is an inherited disease that affects the lungs, digestive system, sweat glands, and fertility. Its name derives from the fibrous scar tissue that develops in the pancreas, one of the principal organs affected by the disease.

Description

Cystic fibrosis affects the body's ability to move salt and water in and out of cells. This defect causes the lungs and pancreas to secrete thick mucus, blocking passageways and preventing proper function.

Genetic profile

Cystic fibrosis is caused by a pathogenic variant (mutation) in the *CFTR* gene. Genes, found in the nucleus of all of the body's cells, contain the instructions for the production of proteins. Proteins carry out a wide variety of functions within cells. *CFTR* stands for cystic fibrosis transmembrane conductance regulator. A simple change in this gene leads to all of the consequences of CF. There are over 500 known variants in the *CFTR* gene that can cause CF. However, 70% of all people with CF have the same variant, known as delta-F508.

Genes can be thought of as long strings of chemical words, each made of chemical letters, called nucleotides. Just as a sentence can be changed by rearranging its letters, the sequence of nucleotide letters of genes can be changed. If the change causes problems, then it is called a pathogenic variant (mutation). The gene variants in CF are called point mutations, meaning that the gene is changed only at one small spot along its length. The delta-F508 mutation results from the loss of one "letter" out of thousands within the *CFTR* gene. As a result, the *CFTR* protein made from its blueprint is made incorrectly and cannot perform its function properly.

The role of the *CFTR* protein is to allow chloride ions to exit the mucus-producing cells. When the chloride ions leave these cells, water follows, thinning the mucus. Mucus is a complex mixture of salts, water, sugars, and proteins that cleanses, lubricates, and protects many passageways in the body, including those in the lungs and pancreas. The *CFTR* protein helps to keep mucus from becoming thick and sluggish, thus allowing it to be moved steadily along the passageways to aid in cleansing.

In CF, the *CFTR* protein does not allow enough chloride ions out of the mucus-producing cells. With less chloride leaving, less water leaves, and the mucus becomes thick and sticky. It can no longer move freely through the passageways, so they become clogged. In the pancreas, clogged passageways prevent secretion of digestive enzymes into the intestine, causing serious impairment of digestion—especially of fat—which may lead to malnutrition. Mucus in the lungs may plug the airways, preventing good air exchange and, ultimately, leading to emphysema. The mucus is also a rich source of nutrients for bacteria, leading to frequent infections.

To understand the inheritance pattern of CF, it is important to realize that genes actually have two functions. First, as noted above, they serve as the blueprint for the production of proteins. Second, they are the material of inheritance: parents pass on characteristics to their

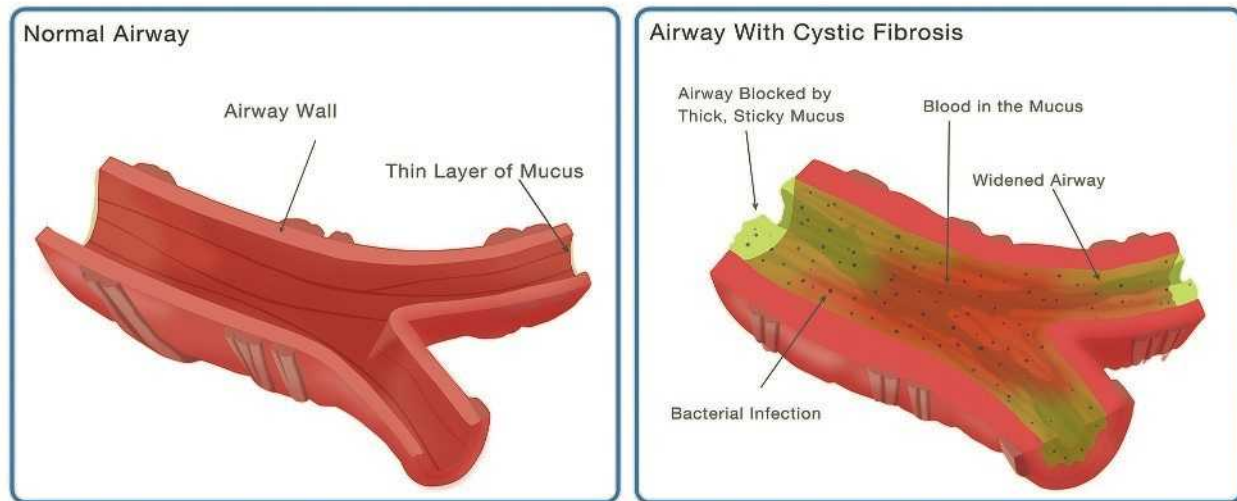


Illustration comparing a normal airway and one blocked because of cystic fibrosis. (Monica Schroeder/Science Source)

children by combining the genes in egg and sperm to make a new individual.

Each person has two copies of each gene, including the *CFTR* gene, in each of his or her body cells. During sperm and egg production, however, these two copies separate, so that each sperm or egg contains only one copy of each gene. When sperm and egg unite, the newly created cell once again has two copies of each gene.

The two gene copies may be the same or they may be different. For the *CFTR* gene, for instance, a person may have two normal copies, one copy with a variant and one normal copy or two copies with a variant. A person who has pathogenic variants in both copies of the *CFTR* gene will develop cystic fibrosis. A person with one variant is said to be a carrier. Most carriers of CF do not have symptoms, although research suggests that carriers may have a higher risk of CF related problems. Carriers but can pass on the *CFTR* gene variant to his or her children.

When two carriers have children, they have a one in four (25%) chance of having a child with CF each time they conceive. They have a two in four chance of having a child who is a carrier (50%), and a one in four (25%) chance of having a child with two normal *CFTR* genes.

Demographics

CF affects approximately 35,000 children and young adults in the United States, and about 3,500 babies are born with CF every year. CF primarily affects people of Northern European descent; rates are much lower in non-Caucasian populations.

Approximately 1 in every 25 Americans of Northern European descent is a CF carrier, while only 1 in 17,000 African-Americans and 1 in 30,000 Asian-Americans

are carriers. Since carriers may be symptom-free, many people are unaware that they are carriers, unless they have a family history of the disease. Two Caucasian Americans with no family history of CF have a 1 in 2,500 chance of having a child with CF.

It may seem puzzling that gene variant with such harmful consequences would remain so common. You might think that the high mortality of CF would quickly lead to loss of the abnormal gene variants from the population. Some researchers believe that CF gene variants persist in the population because they protect carriers from cholera. Cholera is a microorganism that infects the intestine, causing intense diarrhea and eventual death by dehydration. This so-called heterozygote advantage can be seen in other genetic disorders.

Signs and symptoms

The most severe effects of cystic fibrosis are seen in two body systems: the gastrointestinal (digestive) system and the respiratory tract from the nose to the lungs. CF also affects the sweat glands and male fertility. Symptoms develop gradually, with gastrointestinal symptoms often the first to appear.

Gastrointestinal system

Ten to fifteen percent of babies who inherit CF have meconium ileus at birth. Meconium is the first dark stool that a baby passes after birth; ileus is an obstruction of the digestive tract. The meconium of a newborn with meconium ileus is thickened and sticky, due to the presence of thickened mucus from the intestinal glands. Meconium ileus causes abdominal swelling and vomiting, and often requires surgery immediately after birth.

Presence of meconium ileus is considered highly indicative of CF. Borderline cases may be misdiagnosed, however, and attributed instead to a milk allergy.

Other abdominal symptoms are caused by the inability of the pancreas to supply digestive enzymes to the intestine. During normal digestion, as food passes from the stomach into the small intestine, it is mixed with pancreatic secretions, which help to break down the nutrients for absorption. While the intestines themselves also provide some digestive enzymes, the pancreas is the major source of enzymes for the digestion of all types of foods, especially fats and proteins.

In CF, thick mucus blocks the pancreatic duct, which is eventually closed off completely by scar tissue formation, leading to a condition known as pancreatic insufficiency. Without pancreatic enzymes, large amounts of undigested food pass into the large intestine. Bacterial action on this rich food source can cause gas and abdominal swelling. The large amount of fat remaining in the feces makes it bulky, oily, and foul-smelling.

Because nutrients are only poorly digested and absorbed, the person with CF is often ravenously hungry, underweight, and shorter than expected for his age. When CF is not treated for a longer period, a child may develop symptoms of malnutrition, including anemia, bloating, and paradoxically, appetite loss.

Diabetes becomes increasingly likely as a person with CF ages. Scarring of the pancreas slowly destroys those pancreatic cells that produce insulin, producing type I, or insulin-dependent, diabetes.

Gallstones affect approximately 10% of adults with CF. Liver problems are less common, but can be caused by the buildup of fat within the liver. Complications of liver enlargement may include internal hemorrhaging, abdominal fluid (ascites), spleen enlargement, and liver failure.

Other gastrointestinal symptoms can include a prolapsed rectum, in which part of the rectal lining protrudes through the anus; intestinal obstruction; and rarely, intussusception, in which part of the intestinal tube slips over an adjoining part, cutting off blood supply.

Somewhat fewer than 10% of people with CF do not have gastrointestinal symptoms. Most of these people do not have the delta-F508 mutation, but rather a different one, which presumably allows at least some of their *CFTR* proteins to function normally in the pancreas.

Respiratory tract

The respiratory tract includes the nose, the throat, the trachea (or windpipe), the bronchi (which branch off from the trachea within each lung), the smaller bronchioles, and

the blind sacs called alveoli, in which gas exchange takes place between air and blood.

Swelling of the sinuses within the nose is common in people with CF. This usually shows up on x-rays, and may aid the diagnosis of CF. However, this swelling, called pansinusitis, rarely causes problems, and does not usually require treatment.

Nasal polyps, or growths, affect about one in five people with CF. These growths are not cancerous, and do not require removal unless they become annoying. While nasal polyps appear in older people without CF, especially those with allergies, they are rare in children without CF.

The lungs are the site of the most life-threatening effects of CF. The production of a thick, sticky mucus increases the likelihood of infection, decreases the ability to protect against infection, causes inflammation and swelling, decreases the functional capacity of the lungs, and may lead to emphysema. People with CF will live with chronic populations of bacteria in their lungs, and lung infection is the major cause of death for those with CF.

The bronchioles and bronchi normally produce a thin, clear mucus, which traps foreign particles including bacteria and viruses. Tiny hair-like projections called cilia on the surface of these passageways slowly sweep the mucus along, out of the lungs and up the trachea to the back of the throat, where it may be swallowed or coughed up. This “mucociliary escalator” is one of the principal defenses against lung infection.

The thickened mucus of CF prevents easy movement out of the lungs, and increases the irritation and inflammation of lung tissue. This inflammation swells the passageways, partially closing them down, further hampering the movement of mucus. A person with CF is likely to cough more frequently and more vigorously as the lungs attempt to clean themselves out.

At the same time, infection becomes more likely since the mucus is a rich source of nutrients. Bronchitis, bronchiolitis, and pneumonia are frequent in CF. The most common infecting organisms are the bacteria *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*. A small percentage of people with CF have infections caused by *Burkholderia cepacia*, a bacterium which is resistant to most current antibiotics (*Burkholderia cepacia* was formerly known as *Pseudomonas cepacia*). The fungus *Aspergillus fumigatus* may infect older children and adults.

The body's response to infection is to increase mucus production; white blood cells fighting the infection thicken the mucus even further as they break down

and release their cell contents. These white blood cells also provoke more inflammation, continuing the downward spiral that marks untreated CF.

As mucus accumulates, it can plug the smaller passageways in the lungs, decreasing functional lung volume. Getting enough air can become difficult; tiredness, shortness of breath, and intolerance of exercise become more common. Because air passes obstructions more easily during inhalation than during exhalation, over time, air becomes trapped in the smallest chambers of the lungs, the alveoli. As millions of alveoli gradually expand, the chest takes on the enlarged, barrel-shaped appearance typical of emphysema.

For unknown reasons, recurrent respiratory infections lead to digital clubbing, in which the last joint of the fingers and toes becomes slightly enlarged.

Sweat glands

The *CFTR* protein helps to regulate the amount of salt in sweat. People with CF have sweat that is much saltier than normal, and measuring the saltiness of a person's sweat is the most important diagnostic test for CF. Parents may notice that their infants taste salty when they kiss them. Excessive salt loss is not usually a problem except during prolonged exercise or heat. While most older children and adults with CF compensate for this extra salt loss by eating more salty foods, infants and young children are in danger of suffering its effects (such as heat prostration), especially during summer. Heat prostration is marked by lethargy, weakness, and loss of appetite, and should be treated as an emergency condition.

Fertility

Ninety-eight percent of men with CF are sterile, due to complete obstruction or absence of the vas deferens, the tube carrying sperm out of the testes. While boys and men with CF form normal sperm and have normal levels of sex hormones, sperm are unable to leave the testes, and fertilization is not possible. Most women with CF are fertile, though they often have more trouble getting pregnant than women without CF. In both boys and girls, puberty is often delayed, most likely due to the effects of poor nutrition or chronic lung infection. Women with good lung health usually have no problems with pregnancy, while those with ongoing lung infection often do poorly.

Diagnosis

The decision to test a child for cystic fibrosis may be triggered by concerns about recurring gastrointestinal or respiratory symptoms, or salty sweat. A child born with meconium ileus will be tested before leaving the hospital.

Families with a history of CF may wish to have all children tested, especially if there is a child who already has the disease. Some hospitals now require routine screening of newborns for CF.

Sweat test

The sweat test is both the easiest and most accurate test for CF. In this test, a small amount of the drug pilocarpine is placed on the skin. A very small electrical current is then applied to the area, which drives the pilocarpine into the skin. The drug stimulates sweating in the treated area. The sweat is absorbed onto a piece of filter paper, and is then analyzed for its salt content. A person with CF will have salt concentrations that are one-and-one-half to two times greater than normal. The test can be done on persons of any age, including newborns, and its results can be determined within an hour. Virtually every person who has CF will test positive on it, and virtually everyone who does not will test negative.

Collecting enough sweat for the sweat test from infants can be challenging. Currently, a bulky device that fits around the wrist must be worn for 30 minutes. This device can be uncomfortable for the baby and may not be able to collect enough sweat. Researchers from Northwestern University have developed a sticker placed on the skin that measures salt content. This sticker can provide a diagnosis of cystic fibrosis in minutes by changing color. It is more comfortable to wear and collects 33% more sweat than current devices. The sticker also has color sensors, which allows health providers to measure chloride concentration through a smartphone picture.

Genetic testing

The discovery of the *CFTR* gene in 1989 allowed the development of an accurate genetic test for CF. Genes from a small blood or tissue sample are analyzed for specific variants. The presence of a variant in both copies of the *CFTR* gene confirms the diagnosis of CF. In some rare cases of CF, a variant is not detected. This could be because the test done did not look for all variants or the variant in this person has not yet been discovered.

Couples planning a family may decide to have themselves tested. Testing is recommended if they are Caucasian and of European ancestry, or if one or both have a family history of CF. Prenatal genetic testing is possible through amniocentesis. Many couples who already have one child with CF decide to undergo prenatal screening in subsequent pregnancies. Siblings in these families are also usually tested, both to determine if they will develop CF, and to determine if they are carriers, to aid in their

KEY TERMS

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

CFTR—Cystic fibrosis transmembrane conductance regulator. The protein responsible for regulating chloride movement across cells in some tissues. When a person has two defective copies of the *CFTR* gene, cystic fibrosis is the result.

Emphysema—A chronic lung disease that begins with breathlessness during exertion and progresses to shortness of breath at all times, caused by destructive changes in the lungs.

Mucociliary escalator—The coordinated action of tiny projections on the surfaces of cells lining the respiratory tract, which moves mucus up and out of the lungs.

Mucolytic—An agent that dissolves or destroys mucin, the chief component of mucus.

Pancreatic insufficiency—Reduction or absence of pancreatic secretions into the digestive system due to scarring and blockage of the pancreatic duct.

own family planning. If the sibling has no symptoms, determining his or her carrier status is often delayed until the teen years or later, when he or she is closer to needing the information to make decisions.

Newborn screening

Some states now require screening of newborns for CF, using a test known as the IRT test. This is a blood test which measures the level of immunoreactive trypsinogen, which is generally higher in babies with CF than those without it. This test gives many false positive results immediately after birth, and so requires a second test several weeks later. A second positive result is usually followed by a sweat test.

Treatment and management

There is no cure for cystic fibrosis. Treatment has advanced considerably in the past several decades, increasing both the lifespan and the quality of life for most people affected by CF. Early diagnosis is important to prevent malnutrition and infection from weakening the young child. With proper management, many people with CF engage in the full range of school and sports activities.

Nutrition

People with CF usually require high-calorie diets and vitamin supplements. Height, weight, and growth of a person with CF are monitored regularly. Most people with CF need to take pancreatic enzymes to supplement or replace the inadequate secretions of the pancreas. Tablets containing pancreatic enzymes are taken with every meal; depending on the size of the tablet and the meal, as many as 20 tablets may be needed. Because of incomplete absorption even with pancreatic enzymes, a person with CF needs to take in about 30% more food than a person without CF. Low-fat diets are *not* recommended except in special circumstances, since fat is a source of both essential fatty acids and abundant calories.

Some people with CF cannot absorb enough nutrients from the foods they eat, even with specialized diets and enzymes. For these people, tube feeding is an option. Nutrients can be introduced directly into the stomach through a tube inserted either through the nose (a nasogastric tube) or through the abdominal wall (a gastrostomy tube). A jejunostomy tube, inserted into the small intestine, is also an option. Tube feeding can provide nutrition at any time, including at night while the person is sleeping, allowing constant intake of high-quality nutrients. The feeding tube may be removed during the day, allowing normal meals to be taken.

Respiratory health

The key to maintaining respiratory health in a person with CF is regular monitoring and early treatment. Lung function tests are done frequently to track changes in functional lung volume and respiratory effort. Sputum samples are analyzed to determine the types of bacteria present in the lungs. Chest x-rays are usually taken at least once a year. Lung scans, using a radioactive gas, can show closed off areas not seen on the x-ray. Circulation in the lungs may be monitored by injection of a radioactive substance into the bloodstream. Artificial intelligence software can also be used to analyze CT scans to help detect and analyze lung abnormalities.

People with CF live with chronic bacterial colonization; that is, their lungs are constantly host to several species of bacteria. Good general health, especially good nutrition, can keep the immune system healthy, which decreases the frequency with which these colonies begin an infection, or attack on the lung tissue. Exercise is another important way to maintain health, and people with CF are encouraged to maintain a program of regular exercise.

In addition, clearing mucus from the lungs helps to prevent infection, and mucus control is an important aspect of CF management. Bronchial drainage is used to

allow gravity to aid the mucociliary escalator. For this technique, the person with CF lies on a tilted surface with head downward, alternately on the stomach, back, or side, depending on the section of lung to be drained. An assistant thumps the rib cage to help loosen the secretions. A device called a “flutter” offers another way to loosen secretions: it consists of a stainless steel ball in a tube. When a person exhales through it, the ball vibrates, sending vibrations back through the air in the lungs. Some special breathing techniques may also help clear the lungs.

Several drugs are available to prevent the airways from becoming clogged with mucus. Bronchodilators can help open up the airways; steroids reduce inflammation; and mucolytics loosen secretions. Acetylcysteine (Mucomyst) has been used as a mucolytic for many years but is not prescribed frequently now, while dornase alfa (Pulmozyme) is a newer product gaining in popularity. Dornase alfa breaks down the DNA from dead white blood cells and bacteria found in thick mucus.

People with CF may pick up bacteria from other CF patients. This is especially true of *Burkholderia cepacia*, which is not usually found in people without CF. While the ideal recommendation from a health standpoint might be to avoid contact with others who have CF, this is not usually practical (since CF clinics are a major site of care), nor does it meet the psychological and social needs of many people with CF. At a minimum, CF centers recommend avoiding prolonged close contact between people with CF; and scrupulous hygiene, including frequent hand washing. Some CF clinics schedule appointments on different days for those with and without *B. cepacia* colonies.

Some doctors choose to prescribe antibiotics only during infection, while others prefer long-term antibiotic treatment against *S. aureus*. The choice of antibiotic depends on the particular organism or organisms found. Some antibiotics are given as aerosols directly into the lungs. Antibiotic treatment may be prolonged and aggressive.

Supplemental oxygen may be needed as lung disease progresses. Respiratory failure may develop, requiring temporary use of a ventilator to perform the work of breathing.

Lung transplantation is another option for people with CF, although the number of people who receive them is still much lower than those who want them. Transplantation is not a cure, however, and has been likened to trading one disease for another. Long-term immunosuppression is required, increasing the likelihood of other types of infection. About 50% of adults and more than 80% of children who receive lung transplants live

QUESTIONS TO ASK YOUR DOCTOR

- How did my child get cystic fibrosis?
- What factors will determine the kind of life my child will be able to live with this disorder?
- How can I find a support group for parents of children who have cystic fibrosis?
- Are there changes or adjustments we can make in our family's lifestyle to make life easier and more comfortable for my child with cystic fibrosis?

longer than two years. Some CF patients whose livers have been damaged by fibrosis also undergo liver transplants.

Long-term use of ibuprofen has been shown to help some people with CF; presumably by reducing inflammation in the lungs. Close medical supervision is necessary, however, since the effective dose is high and not everyone benefits. Ibuprofen at the required doses interferes with kidney function, and together with aminoglycoside antibiotics, may cause kidney failure.

A number of experimental treatments are currently the subject of much research. Some evidence indicates that aminoglycoside antibiotics may help overcome the genetic defect in some CF mutations, allowing the protein to be made normally. While promising, these results would apply to only about 5% of those with CF.

Gene therapy is currently the most ambitious approach to curing CF. In this set of techniques, non-defective copies of the *CFTR* gene are delivered to affected cells, where they are taken up and used to create the *CFTR* protein. While elegant and simple in theory, gene therapy has met with a large number of difficulties in trials so far, including immune resistance, very short duration of the introduced gene, and inadequately widespread delivery.

CFTR modulators

CFTR modulators are a class of drugs that improve or restore the function of the *CFTR* protein but only work for people with certain *CFTR* gene variants. There are three types of *CFTR* modulators currently in development: potentiators, correctors, and amplifiers. Only potentiators and correctors have been approved by the FDA.

Potentiators work by increasing the chances that the *CFTR* protein gate will be open to allow more chloride to flow through the cell membrane. The drug ivacaftor

(Kalydeco) is an example. Potentiators work for people who have CFTR gene variants where the protein produced is normal but is produced in an insufficient amount or where the CFTR protein gate does not work properly.

Correctors help the CFTR protein form a normal shape, move to the cell surface, and stay there longer. Lumacaftor, elxacaftor, and tezacaftor are examples of correctors. Correctors do not work well enough by themselves, since they do not allow enough of the proteins to reach the cell surface and do not allow enough chloride to pass out of the cell. Correctors are therefore usually combined with potentiators like ivacaftor. Trikafta and Symdeko are examples of drugs that combine correctors and potentiators.

Prognosis

People with CF may lead relatively normal lives but in many cases will have a reduced lifespan. Because of better and earlier treatment, a person born today with CF is expected on average to live into their mid-40s. Many of the symptoms of CF can be treated with drugs or nutritional supplements. Close attention to, and prompt treatment of, respiratory and digestive complications have dramatically increased the expected lifespan of a person with CF. Several decades ago, most children with CF died by the age of two; today, about half of all people with CF live past age 31. That median age is expected to grow as new treatments are developed, and it is estimated that a person born in 2021 with CF will likely live to their 40s and beyond. The possible effect of pregnancy on the health of a woman with CF requires careful consideration before beginning a family, as do issues of longevity and her children's status as carriers. Although most men with CF are functionally sterile, new procedures for removing sperm from the testes are being tried, and may offer more men the chance to become fathers.

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Cystic Fibrosis Foundation, 4550 Montgomery Ave., Suite 1100 N, Bethesda, MD 20814, (301) 951-4422, (800) 344-4823, (301) 951-6378, info@cff.org, <http://www.cff.org>

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Cystinosis

Definition

Cystinosis is a rare genetic metabolic disease that causes cystine, an amino acid, to accumulate in lysosomes (organelles within cells that contain enzymes) of various organs of the body, such as the kidneys, liver, eyes, muscles, pancreas, brain, and white blood cells. Although cystinosis primarily affects children, a form of the disease also occurs in adults.

Description

In cystinosis, the cystine content of cells increases to an average of 50 to 100 times its normal value. This

increase is caused by an abnormality in the transport of cystine out of a sac-like compartment of the cell called the lysosome. Because of cystine's low solubility in water, this amino acid forms crystals that accumulate within the lysosomes of cells. The accumulation of cystine is believed to destroy the cells.

There are three basic forms of cystinosis: infantile nephropathic cystinosis; late-onset nephropathic cystinosis; and benign non-nephropathic cystinosis.

Infantile nephropathic cystinosis

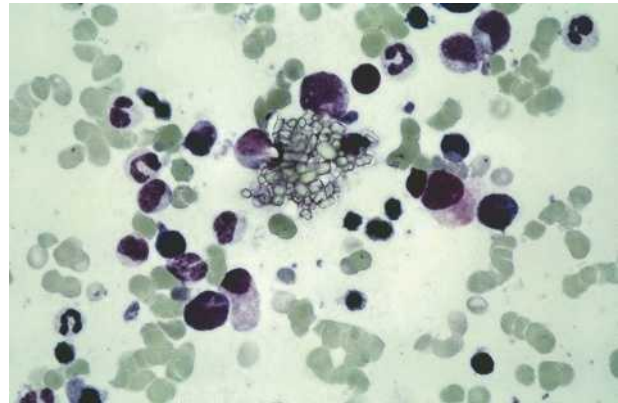
Children with infantile cystinosis usually appear normal at birth and during the first six to eight months of life. As Fanconi syndrome (a tubular dysfunction of the kidneys causing impairment in the kidneys' ability to reabsorb minerals and nutrients back into the bloodstream) develops, sodium and water depletion occurs, leading to polyuria (excessive urination) and polydipsia (excessive thirst). Affected children become especially vulnerable to dehydration. This tubular abnormality, in addition to an abnormality in sweat production, often leads to recurrent fevers as a presenting symptom.

By one year of age, children with infantile cystinosis generally exhibit growth retardation; rickets (inadequate deposition of minerals in developing cartilage and newly formed bone, causing abnormalities in shape and structure of bones); metabolic acidosis (excessive acid in the blood); and other chemical evidence of renal tubular abnormalities of the kidney, such as increased renal (kidney) excretion of glucose, amino acids, phosphate, and potassium. However, more subtle clinical and biochemical evidence of the disease can be detected at a much earlier age by careful examination of at-risk children (those with a sibling or other relative with the disease). As a child with infantile nephropathic cystinosis ages, failure to thrive is apparent.

Without therapeutic intervention, children with this disorder remain below the norm in both height and weight throughout life. The typical patient with infantile nephropathic cystinosis has short stature, retinopathy (retinal disorder), photophobia (light sensitivity), and onset of Fanconi syndrome in the first year of life. By one to two years of age, corneal cystine crystals and rickets are evident. Glomerular failure (the glomerulus is a small structure in the kidney made up of a cluster of capillaries) progresses, and end-stage renal disease occurs by about nine to ten years of age.

Late-onset nephropathic cystinosis

In late-onset nephropathic cystinosis, the age of onset ranges from 2 to 26 years; however, the typical age at which the condition presents is 12 to 13 years. If more than



Light micrograph of crystals of cystine among blood cells in a sample of bone marrow. (CNRI/Science Source)

one sibling develops late-onset cystinosis, their age of onset and symptoms are generally similar. Patients with this condition develop crystalline deposits in the cornea and conjunctivae (mucous membranes lining the eyelids), as well as in the bone marrow. Although patients with late-onset cystinosis often do not develop full-blown Fanconi syndrome, renal failure progresses to such a degree that kidney transplantation is necessary, as in the case of infantile nephropathic cystinosis. These individuals are usually in end-stage renal failure within a few years of diagnosis.

Benign non-nephropathic cystinosis

Formerly known as adult cystinosis, benign non-nephropathic cystinosis is usually discovered by chance when an ophthalmologic (eye) examination reveals crystalline opacities within the cornea and conjunctiva. As in patients with infantile nephropathic cystinosis, those with benign cystinosis may also have photophobia; however, light sensitivity may not develop until middle age and is usually not as debilitating. Because the only patients diagnosed with benign cystinosis are those who undergo slit-lamp (a lamp constructed such that intense light is emitted through a slit) eye examination by an eye specialist, it is possible that many individuals with this form of the disease never experience eye symptoms and are never diagnosed. Patients with benign cystinosis develop crystalline deposits in their bone marrow and white blood cells, but do not develop renal dysfunction or retinopathy.

Genetic profile

Cystinosis is an autosomal recessive genetic disease. The term "autosomal" refers to a gene situated on one of the 23 pairs of chromosomes other than a sex chromosome (the X or Y chromosomes). The term "recessive"

KEY TERMS

Cystine—A sulfur-containing amino acid, sometimes found as crystals in the kidneys or urine, that forms when proteins are broken down by digestion.

Fanconi syndrome—A disorder of reabsorption in the kidney tubules.

Glomerulus (plural, glomeruli)—A structure in the kidney composed of blood vessels that are actively involved in the filtration of the blood.

Lysosome—A membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

Nephropathy—Kidney disease.

Photophobia—Extreme sensitivity to light.

Retinopathy—Any disorder of the retina.

refers to an allele, or a form of a gene that may be expressed and/or active; however, the “dominant” form of the gene on the other chromosome usually takes over enough of the gene’s normal function to prevent symptoms of a disorder. Each parent of a child with cystinosis carries one abnormal (recessive) gene and one normal gene. Thus, the child must inherit an abnormal (or altered) gene from each parent to develop the disease. In addition, when a child develops cystinosis, the parents are almost always surprised because they never exhibited any symptoms of the disease. The recessive gene may lie dormant for generations until two people with the abnormal gene come together and have children.

Each time two such cystinosis carriers—persons with one copy of the altered gene and one copy of a normal or functioning gene—have a child together, there is a 1-in-4 chance (25% risk) of having a child with cystinosis; a 2-in-4 chance (50% risk) the child will not have cystinosis but will be a carrier; and a 1-in-4 chance the child will not have cystinosis or be a carrier. Also, every unaffected sibling of a child with cystinosis has a 2-in-3 (67%) chance of being a carrier (having one copy of the abnormal gene and one copy of a normal gene), like his or her parents.

Scientists have mapped the cystinosis gene, *CTNS*, to the short arm of chromosome 17 (at location 17p13). Mutations (changes) in the cystinosis gene (specifically, a deletion of a particular part of the gene) have been found to cause all three types of cystinosis. However, this deletion is difficult to identify in some individuals for reasons that are uncertain. In these individuals, extensive

and very sophisticated laboratory work (molecular genetic testing) to identify and prove the existence of the deletion would be necessary.

In patients of Northern European descent, for example, there is about a 50/50 probability that an individual with cystinosis has the deletion. Genetic testing is under investigation for populations of these regions, but until details of the methodology are refined, measurement of lysosomal cystine in white cells and fibroblasts (any cell or corpuscle from which connective tissue is developed) will remain state-of-the-art and the most broadly based general method for diagnosing cystinosis. Molecular genetic testing for mutations of the *CTNS* gene was, however, available at several laboratories in the United States as of 2021. The tests involve deletion/duplication analysis or sequence analysis of the entire coding region.

Demographics

It is estimated that 2,000 individuals worldwide have cystinosis, although exact figures are difficult to obtain because the disease often remains undiagnosed. In the United States, the disease is believed to affect 1 in every 100,000 to 200,000 live births, or approximately 400 individuals, with about 15 new cases identified each year. Cystinosis is more common in Brittany, a province of France, where it affects about 1 person in every 26,000. In Canada, the disorder is more common among French Canadians living in Quebec than among English-speaking Canadians in the other provinces. The male:female ratio in cystinosis is about 1.4:1.

Signs and symptoms

Although the symptoms of cystinosis vary depending on the type of disease present, general symptoms include the following:

- acidosis
- dehydration
- rickets
- growth retardation
- renal glomerular failure
- corneal ulcerations and retinal blindness
- delayed puberty
- swallowing difficulties

Diagnosis

Cystinosis may be diagnosed prenatally by examining cystine levels in chorionic villi (obtained by chorionic villus sampling, usually done at 10–12 weeks gestation) or in cells contained in amniotic fluid (obtained by amniocentesis, usually done at 16–18 weeks gestation).

In early infancy, cystinosis is usually diagnosed by measuring free cystine in white blood cells and skin fibroblasts.

Chorionic villus sampling

Chorionic villus sampling (tissue sample of tiny pieces of placental tissue obtained by inserting a thin needle or narrow tube into the uterus) is performed at 10–12 weeks of gestation. Intracellular cystine levels are measured. The values in a fetus with cystinosis are more than ten times greater than normal.

Amniocentesis

Amniocentesis (sample of amniotic fluid obtained by inserting a thin needle into the uterus) can be performed at 16–18 weeks gestation.

White blood cell testing

When diagnosed early, the progressive kidney failure, retarded growth, and vision problems can be prevented or delayed by proper management and medication. The metabolic abnormality in cystinosis is the failure of the cellular lysosomes to release cystine. As a result, the free cystine in the lysosomes accumulates to many times the normal value. The diagnosis of cystinosis is therefore based in part on the measurement of free cystine in the tissues that accumulate this amino acid. This measurement is most easily accomplished in white blood cells. Whole blood contains red cells, which are rich in glutathione, a compound that can react with cystine. To prevent this reaction, white cells are separated from red cells. The white cells are kept cold to slow down reactions, and then broken open and frozen. Freezing prevents the reaction of cystine with such compounds as glutathione and precipitates the cell protein. These steps stabilize the cystine content of the preparation.

Skin fibroblast testing

Cultured skin fibroblasts may also be used to diagnose cystinosis. Because of the increased time and costs, white blood cells are usually sent for testing first. Skin fibroblast testing (biopsy) is also more invasive than a blood sample. On rare occasions the expression of the abnormality in white cells is borderline for diagnosis. Thus, confirmation using fibroblasts is definitive.

Treatment and management

Cystinosis is treated by a variety of pharmacologic and nonpharmacologic therapies, as well as by surgical transplantation.

QUESTIONS TO ASK YOUR DOCTOR

- How do the three types of cystinosis differ from one another?
- What did my physician mean when he recommended cysteamine treatment for my child with cystinosis?
- If my child stays on cysteamine throughout his life, will he be spared the worst consequences of this disease?
- What services does the Cystinosis Foundation provide for parents of children with the disorder? For adults with the condition?

Pharmacologic therapy

The aim of specific treatment for cystinosis is to reduce cystine accumulation within the cells. This goal is achieved by cysteamine treatment, which has proven effective in delaying or preventing renal failure. Cysteamine treatment also improves growth in children with cystinosis. The growth improvement with cysteamine bitartrate usually allows the patient to maintain growth along a percentile but does not usually aid in achieving catch-up growth.

The Food and Drug Administration (FDA) approved a capsule form of cysteamine bitartrate called Cystagon in August 1994. However, oral cysteamine does not prevent the progression of ocular lesions and has many potential side effects. Little is known about the drug's long-term effects. The main disadvantage of cysteamine treatment is the need for four daily capsules (every six hours) and the sulfurous breath it causes. Cysteamine treatment is also expensive. In 2013, the FDA approved Procysbi, an extended-release formulation of cysteamine, for the treatment of cystinosis in adults and children over six years of age. This formulation is taken only twice a day, or every 12 hours.

Many children with cystinosis receive growth hormone, and some have had improvements in height. There is also evidence that indomethacin (Indocin) increases appetite, decreases urine volume, decreases water consumption, and improves growth in pretransplanted patients with cystinosis.

Vitamin/mineral supplementation

The symptomatic treatment of Fanconi syndrome is essential in patients with cystinosis. The urinary losses of water, salts, bicarbonate, and minerals must be replaced.

Most children receive a solution of sodium and potassium citrate as well as phosphate. Some also receive extra vitamin D.

Organ transplantation

Kidney transplantation has proven useful in patients with cystinosis. If a patient with cystinosis receives a kidney transplant and reaches adulthood, the new kidney will not be affected by the disease. However, without cysteamine treatment, kidney transplant recipients can develop complications in other organs due to the continued cystine accumulation in the body. These complications can include muscle wasting, difficulty swallowing, diabetes, hypothyroidism, and blindness. Not all older patients, however, develop these symptoms.

In both young children with cystinosis and older patients with a kidney transplant, cysteamine eye drops may be useful in removing the corneal cystine crystals and reducing photophobia. In 2013, the FDA approved an ophthalmic solution of cysteamine called Cystaran for the treatment of cystine crystals in the cornea of the eye.

Prognosis

Since 1980, the prognosis of a child with cystinosis has greatly improved. However, if children with the disease receive no treatment, they rarely survive past the age of nine or ten. As of 2021, with proper treatment, many patients survive into the third or fourth decade of life.

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- Cystinosis Foundation, 58 Miramonte Dr., Moraga, CA 94556, (888) 631-1588, (925) 631-1588, <http://cystinosisfoundation.org/>
- Cystinosis Research Network, P.O. Box 702, Lake Forest, IL 60045, (847) 735-0471, (866) 276-3369, (847) 235-2273, info@cystinosis.org, <https://cystinosis.org>
- National Center for Biotechnology Information, National Library of Medicine, Building 38A, Room 8N805, Bethesda, MD 20894, (301) 496-2475, info@ncbi.nlm.nih.gov, <http://www.ncbi.nlm.nih.gov>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Cystinuria

Definition

Cystinuria is a relatively common inherited disorder characterized by the formation of cystine urinary tract stones that can lead to obstruction, infection, and eventual loss of renal function.

Description

In cystinuria, there is a defect in the movement of cystine and the dibasic amino acids (lysine, arginine, and ornithine) across the epithelial cells of the kidneys and the small intestine. In the kidney, most amino acids are filtered by the glomerulus and reabsorbed by the proximal tubules with little residual amino acid in the urine. In cystinuria, cystine and the dibasic amino acids are not reabsorbed by the tubules of the kidney, and eventually build up in the urine. Cystine in high concentrations is insoluble in urine and will form stones (calculi) in the kidneys, bladder, and ureters. The transport defect in the small intestine leads to the accumulation of digestion breakdown products of cystine and the dibasic amino acids in the stool, urine, and plasma. The intestinal defect does not appear to result in any adverse symptoms for the affected individual.

Cystinuria has been classified into three types (I, II, and III) based on the urinary excretion of cystine and the dibasic amino acids among carriers of the disease

(heterozygotes), and on the nature of the intestinal transport defect among affected individuals (homozygotes).

The name cystine is derived from the Greek word for bladder, “kystis.” When the disease was first described in the 1800s, it was thought that the origin of the cystine stones was the bladder. Historically, cystinuria is important because it was one of the four inborn errors of metabolism reported by Sir Archibald Garrod in his famous Croonian Lecture in 1908. Although alternate names for the disorder include cystine-lysinuria, cystine-lysine-arginine-ornithinuria, and cystinuria dibasic aminoaciduria, the term “cystinuria” is used most often to describe the disease.

Genetic profile

Cystinuria is a complex autosomal recessive disorder. Type I cystinuria is completely recessive; carriers have no manifestations. Types II and III cystinuria are incompletely recessive; carriers can display symptoms. Two amino acid transporter genes, *SLC3A1* (solute carrier family 3, member 1) located on chromosome 2p, and *SLC7A9* (solute carrier family 7, member 9) located on chromosome 19q, are known to cause cystinuria. The proteins produced by these two genes apparently interact with one another. An individual with two mutations in the *SLC3A1* gene (homozygote) has type I disease. Mutations in the *SLC7A9* gene lead to types II and III cystinuria. Types II and III cystinuria are allelic; different changes (mutations) in the same gene lead to alternative forms of the disease. There are some patients who are genetic compounds—they have a type II mutation on one copy of the gene and a type III mutation on the other copy. There are also individuals who may have mutations in both the *SLC3A1* gene and the *SLC7A9* gene.

Demographics

Cystinuria is considered one of the more common genetic disorders with an estimated prevalence of 1 in 7,000. Most affected individuals have type I disease. Type II disease is relatively rare. Due to a founder effect, an increased incidence of cystinuria exists among individuals of Libyan Jewish ancestry. Approximately 1 in 2,500 persons of Libyan Jewish descent has type II disease. The carrier frequency in this population is around 1 in 25.

Signs and symptoms

Symptoms of cystinuria develop due to the high level of cystine in the urine. Since cystine at high concentrations is insoluble in urine, undissolved cystine accumulates in the urine and affected individuals are prone to recurrent urinary tract stone formation (nephrolithiasis). Also, hexagonal-shaped crystals form in the urine; these

crystals signify the presence of cystine in potentially stone-forming concentrations. The onset of cystinuria is variable and symptoms can appear anytime between the first year of life and the ninth decade. Most cystinurics develop symptoms in the second and third decades of life. In many affected individuals the first sign of the disorder is renal colic, a painful condition caused by obstruction of the urinary tract. Obstruction of the urinary tract due to calculi can lead to infection and eventually to renal insufficiency. Less often, complaints such as infection, hypertension, and renal failure are the first reasons cystinuric patients seek medical attention.

Unlike most autosomal recessive disorders, carriers for types II and III cystinuria can be symptomatic. Type II carriers have high urinary excretion of cystine and lysine, and type II carriers have moderate excretion of cystine, lysine, arginine, and ornithine. Both type II and type III carriers are at risk to develop stones. Type I carriers have no excess cystine or dibasic amino acids in their urine, and are without symptoms of the disorder.

Although there are reports of an association between cystinuria and neurologic abnormalities, little is known about the mechanism responsible for this, nor is the prevalence of this complication among affected individuals known.

Diagnosis

The diagnosis of cystinuria is made at the biochemical level. Molecular (genetic) testing is also available but is generally not the first means of making a cystinuria diagnosis. The simplest approach to diagnosis of this condition is microscopic examination of the urine for the characteristic hexagonal-shaped crystals. Urinary microscopic examination was the primary means of cystinuria diagnosis for many years since the discovery of these crystals by Stromeyer in 1824, and it remains a useful aid in the diagnosis of this condition today. Another widely used screening procedure is the cyanide-nitroprusside test, a test that measures the amount of cystine excreted in the urine in comparison to the amount of creatinine (a protein normally found in urine). In those patients who display crystals and have a positive nitroprusside test, further diagnostic tests such as thin-layer chromatography or high-voltage electrophoresis can identify the specific amino acids (cystine, lysine, arginine, ornithine); and other techniques such as ion-exchange chromatography, liquid chromatography-mass spectrophotometer, and high-performance liquid chromatography may be performed to measure the amounts of these amino acids in the urine.

The type (I, II, or III) of cystinuria in an affected patient can be determined by family studies and/or by study of the intestinal transport defect in an affected

KEY TERMS

Alkalinization—The process of making a solution more basic, rather than more acidic, by raising the pH.

Allelic—Related to the same gene.

Amino acid—Organic compounds that form the building blocks of protein. There are 20 types of amino acids (eight are essential amino acids, which the body cannot make and must therefore be obtained from food).

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Catheter—A narrow, flexible tube used to create a pathway for introducing drugs, nutrients, fluids, or blood products into the body and/or for removing fluid or other substances from the body.

Chromosome—A microscopic thread-like structure found within each cell of the body and consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Cystine—A sulfur-containing amino acid, sometimes found as crystals in the kidneys or urine, that forms when proteins are broken down by digestion.

Epithelial cells—The layer of cells that cover the open surfaces of the body such as the skin and mucous membranes.

Founder effect—Increased frequency of a gene mutation in a population that was founded by a

small ancestral group of people, at least one of whom was a carrier of the gene mutation.

Glomerulus—A structure in the kidney composed of blood vessels that are actively involved in the filtration of the blood.

Homozygote—Having two identical copies of a gene or chromosome.

Obligate carrier—An individual who, based on pedigree analysis, must carry a genetic mutation for a particular genetic disease. Parents of a child with an autosomal recessive disorder are obligate carriers.

Oral loading test—A procedure in which cystine is administered orally to a patient and plasma levels of cystine are measured. Under normal circumstances, amino acids are absorbed by the intestine and result in an increase in plasma amino acid levels. However, in cystinuria, there is a problem in the absorption process and blood levels of amino acids do not rise, or rise slowly after eating.

Plasma—The liquid part of the blood and lymphatic fluid that contains antibodies and other proteins.

Renal—Related to the kidneys.

Renal colic—A spasmodic pain, moderate to severe in degree, located in the back, side, and/or groin area.

Small intestine—The part of the digestive tract that lies between the stomach and the large intestine.

Tubule—A small tube lined with glandular epithelium in the kidney.

Ureters—Tubes through which urine is transported from the kidneys to the bladder.

individual. Type I obligate carriers have normal amounts of urinary cystine and dibasic amino acids. Type II carriers have between nine and fifteen times the normal amount of cystine and lysine in their urine. Type III carriers have up to twice the normal range of cystine and the dibasic amino acids in their urine. The intestinal absorption defect in an affected individual can be demonstrated by oral loading tests and/or by study of the transport of cystine and the dibasic amino acids in an intestinal biopsy specimen from an affected individual.

Testing for mutations in the *SLC3A1* gene and the *SLC7A9* gene is possible. Over 40 mutations in the *SLC3A1* gene have been found and almost as many have been detected in the *SLC7A9* gene.

Treatment and management

Prevention

The primary goal of treatment of cystinuria is prevention of existing cystine stones through noninvasive means. There are three main categories of treatment: increase cystine solubility, reduce cystine production and excretion, and convert cystine into a more soluble compound. The first step in treatment is to increase cystine solubility via hydration therapy. It is recommended that patients increase their fluid intake such that the concentration of cystine is 200-250 mg/liter of urine. This therapy prevents stone formation approximately two-thirds of the time. Another therapy that increases cystine

QUESTIONS TO ASK YOUR DOCTOR

- Please explain the process by which stones form in the kidney as a result of cystinuria.
- How do the various types of cystinuria differ from each other?
- Under what circumstances, if any, is surgery required for the treatment of my cystinuria?
- How does a physician diagnose a case of cystinuria, and how does that diagnosis distinguish the disease from similar medical conditions?

solubility is known as oral alkalinization. Medications such as sodium citrate, potassium citrate, or sodium bicarbonate increase the pH of urine to levels at which cystine becomes a more soluble compound. To reduce cystine excretion and production, individuals with cystinuria may follow a diet low in sodium and protein.

If the above measures are not successful in preventing stones and/or dissolving existing ones, drug therapy may be necessary. Tiopronin and d-penicillamine are two drugs that are known to bind excess cystine into a form that is more soluble than cystine alone and thus reduce the excessive urinary excretion of this amino acid. Since both tiopronin and d-penicillamine can have adverse side effects, patients on these regimens require follow-up to monitor the efficacy and tolerance of the medication. Other medications that reduce cystine excretion include mercaptopropionylglycine (MPG) and captopril. Although they are not as effective as tiopronin or d-penicillamine, MPG and captopril have fewer side effects.

If stones form despite the above therapeutic regimens, surgical intervention may be required. Surgical management of cystine stones may include dissolution of calculi by irrigation through a catheter, removal of cystine stones by lithotripsy or lithotomy, and renal transplantation. Catheter irrigation is a minimally invasive procedure in which catheters are placed into the ureters and the urinary tract is irrigated with a solution that dissolves the stones over a period of one week to several months. Lithotripsy is a medical procedure used to break a kidney stone into small pieces that can be passed in the urine. In extracorporeal shock wave lithotripsy, a shock

wave produced outside the body is used to break up the stone and a catheter placed in the ureter facilitates passage of the stone fragments. In percutaneous nephrolithotripsy, an opening (port) is created by puncturing the kidney through the skin; a specialist then inserts instruments via this opening into the kidney to break up the stone and remove the debris. Lithotomy is the surgical removal of a (kidney) stone.

Prognosis

The prognosis of cystinuria is variable and depends on the level of renal function at the time of diagnosis and initiation of therapy, and the success of preventive measures and surgical management. It is known that males tend to have a more severe course and a higher mortality rate.

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ORGANIZATIONS

- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Dawn Cardeiro, MS, CGC

Cytogenetic mapping see **Genetic mapping**

D

Dandy-Walker malformation

Definition

Dandy-Walker malformation is a congenital (present at birth) condition involving several abnormalities in the development of the brain. The malformation appears to result from destructive processes, such as inflammation or trauma, which block the circulation of cerebrospinal fluid (CSF) inside the head after the brain has been formed in the embryo.

Description

Dandy-Walker malformation was first described in 1914 by Drs. Walter Dandy and Kenneth Blackfan. The disorder typically includes the following abnormalities in brain structure:

- Absence or incomplete formation of the vermis, the middle portion of the cerebellum, which is the part of the human brain that is attached posteriorly to the brainstem.
- Cysts in the fourth ventricle, one of the human brain's four interconnected ventricles (inner cavities or chambers) that produce cerebrospinal fluid (CSF), cause enlargement. In Dandy-Walker malformation, the CSF cannot circulate freely through the ventricles and the rest of the central nervous system (CNS), so it builds up inside the fourth ventricle and causes it to enlarge.
- Enlargement of the posterior fossa, which is a hollow at the back of the skull that contains the cerebellum.
- Absence or incomplete formation of the three apertures (small openings or holes) in the fourth ventricle.

In Dandy-Walker malformation, the CSF produced by the ventricles of the brain is not fully reabsorbed by the body; thus the excess fluid accumulates in the fourth ventricle and the posterior fossa. As cysts in these areas grow, pressure from the fluid rises, producing a condition known as obstructive, or noncommunicating, hydrocephalus (excess fluid on the brain). Hydrocephalus develops

in 20%–80% of children diagnosed with Dandy-Walker malformation. The size of the head may or may not be affected by the fluid pressure.

Genetic profile

The genetic transmission of Dandy-Walker malformation is not fully understood because the disorder often occurs with other birth abnormalities, including cleft palate, extra fingers (polydactyly) or fingers joined together (syndactyly), cataracts, and malformations of the face or heart. An abnormality in the central nervous system that often occurs together with Dandy-Walker malformation is agenesis (absence or failure to develop) of the corpus callosum, the thick band of nerve fibers that joins the two cerebral hemispheres. It is not yet clear whether these and other abnormalities in CNS development are determined by the same gene or whether they are inherited separately.

Dandy-Walker malformation appears to be transmitted in some families in an autosomal, or X-linked, recessive pattern, which means that both parents have one copy of the changed (mutated) gene but do not have the malformation. These families have a high risk of recurrence of the malformation. Families in which there has been inbreeding among close relatives also appear to transmit Dandy-Walker in an autosomal recessive pattern. Several chromosomal abnormalities have been associated with Dandy-Walker.

Demographics

Dandy-Walker malformation is a rare disorder. It is estimated to occur in about 3% of children with hydrocephalus, which occurs in 1–2 per 1,000 births. It appears to affect females more often than males. While there is no known association with specific races or ethnic groups, recent genetic case studies of Dandy-Walker malformation include cases from Argentina, Poland, Germany, Brazil, Austria, and Japan.

Signs and symptoms

Some signs of Dandy-Walker malformation may appear before birth. It is possible to detect hydrocephalus by ultrasound as early as 15–18 weeks after conception. A newborn with hydrocephalus may have difficulty breathing, dilated veins visible on the scalp, and rapid head growth. Infants with Dandy-Walker may be slow to develop motor (movement) skills, and may have abnormally large skulls as a result of the fluid pressure inside the head.

Older children with Dandy-Walker malformation may have symptoms associated with fluid pressure inside the head, including vomiting, convulsions, and emotional irritability. If the cerebellum has been damaged, the child's sense of balance and coordination will be affected. About 20% of older children with Dandy-Walker have difficulty coordinating movements of the hands or feet (ataxia) or have involuntary jerking movements of the eyes (nystagmus). Developmental delays and intellectual disability are more common. In some cases Dandy-Walker may be associated with an abnormal pituitary gland and delayed puberty. Other symptoms that sometimes appear in this group include unusually large head size, a bulge at the back of the head caused by fluid pressure in the posterior fossa, and abnormal breathing patterns.

Diagnosis

About 80% of children with Dandy-Walker malformation are diagnosed before the end of the first year, usually as a result of the signs of hydrocephalus. Following birth, the newborn's head circumference is measured to determine whether it has been enlarged by the development of cysts. As has already been mentioned, ultrasound screening before birth can detect some signs of hydrocephalus. Ultrasound screening is recommended if the family has a history of congenital neurologic abnormalities. Genetic counseling is recommended for parents who have already had a child with Dandy-Walker malformation as there is an increased risk that the malformation will recur in later pregnancies.

Imaging studies used to diagnose and monitor Dandy-Walker include:

- x-rays of the skull to determine that the posterior fossa has been enlarged
- CT scan or magnetic resonance imaging (MRI) tests to evaluate the size and shape of the fourth ventricle, the presence and size of the vermis, and the displacement of other parts of the brain by fluid pressure
- cranial ultrasound to evaluate the size of the ventricle or to assess the progression of hydrocephalus, or

KEY TERMS

Agenesis—Failure of an organ, tissue, or cell to develop or grow.

Congenital—Refers to a disorder that is present at birth.

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

Cyst—An abnormal sac or closed cavity filled with liquid or semisolid matter.

Foramen—A small opening or hole in a body part or tissue.

Hydrocephalus—The excess accumulation of cerebrospinal fluid within the brain, often causing enlargement of the head.

Posterior fossa—Area at the base of the skull that contains the brain stem and cerebellum.

Shunt—A small tube placed in a ventricle of the brain to direct cerebrospinal fluid away from the blockage into another part of the body.

Trisomy—The condition of having three identical chromosomes, instead of the normal two, in a cell.

Ventricle—The fluid-filled spaces in the center of the brain that hold cerebral spinal fluid.

Vermis—The central portion of the cerebellum, which divides the two hemispheres. It functions to monitor and control movement of the limbs, trunk, head, and eyes.

- transillumination, a technique that shines a strong light through an organ or body part to assist in diagnosis. The posterior fossa may be transilluminated as part of the differential diagnosis of Dandy-Walker.

Treatment and management

Treatment of Dandy-Walker malformation is usually focused on managing hydrocephalus when it is present. Hydrocephalus cannot be cured, but it can be treated surgically by placing a shunt in the ventricles of the brain to reduce fluid pressure. The shunt carries some of the CSF into another part of the body where it can be reabsorbed.

Another important part of managing Dandy-Walker is treatment of conditions or abnormalities associated with it—such as giving anticonvulsant medications for

seizures or hormones to bring on puberty that has been delayed.

Prognosis

The prognosis for children with Dandy-Walker malformation is usually not encouraging because of the associated multiple abnormalities. Children with other congenital abnormalities occurring together with Dandy-Walker often do not survive. The affected person's chances of normal intellectual development depend on the severity of the malformation and the presence of other abnormalities.

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ORGANIZATIONS

- Hydrocephalus Association, 4340 East West Hwy., Suite 950, Bethesda, MD 20814-4447, (301) 202-3811, (888) 598-3789, (301) 202-3813, info@hydroassoc.org, <http://www.hydroassoc.org>
- National Institute of Neurological Disorders and Stroke, NIH Neurological Institute, PO Box 5801, Bethesda, MD 20824, (301) 496-5751, (800) 352-9424, <http://www.ninds.nih.gov>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Rebecca J. Frey, PhD

De novo

Definition

De novo is from the Latin meaning "anew" or "from the beginning." A *de novo* mutation is a change in genetic information that is not inherited from the parents; rather, the mutation occurs in an egg or sperm cell (germ cell or gamete), in the fertilized egg, during embryonic or fetal development, or during the lifetime of an individual. *De novo* mutations can cause genetic disorders ranging from developmental abnormalities in a newborn to cancer in an adult.

Description

Genetic information is contained in DNA (deoxyribonucleic acid). DNA consists of very long strings of building blocks called nucleotides. The nucleotides are paired to form the DNA double helix. Most cells in the human body have about three billion of these nucleotide pairs organized into 23 pairs of chromosomes, with one chromosome of each pair inherited from the mother and one from the father. Genes are the sequences of nucleotides in DNA that contain the instructions for making proteins via mRNAs (messenger ribonucleic acids). There are some 20,000 protein-coding genes in the human genome, accounting for about 1%–2% of the DNA. Other genes code for RNAs that synthesize proteins (ribosomal RNAs and transfer RNAs) or regulate the activities of genes and proteins. Some noncoding DNA regions control the activities of genes. Still, the vast majority of the DNA in the human genome is either extraneous or has as-yet-undiscovered functions.

Every time a cell divides, all of its DNA must be copied (replicated) so that each of the two daughter cells receives a full complement of genomic information. However, in the formation of germline (egg and sperm) cells, the DNA is copied, but each cell gets only one member of each chromosome pair. During fertilization, the chromosomes from the egg and sperm combine so that the cells of the human embryo again have 23 pairs of chromosomes.

Mutations

Mistakes are made during DNA replication. DNA is also damaged by toxins; radiation such as ultraviolet radiation from sunlight; reactive oxygen species that are normal products of metabolism; bacteria, viruses, and other pathogens; and other mechanisms. Fortunately, human cells have excellent mechanisms for repairing replication mistakes and DNA damage and for eliminating cells when the damage cannot be repaired. However, the

KEY TERMS

Aneuploidy—An abnormal number of chromosomes in a cell. Trisomy 18 and trisomy 13 are examples of aneuploid conditions.

Autism spectrum disorder (ASD)—A general term for a group of neurodevelopmental disorders characterized by difficulties in social interactions, significant abnormalities in speech patterns, and limited but repetitive interests and activities.

Copy number variations (CNVs)—Variations within the population in the number of copies of a specific gene.

Down syndrome—A chromosomal disorder caused by the presence of all or part of an extra 21st chromosome.

Exome—The protein-coding portions of the genome.

Gamete—A reproductive cell; an ovum or sperm.

Genome—The entire DNA sequence of a cell or organism.

Germ cell—An egg or sperm cell or the cells that develop into them.

Germline—The cell line from which gametes arise.

Mosaicism—A condition in which an individual's cells are not all genetically identical.

Mutation—An inherited or *de novo* change in the DNA sequence of the genome.

Polymorphism—A change in the base pair sequence of DNA that may or may not be associated with a disease.

Replication—Copying of DNA prior to cell division.

Schizophrenia—A psychotic disorder characterized by loss of contact with one's environment, deterioration of everyday functioning, and personality disintegration.

Single nucleotide polymorphism (SNP)—Single nucleotide variant (SNV); a variation or point mutation in a single nucleotide building block of DNA.

Somatic mutations—*De novo* mutations that are acquired throughout life and affect only some cells in the body.

machinery for correcting or repairing DNA is also prone to errors. If the DNA is not repaired or the cell eliminated, the result is a *de novo* mutation that becomes a permanent part of an individual's genome. However, the mutation is not passed on to offspring unless it is in a germline cell.

There are various types of mutations:

- Single nucleotide polymorphisms (SNPs) or single nucleotide variants (SNVs) are the most common mutations and result from adding the wrong nucleotide, deleting a nucleotide, or adding an extra nucleotide.
- Other common mutations are the deletion or duplication of a region of the DNA. Deletions and duplications range from very short to very long.
- Copy number variants (CNVs) are extra copies of entire genes.
- Chromosome abnormalities are mutations that occur when chromosomes do not segregate correctly into daughter cells. A daughter cell may lack a chromosome or have an extra chromosome, or a piece of a chromosome may have broken off and joined to a different chromosome. For example, Down syndrome (trisomy 21) is a genetic disorder caused by all or part of an extra chromosome 21.

Some mutations, especially SNPs, are very common and occur both within genes and in 1%–4% of noncoding DNA. DNA alterations that are present in more than 1% of the population are called polymorphisms or neutral gene variants. These result in unique individual characteristics, such as eye and hair color and blood type. Other polymorphisms can cause genetic susceptibility to certain diseases and disorders or help protect against them.

Pathogenic mutations that cause genetic disorders are not common in the general population, although they may run in families. These are mutations that change or destroy the functioning of a cell by failing to produce a required protein, producing an abnormal protein, or producing too much of a protein. Such mutations can interfere with development or the functioning of organs or organ systems. Sometimes they are beneficial as well as harmful. For example, inheriting a mutation that produces abnormal hemoglobin—the protein in red blood cells that carries oxygen throughout the body—confers resistance to malaria. However, inheriting two copies of the gene mutation—one from each parent—causes sickle cell disease.

De novo mutations

Evolution proceeds through *de novo* mutations, and all mutations were *de novo* at some point in the ancestral past. Some mutations probably arose anew many times in human populations. However, once a *de novo* mutation enters the germline and is passed down through families, it is considered an inherited rather than a *de novo* mutation. Many, if not most, human disorders and diseases involve inherited or *de novo* mutations that may directly cause a disorder or increase susceptibility to a disease in association with other genetic factors or environmental triggers.

Genetic disorders that do not run in families but rather appear for the first time in an affected individual are caused by *de novo* mutations. These are also called sporadic mutations because they were not inherited from a parent. The mutation may have occurred in a parent's egg or sperm, in the fertilized egg, or in the early embryo. This type of *de novo* mutation will be carried in most or all of the cells of the body. If the mutation is in germline cells, it becomes an inherited mutation that may be passed on to offspring. *De novo* mutations that occur later in development may be carried in only some cells and may or may not be in germline cells. Fortunately, the vast majority of surviving *de novo* mutations are not harmful, either because they do not affect an important region of DNA or because they do not cause the loss of an essential gene or the production of an abnormal protein. However, *de novo* mutations that are lethal to the fetus or prevent fetal development are a frequent cause of miscarriage.

Mosaicism

De novo mutations that occur later in embryonic or fetal development cause mosaicism, in which some cells in the body carry the mutation and others do not—only cells that arose from the mutation-containing cell have the alteration. The specific mutation and the stage of development at which it occurred determine which cells carry the mutation, whether the mutation results in a genetic disorder, and whether it is in the germline and can be passed to offspring. Researchers are discovering that mosaicism is much more common than previously believed.

Acquired (somatic) *de novo* mutations occur throughout life and are present in only some cells of the body. As people age, their cells accumulate more and more *de novo* mutations. A 2015 study reported that these somatic *de novo* mutations may account for up to 6.5% of an individual's genomic variation. Although they are not inherited or passed on to offspring, somatic mutations can cause disease. For example, cancer is caused by multiple *de novo* somatic mutations in just one or a few cells. These mutations enable the cells to grow and divide uncontrollably.

It has been difficult to determine whether a complex genetic disorder was inherited from combinations of multiple genes contributed by the parents, inherited from a mosaic parent without symptoms of the disorder, or caused by a *de novo* mutation. However, this information is important because it indicates whether the parents are likely to conceive another child with the disorder. It is also important for deciding whether other family members should be tested for the mutation. A 2014 study found that among children with disorders presumed to be caused by *de novo* DNA deletions, a small percentage of the parents had the same mutations in some but not all of their cells. Such parents are more likely to have another affected child.

QUESTIONS TO ASK YOUR DOCTOR

- What is the difference between an inherited and a *de novo* mutation?
- What type of mutation caused my child's disorder?
- Could my child's disorder have been due to older parental age?
- Should our family members have genetic testing for the mutation?
- What are the chances that we will have another child with the disorder?

De novo mutation rates

Studies have reported an average *de novo* mutation rate of 1.2×10^{-8} mutations per nucleotide per generation. On average, each person accumulates approximately 74 *de novo* point mutations (SNPs) over the course of a lifetime. Because of *de novo* mutations occurring during development, even identical twins are not born genetically identical. A study that sequenced the entire genomes of two sets of parents and their children found 35 and 40 *de novo* germline point mutations in the children.

It has been estimated that large *de novo* CNVs occur in about 1 in 50 people.

In 2015, researchers from the United States and the Netherlands analyzed 11,000 *de novo* mutations in 250 healthy families and published a map of *de novo* mutation rates for different regions of the human genome. Most were germline mutations. The map revealed regions of the genome that are prone to mutation, with clusters of *de novo* mutations that tended to be caused by a different mechanism than the non-clustered mutations. They further reported that *de novo* mutation rates in the children increased with increasing age of the fathers at the time of conception.

Multiple studies have reported that the rate of *de novo* mutations appears to be higher in people with genetic disorders, especially those with sporadic developmental disorders such as intellectual disability and autism spectrum disorder (ASD). Furthermore, *de novo* mutations that cause CNVs appear to be somewhat higher than *de novo* SNPs. Such studies have also found an association between increased *de novo* mutation rates and paternal age: about two additional mutations for every year of the father's age at the time of conception.

Diseases and disorders

De novo mutations have long been known to cause many genetic disorders. Large-scale *de novo* chromosome abnormalities that are visible under a microscope have been recognized for many decades, and *de novo* CNVs can be detected using a technique called microarrays. However, until recently it was very difficult to study *de novo* point mutations. With the introduction of high-throughput next-generation DNA sequencing technologies, researchers can rapidly sequence whole genomes (all of the DNA in a cell) or all the protein-coding regions of the genome (the exome). This enables them to compare parents and their children to identify *de novo* mutations in the entire genome or exome, and correlate *de novo* point mutations with specific disorders. These new technologies have identified numerous *de novo* point mutations that cause sporadic cases of rare genetic disorders. Nevertheless, because of the large number of *de novo* mutations per generation, it remains difficult to identify *de novo* point mutations that contribute to or are responsible for a particular disorder.

Examples of *de novo* mutations that have been linked to rare genetic disorders include mutations in the following:

- *SETBP1* gene encoding SET binding protein 1, which causes Schinzel-Giedion syndrome characterized by intellectual disability and neurodegeneration
- *MLL2* (mixed-lineage leukemia 2) gene, which causes Kabuki syndrome characterized by congenital abnormalities and intellectual disability
- *ASXL1* (additional sex-like combs) gene, which causes Bohring-Opitz syndrome with severe intellectual disability and birth defects
- *ANKRD11* (ankyrin repeat domain 11) gene, which causes KBG syndrome with facial and skeletal malformations and developmental delays
- *CHD7* (chromodomain helicase DNA binding protein 7) gene, which causes CHARGE syndrome with heart defects, other birth defects, and breathing problems
- *ACTB/ACTG1* (actin beta/actin gamma 1) gene, which causes brain malformation in Baraitser-Winter syndrome
- *AKT1* (V-akt murine thymoma viral oncogene homolog 1) gene, which causes Proteus syndrome with abnormal bone development and skin overgrowth

While most *de novo* mutations are harmless, they tend to be more damaging than inherited mutations or variations, presumably because they have not undergone evolutionary selection. *De novo* mutations that have been associated with sporadic disorders tend to be highly damaging. They often affect genes that are important for development, especially neurodevelopment. Multiple studies have reported links

between *de novo* mutations—both point mutations and CNVs—and ASD, schizophrenia, and intellectual disabilities. A 2014 study found some of the same *de novo* mutations in ASD and schizophrenia. These mutations affected proteins that are important for brain functioning. Furthermore, the number of *de novo* mutations in individuals with intellectual disabilities appears to correlate with the severity of symptoms.

By sequencing the genomes of sperm and comparing them to the germline sequences, researchers can identify *de novo* mutations that have occurred in individual sperm cells. It has long been known that *de novo* aneuploidy (variations in chromosome number) most often occurs in older egg cells and that the risk of Down syndrome and other *de novo* aneuploidies increases with increasing maternal age. It now appears that increasing paternal age increases the risk of several common neurodevelopmental disorders such as schizophrenia and ASD. It has been suggested that there is an association between the dramatic increase in ASD diagnoses and an ongoing trend toward older paternity, and that this association is related to an increase in *de novo* mutations in older sperm.

Resources

BOOKS

- Griffiths, Anthony J. F., et al., eds. *Introduction to Genetic Analysis*. 12th ed. New York: Macmillan, 2020.
- Milunsky, Aubrey, and Jeff M. Milunsky, eds. *Genetic Disorders and the Fetus: Diagnosis, Prevention, and Treatment*. 8th ed. Hoboken, NJ: Wiley-Blackwell, 2021.

PERIODICALS

- Li, Xinru, et al. "Clinical and Genetic Findings in Patients with Congenital Cataract and Heart Diseases." *Orphanet Journal of Rare Diseases* 16, no. 1 (May 31, 2021): 242. DOI: 10.1186/S13023-021-01873-7.

WEBSITES

- "What is a gene variant and how do variants occur?" MedlinePlus. March 25, 2021. <https://medlineplus.gov/genetics/understanding/mutationsanddisorders/genemutation/> (accessed June 1, 2021).

ORGANIZATIONS

- Autism Speaks, 1 E. 33rd St., Fourth Floor, New York, NY 10016, (212) 252-8584, (888) 288-4762, (212) 252-8676, familyservices@autismspeaks.org, <https://www.autismspeaks.org>
- National Genetics and Genomics Education Centre. c/o National School of Healthcare Science, St Chad's House, 213 Hagley Rd., Birmingham B16 9RG, UK enquiries@geneticseducation.nhs.uk, <http://www.geneticseducation.nhs.uk>

Rebecca J. Frey, PhD

Dementia, hereditary forms

Definition

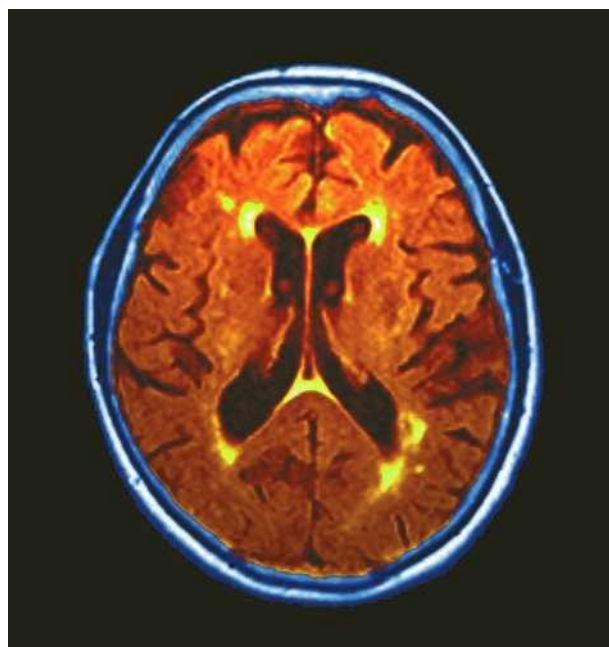
Dementia is a syndrome (group of symptoms) associated with a progressive loss of memory and other intellectual functions that is serious enough to interfere with the tasks of daily life. There are many types of dementia, including forms that are inherited. Alzheimer's disease (AD)—by far the most common type of dementia—can be caused by inheriting specific variants (alleles) of certain genes. Inherited variants or mutations (changes) in certain other genes increase the risk of developing AD.

Description

Dementia is characterized by memory loss and an overall decline in intellectual functioning, including difficulties with language, simple calculations, planning, and judgment and motor (muscular movement) skills. Although dementia is not caused by aging, it most often affects older people. Signs and symptoms occur as nerve cells (neurons) in the brain stop functioning, lose connections with other neurons, and begin to die.

Dementia can be caused by some 40 different diseases and conditions, many of which are at least partially inherited. Some gene variants increase susceptibility to certain types of dementia. Other dementias may have underlying genetic causes that have not yet been identified.

- Primary dementia is characterized by damage to or wasting away of the brain tissue itself, in the absence of other disorders. Primary dementias include AD and frontotemporal disorders (FTD) that mainly affect the frontal and temporal lobes of the brain. Frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17) is a rare type of inherited dementia.
- Vascular dementia (VaD) is caused by blood clots in small blood vessels of the brain. When the clots cut off blood supply to the brain tissue, the brain cells are damaged and may die. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited type of VaD.
- Lewy body dementia (LBD), which includes dementia associated with Parkinson's disease, is characterized by protein aggregates called Lewy bodies that form inside nerve cells in the brain.
- Creutzfeldt-Jakob disease (CJD) is caused by infectious abnormal proteins, but some forms appear to have a genetic basis.
- Huntington's disease is caused by excessive repeats of a specific DNA sequence in the gene encoding a protein



Colored magnetic resonance imaging scan of the brain of a 76-year-old patient with dementia. The brain has shrunk and the ventricles (dark brown spaces in the center) have become enlarged. (Zephyr/Science Source)

called huntingtin. Huntington's disease is characterized by abnormal, uncontrolled movements and dementia, usually beginning between the ages of 30 and 40. It is an autosomal dominant trait, which means that the children of a parent with Huntington's disease have a 50% risk of developing the disorder.

Although most dementias, especially those that are at least partially inherited, are progressive neurodegenerative diseases that ultimately end in death, some dementias—especially those caused by outside agents such as heavy metals, alcoholism, overuse of certain drugs, or infectious diseases—may be reversible. In addition to heredity and environmental factors, dementias can be caused by abnormalities in the structure of the brain, tumors, brain trauma or injury, blood collecting beneath the membrane that covers the brain (subdural hematoma), depression, thyroid dysfunction, and niacin or vitamin B₁₂ deficiency.

AD, FTD, and certain rarer types of dementia are characterized by abnormal clumps called beta-amyloid plaques and bundles of fibers called neurofibrillary tangles. The plaques are sticky clumps or clusters of dead and dying neurons and other cellular debris surrounding insoluble deposits of beta-amyloid. The latter are fragments of a larger protein called amyloid precursor protein (APP) that has not been properly processed. These plaques are situated between neurons and are believed to

interfere with normal communication between neurons, eventually causing the nerve cells to die. Neurofibrillary tangles are accumulations of twisted fragments of tau proteins inside neurons. Tau proteins normally bind and stabilize neurons. When tau proteins are damaged by the addition of phosphate, a process called hyperphosphorylation, they form filaments that twist around each other to form neurofibrillary tangles that can no longer stabilize the neurons. Increased beta-amyloid may cause the formation of neurofibrillary tangles; however, it is not known whether the plaques and tangles cause AD and other dementias or are the result of them. Plaques and tangles occur as part of the normal aging process but are far less prevalent in normal brains. As increasing numbers of neurons die and nerve cell connections are disrupted, areas of the brain that are essential for memory and learning are destroyed, followed by areas responsible for language and reasoning. Eventually many areas of the brain atrophy (become shrunken and dysfunctional).

Genetic profile

AD is believed to most often be caused by a combination of genetic and environmental factors. Most cases of AD are late-onset, developing after ages 60–65, and more than 75% of patients have no family history of the disease. About 25% of AD cases are familial, with patients having family histories of AD. They may have inherited AD susceptibility or risk genes from their parents and/or share environmental or lifestyle risk factors with family members. Familial AD may be either early-onset or late-onset. Many other dementias share genetic factors, as well as symptoms, with AD. AD, FTD, VaD, and LBD—the four most common types of dementia—all involve genes associated with abnormal tau protein and/or brain inflammation. AD, VaD, and LBD are all thought to involve genes that produce amyloid protein. LBD and dementia associated with Parkinson's disease are believed to involve genes associated with alpha-synuclein, a protein that aggregates in Lewy bodies.

Early-onset AD

Early-onset AD develops between the ages of 30 and 60 and can be caused by inheriting one of three defective genes. Variant alleles or mutations in any of these three genes result in the production of abnormal proteins that can directly cause familial early-onset AD. Because these genes are located on chromosomes other than the X and Y sex chromosomes, they are called autosomal genes and affect males and females with equal frequency. A defective version of one of these genes, inherited from one parent, can cause AD even if a normal version of the same gene is inherited from the other parent. Therefore, the defective gene is described as dominant, and AD

caused by one of these defective genes is known as autosomal dominant Alzheimer's disease (ADAD). Each child of a parent with one of these defective genes has a 50% risk of inheriting the gene and AD. If both parents have one copy of the mutant gene, each of their children has a 75% chance of inheriting at least one copy of the gene. Parents carrying two copies of the mutant gene will pass on the defective gene to all of their offspring.

All three of the abnormal proteins produced by these early-onset AD genes increase the amount of beta-amyloid in the brain.

- Mutations in the *APP* gene, located on chromosome 21, are associated with AD onset between the ages of 55 and 60, which is sometimes called AD1.
- Variations or mutations in the presenilin-1 (*PS-1*) gene on chromosome 14 are the most common cause of early-onset AD, sometimes referred to as AD3. PS-1 may be one of the enzymes that cuts APP into beta-amyloid. It also may be important for the functioning of synaptic connections between neurons.
- AD4 is an extremely rare genetic defect in the presenilin-2 (*PS-2*) gene located on chromosome 1. Presenilin 2 is involved in processing APP.

AD-causing mutations in these “deterministic” genes are very rare, accounting for less than 5% of AD cases. They do not appear to be involved in late-onset AD. Since mutations in these genes account for only about 50% of early-onset familial AD, there are presumed to be other as-yet-unidentified genes associated with early-onset AD.

Early-onset AD is also associated with Down syndrome—a genetic disorder caused by the presence of part or all of an extra chromosome 21. People over age 40 with Down syndrome develop the brain changes characteristic of AD. This is thought to be due to the overproduction of APP caused by the *APP* gene on the extra chromosome 21. Down syndrome-associated AD accounts for less than 1% of all AD cases.

Late-onset AD

As of 2021, 25 different genes had been associated with late-onset AD. It is expected that many more associated genes will be identified in the future. The presence of specific versions of these genes or mutations in these genes may increase the risk of late-onset AD.

The gene with the strongest influence on AD is the apolipoprotein E (*APOE*) gene located on chromosome 19. Familial late-onset AD associated with the *APOE* gene is sometimes called AD2. The *APOE* gene codes for a protein that helps remove cholesterol from the blood. There are three common versions of *APOE*:

APOE-2, *APOE-3*, and *APOE-4*. *APOE-2*, which is relatively rare, may provide some protection against AD. *APOE-3*, the most common *APOE* variant, does not appear to affect AD risk. *APOE-4* occurs in 10%–15% of the population and in 40%–60% of all people with late-onset AD. People who inherit an *APOE-4* gene from one parent are at increased risk for AD; those who inherit two copies of *APOE-4*—one from each parent—are at higher risk for AD. *APOE-4* may also cause AD at a younger-than-average age. Nevertheless, many people with one or two copies of *APOE-4* do not develop AD, and many people with AD do not have an *APOE-4* gene.

Other genes with variant alleles that have been associated with AD risk include the following:

- *BINI*, which encodes a protein that interacts with tau protein
- *CLU*, which helps regulate clearance of beta-amyloid from the brain
- *PICALM*, which is involved in communication between neurons
- *SORL1*, which is involved in regulating the transport of APP and lipoproteins
- *CRI*, which encodes a protein that, when deficient, may contribute to chronic inflammation in the brain, which may be a factor in AD
- *TREM2*, which is involved in regulation of the response to inflammation in the brain

Frontotemporal disorders

Frontotemporal disorders account for up to 10% of all dementias. Tau aggregates are present in some FTD cases and are associated with mutations in the *MAPT* (“microtubule-associated protein tau”) gene that produces tau protein. Other types of FTD exhibit aggregates of a protein called TDP-43. Abnormal TDP-43 protein is found in people with an inherited form of amyotrophic lateral sclerosis (ALS), a motor neuron disease that may be accompanied by frontotemporal dementia. Mutations affecting the protein progranulin may also be involved in some cases of TDP-43-related FTD. Yet another FTD that runs in families is associated with a variant of the *TREM2* gene. FTDP-17 is a rare form of dementia that is believed to be caused by an autosomal dominant mutation in a *MAPT* gene that is inherited from one parent. A mutation in the *TREM2* gene is common in people with a very-early-onset FTD that occurs in some Turkish families.

Vascular dementia

Although most cases of VaD are related to high blood pressure and other vascular problems, CADASIL is an

early-onset, autosomal dominant dementia inherited from one parent. It is caused by mutations in the *NOTCH3* gene that thickens the walls of small and medium blood vessels, slowing blood flow to the brain.

Creutzfeldt-Jakob disease

Although CJD is caused by an infectious protein called a prion, researchers believe that 5%–15% of cases may have a genetic component. These include Gerstmann-Sträussler-Scheinker disease and fatal familial insomnia, which is characterized by degeneration of areas of the brain that are important for sleep.

Demographics

It is estimated that more than 15% of North Americans older than age 65—and 40% of those older than 80—have dementia. However, it can be difficult to determine the specific type of dementia, and many people may have more than one type.

AD, the most common cause of dementia in the elderly, accounts for 50%–70% of dementias and 75% in people over age 65. As of 2021, an estimated 6.5 million Americans were living with AD—6.2 million of them aged 65 and older. In 2014, AD was an underlying cause of death for an estimated 700,000 Americans aged 65 and over. If current trends in AD incidence and life expectancy continue, it is estimated that by 2050, 12.7 million Americans aged 65 and over will have AD. Although two-thirds of Americans with AD are female, this is generally attributed to their longer life expectancy. African Americans and Latino Americans have higher rates of both AD and vascular disease than other racial and ethnic groups.

The incidence of AD in other developed countries with aging populations is similar to that in the United States. The risk of AD doubles every five years after age 65, to almost 50% in people over 85. Furthermore, AD is both underdiagnosed and misdiagnosed, at least until its later stages. It is estimated that at least half of affected people are unaware of their disease.

Signs and symptoms

Common symptoms of dementia include the following:

- Weakening of the memory with regard to learning new information as well as recalling previously learned information
- Aphasia or the loss of language function, including the frequent use of vague words such as “it” or “thing,” echoing what others say, repeating words or phrases over

and over, or not speaking at all in the later stages of dementia

- Apraxia or loss of the ability to perform intentional movements, such as brushing one's teeth or tying one's shoelaces
- Agnosia or loss of the ability to recognize objects or even family members or one's own face reflected in a mirror
- Problems with abstract thinking and complex behavior and loss of the ability to plan, carry out the steps of a task in the proper order, make appropriate decisions, evaluate situations, or show good judgment, such as lighting a stove burner with nothing in the pan or being unable to record checks and balance a checkbook.

The following sections focus on signs and symptoms that can differentiate among the various types of dementia.

Alzheimer disease

Dementia related to AD often progresses slowly, but at different rates in different people. In early stages, short-term memory loss may be accompanied by irritability, wide mood swings, and personality changes. In second-stage AD, the patient typically gets easily lost, is disoriented with regard to time and space, and may become angry, uncooperative, or aggressive. Language difficulties develop, and daily tasks may become difficult. Late-stage AD patients require constant supervision. Those who can rise from bed may wander aimlessly, although muscle stiffening may make walking difficult. Patients are often unable to reason or demonstrate appropriate judgment. They may become uninhibited and confrontational. They may experience delusions or hallucinations. In final-stage AD, patients are completely bedridden, have lost control over bowel and bladder functions, and may be unable to eat or swallow. The risk of seizures increases. Death usually results from an infection or malnutrition.

Frontotemporal dementia

Frontal lobe dementias are gradual in onset. The first symptoms often include socially inappropriate behavior (rude remarks, sexual acting-out, and poor personal hygiene). Patients are often obsessed with eating and may put nonfood items in their mouths, as well as make frequent sucking or smacking noises. In the later stages, the patient may develop muscle weakness, twitching, and delusions or hallucinations.

Vascular dementia

In early-stage VaD, patients tend to retain their personality more fully than with AD. This type of dementia often progresses in a stepwise fashion; that is, the patient shows rapid changes in functioning, and then remains at a plateau for a time rather than showing a

continuous decline. The symptoms may also have a "patchy" quality; that is, some of the patient's mental functions may be severely affected, whereas others are relatively undamaged. Other symptoms can include exaggerated reflexes, an abnormal gait (manner of walking), loss of bladder or bowel control, and inappropriate laughing or crying. CADASIL can first appear in people as young as 20–40.

Lewy body dementia

LBD may combine some features of AD, such as severe memory loss and confusion, with certain symptoms associated with Parkinson's disease, including stiff muscles, a shuffling gait, and trembling or shaking of the hands. Visual hallucinations may be one of the first symptoms of LBD.

Creutzfeldt-Jakob disease

CJD occurs most often in people between the ages of 40 and 60. It is typically preceded by a period of several weeks in which the patient complains of unusual tiredness, anxiety, loss of appetite, or difficulty concentrating. This type of dementia generally progresses much more rapidly than other dementias, usually over a span of a few months.

Diagnosis

Dementia may be diagnosed by a patient's primary physician; in many instances, however, the patient will be referred to a neurologist or a specialist in geriatric medicine. The differential diagnosis of dementia is complicated because of the multiple possible causes, because more than one cause may be present, and because dementia can coexist with other conditions such as depression or delirium. Delirium is a temporary disturbance of consciousness marked by confusion, restlessness, inability to focus one's attention, hallucinations, or delusions. In elderly people, delirium is frequently a side effect of surgery, medications, infectious illnesses, or dehydration. Delirium can be distinguished from dementia because delirium usually comes on fairly suddenly (in a few hours or days) and may vary in severity—it is often worse at night. Dementia develops much more slowly, over a period of months or years, and the patient's symptoms are relatively stable. It is possible to have delirium and dementia at the same time. It is also important to distinguish between dementia and age-associated memory impairment (AAMI). Older people with AAMI have a mild degree of memory loss, they do not learn new information as quickly as younger people, and they may take longer to recall a certain fact or to balance their checkbook. However, they do not suffer the degree of memory impairment that characterizes dementia, and they do not get progressively worse.

KEY TERMS

Age-associated memory impairment (AAMI)—A condition in which an older person suffers some memory loss and takes longer to learn new information; AAMI is distinguished from dementia in that it is not progressive and does not represent a serious decline from the person's previous level of functioning.

Agnosia—Loss of the ability to recognize objects by use of the physical senses.

Allele—Any of the alternative versions of a gene that are present in the population.

Alpha-synuclein—A protein that forms aggregates in nerve cells in certain types of dementia.

Alzheimer's disease (AD)—A progressive neurodegenerative disease characterized by loss of function and death of nerve cells in several areas of the brain, leading to mental deterioration; the most common cause of dementia.

Amyloid precursor protein (APP)—A protein that forms beta-amyloid in the brain when it is not properly broken down; mutations in the *APP* gene can cause early-onset familial Alzheimer's disease.

Aphasia—Loss of previously acquired ability to speak or understand written or spoken language.

Apolipoprotein E (APOE)—A protein that transports cholesterol and helps remove it from the bloodstream; the gene encoding one form of this protein, *APOE-4*, is associated with an increased risk of late-onset Alzheimer's disease.

Apraxia—Impairment of the ability to make purposeful movements without paralysis or loss of sensation.

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a nonsex chromosome is required for a disease or inherited trait to develop in an individual.

Beta-amyloid plaques—Dead or dying nerve cells and cell debris surrounding deposits of beta-amyloid protein in the brain; excess plaques are diagnostic of Alzheimer's disease.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)—An inherited type of vascular dementia.

Creutzfeldt-Jakob disease (CJD)—A degenerative disease of the central nervous system caused by an abnormal protein called a prion.

Delirium—A disturbance of consciousness marked by confusion, difficulty paying attention, delusions, hallucinations, or restlessness; it can be distinguished from dementia by its relatively sudden onset and variation in the severity of the symptoms.

Frontotemporal disorders (FTD)—Various types of dementia that affect the frontal and temporal lobes of the brain; FTDP-17 is a rare inherited FTD.

Hematoma—An accumulation of blood, often clotted, in a body tissue or organ, usually caused by a break or tear in a blood vessel.

Huntington's disease—A midlife-onset inherited disorder characterized by progressive dementia and loss of control over voluntary movements.

Lewy body dementia (LBD)—A common progressive form of dementia in which protein aggregates called Lewy bodies form in neurons.

Mental status examination (MSE)—An evaluation of the ability to communicate, follow instructions, recall information, and complete movement and coordination tasks, as well as emotional state and general sense of space and time.

Neurofibrillary tangles—Accumulations of twisted tau protein fragments inside nerve cells in the brain that are diagnostic of Alzheimer's disease.

Parkinson's disease—A nervous system disease, most common in people over 60, and characterized by a shuffling gait, trembling of the fingers and hands, muscle stiffness, and possibly dementia.

Presenilins (PS-1; PS-2)—Proteins involved in processing amyloid precursor protein; mutations in the genes encoding these proteins can cause early-onset familial Alzheimer's disease.

Tau—A protein involved in maintaining the internal structure of nerve cells; tau is damaged in Alzheimer's disease and forms neurofibrillary tangles.

Vascular dementias (VaD)—Dementias caused by damage to blood vessels in the brain.

Although skilled physicians can diagnose probable AD with 90% accuracy, a definitive diagnosis is only possible by examination of brain tissue after death. Beta-amyloid plaques and intraneuronal neurofibrillary

tangles normally occur with age but are greatly increased in AD. The plaques and tangles are similar regardless of whether the AD is sporadic, familial early-onset, familial late-onset, or Down syndrome-related. The

further the disease has progressed, the smaller the brain at death.

Patient history

The doctor will begin by taking a full history, including the patient's medical history, occupation, and educational level. The occupational and educational history allows the examiner to make a more accurate assessment of the extent of the patient's memory loss and other evidence of intellectual decline. In some cases, occupational history may indicate exposure to heavy metals or other toxins. A complete medical history allows the doctor to assess possibilities such as delirium, depression, alcohol-related dementia, dementia related to head injury, or dementia caused by infection. It is particularly important for the doctor to have a list of all the patient's medications, including over-the-counter preparations, because of the possibility that the patient's symptoms are related to drug side effects.

Mental status examination

A mental status examination (MSE) evaluates the patient's ability to communicate, follow instructions, recall information, and perform simple tasks involving movement and coordination, as well as emotional state and general sense of space and time. The MSE includes the doctor's informal evaluation of the patient's appearance, vocal tone, facial expressions, posture, and gait, as well as formal questions and instructions. A common form that has been used since 1975 is the Folstein Mini-Mental Status Examination or MMSE. Questions that are relevant to diagnosing dementia include asking the patient to count backward from 100 by 7s, to make change, to name the current president, to repeat a short phrase after the examiner, to draw a clock face or geometric figure, and to follow a set of instructions involving movement (e.g., "Show me how to throw a ball" or "Fold this piece of paper and place it under the lamp on the bookshelf"). The examiner may test abstract reasoning ability by asking the patient to explain a familiar proverb or test judgment by asking about a problem with a common-sense solution, such as what one does when a prescription runs out.

Neurologic examination

A neurologic examination includes an evaluation of the patient's cranial nerves and reflexes. The cranial nerves govern the ability to speak as well as sight, hearing, taste, and smell. The patient will be asked to stick out the tongue, follow the examiner's finger with the eyes, raise the eyebrows, and so on. The patient is also asked to perform certain actions (e.g., touching the nose with the eyes closed) that test coordination and spatial orientation.

QUESTIONS TO ASK YOUR DOCTOR

- How is early dementia distinguished from normal age-associated memory impairment?
- What types of dementia am I at risk for?
- Should I have genetic testing for dementia risk genes?
- Should my family members undergo genetic testing?
- Are there other tests for hereditary dementia?
- Are there treatments for hereditary forms of dementia?

The doctor will usually touch or tap certain areas of the body, such as the knee or sole of the foot, to test the patient's reflexes. Failure to respond to the touch or tap may indicate damage to certain parts of the brain.

Laboratory tests

Blood and urine samples are collected to rule out causes of dementia such as thyroid deficiency, vitamin deficiency, heavy metal poisoning, liver disease, HIV infection, syphilis, anemia, medication reactions, or kidney failure. A lumbar puncture (spinal tap) may be done to rule out neurosyphilis.

Diagnostic imaging

A CT (computed tomography) scan or MRI (magnetic resonance imaging) may be used to detect evidence of strokes, disintegration of the brain tissue in certain areas, blood clots or tumors, a buildup of spinal fluid, or bleeding into the brain tissue. PET (positron-emission tomography) or SPECT (single photon emission computed tomography) imaging is not used routinely to diagnose dementia, but it may be used to rule out AD or FTD if a patient's CT scan or MRI is unrevealing.

Genetic testing

Genetic testing is available for some genes associated with dementia, including early-onset AD genes, *APOE*, and *NOTCH3*, which causes CADASIL. Most experts do not recommend *APOE* gene testing because people with *APOE-4* do not necessarily develop AD and people without *APOE-4* may develop the disease. Furthermore, there is no preventive or effective treatment for AD. In some cases, genetic testing for early-onset AD may be

appropriate; for example, for advanced planning or for diagnosis and ruling out other causes of the symptoms.

Treatment and management

Most dementias, including hereditary forms, are irreversible. There are no “magic bullets” that can slow or stop the progression of dementias such as AD, FTD, VaD, or LBD. Medications can ease symptoms such as depression, anxiety, sleep disturbances, and psychosis. Dementia patients are more susceptible to the side effects of medications, especially psychoactive drugs, and are usually given lower doses. Physicians often recommend first trying to reduce behavioral symptoms with changes to the patient’s environment. LBD appears to respond better to treatment with newer antipsychotic medications than to treatment with older drugs such as haloperidol (Haldol). Cholinesterase inhibitors—galantamine, rivastigmine, and donepezil—are prescribed for mild-to-moderate AD and may delay some symptoms or prevent them from worsening for a limited time. They may also help control some behavioral symptoms. Acetylcholine is a neurotransmitter that is important for memory and thinking. Cholinesterase inhibitors increase the amount of acetylcholine in the brain by preventing its breakdown. However, as AD progresses, the brain produces less and less acetylcholine, and the drugs become ineffective. Memantine is an N-methyl D-aspartate (NMDA) antagonist that lowers the amount of glutamate in the brain, since excess glutamate can cause brain cell death. Memantine is used to delay the progression of some symptoms of moderate-to-severe AD. It may help patients maintain some activities such as toileting for a bit longer. However, all of these drugs are ineffective for many patients.

Patients in the early stages of dementia can often remain at home with help from family members or other caregivers, especially if the home can be fitted with safety features (handrails, good lighting, locks for cabinets containing dangerous products, nonslip treads on stairs, etc.). Patients in the later stages of dementia usually require skilled care in a nursing home or hospital.

Prognosis

Most common dementias, including hereditary forms, progress with a gradual deterioration in functioning. Although there is considerable variation in the rate of disease progression, symptoms continue to worsen, usually over a period of years. Eventually, loss of brain cells and brain damage result in the impairment of autonomic body functions, the failure of various organ systems, coma, and death. Most AD patients die within 8–10 years of diagnosis, although survival can be as

short as one year or as long as 20 years. The life expectancy of AD patients is increasing because the disease is generally being diagnosed at an earlier stage. Infection is the most common direct cause of death in AD patients. People with AD are often in poor health and may be malnourished, which puts them at increased risk for life-threatening infections such as pneumonia. They are also susceptible to other conditions and diseases of old age. The consequences of cancer, stroke, and heart disease can be more severe in patients with AD than in otherwise healthy people.

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Alzheimer’s Association, 225 N. Michigan Ave., Fl. 17, Chicago, IL 60611-7633, (800) 272-3900, (312) 335-8700, (866) 699-1246, info@alz.org, <http://www.alz.org>

Alzheimer’s Disease Information and Referral Center, National Institute on Aging, NIA Information Center, 31 Center Drive, MSC 2292, Bethesda, MD 20892, (800) 438-4380, (301) 496-1752, adear@nia.nih.gov, <https://www.nia.nih.gov/health/alzheimers>

Alzheimer’s Disease International, 57A Great Suffolk St., London SE1 0BB, UK+44 20 79810880, +44 20 79282357, info@alz.int.org, <https://www.alzint.org/>

National Institute of Mental Health. Science Writing, Press, and Dissemination Branch, 6001 Executive Blvd., Rm. 6200, MSC 9663, Bethesda, MD 20892-9663, (866) 615-6464, (301) 443-4279, <http://www.nimh.nih.gov>

National Institute of Neurological Disorders and Stroke. NIH Neurological Institute, PO Box 5801, Bethesda, MD 20824, (800) 352-9424, (301) 496-5751, <http://www.ninds.nih.gov>

Rebecca J. Frey, PhD
and Margaret Alic, PhD

Dent disease

Definition

Dent disease is a rare X-linked recessive genetic disease that adversely affects the kidneys of male patients. First described in 1964 by Charles Enrique Dent (1911–1976), a British physician, and his colleague M. Friedman, the disease is marked by dysfunction of the proximal tubules of the kidney. As of 2021, Dent disease was classified in two forms: Dent disease 1, with symptoms primarily related to kidney function; and Dent disease 2, with additional symptoms that include mild intellectual disability, poor muscle tone (hypotonia), and eye problems. Dent disease 1 is the more common of the two forms.

Description

A renal tubular disorder, Dent disease causes elevated levels of calcium in the urine, low levels of phosphorus in the blood, leakage of small proteins into the urine, weak bones, renal dysfunction, and kidney calcification. Consequently, the disorder causes damage to the proximal tubules of the kidneys (the portion of the duct system of the nephron leading from Bowman's capsule to the loop of Henle). Such damage eventually results in progressive kidney dysfunction (the inability of the kidneys to excrete the products of metabolism from the blood) and ultimately to kidney failure.

Patients with Dent disease 1 may experience such symptoms of the disease as abdominal cramps, bloody urine (hematuria), kidney stone formation, pain on passage of the kidney stones, bone pain, and weakening of the bones in early childhood; or they may have mild symptoms that are not correctly diagnosed until the early adult years. In many cases of Dent disease 1, progressive loss of kidney function leads to end-stage renal disease (ESRD) by the middle adult years (30s to 50s).

Patients with Dent disease 2 typically have mild visual disturbances, low muscle tone, and a risk of intellectual disability in addition to the progressive kidney insufficiency and abnormal laboratory findings (particularly hypercalciuria) characteristic of Dent disease 1.

Genetic profile

Dent disease is inherited in an X-linked recessive pattern; both genes associated with the disorder are located on the X chromosome, which means that a male inheriting a defective gene from his mother will manifest the disorder because he lacks a second X chromosome with a normal gene. A female inheriting a mutated gene for Dent disease will be a carrier but will not develop symptoms of the disorder herself.

The gene responsible for Dent disease 1 is *CLCN5*, which encodes a kidney-specific voltage-gated chloride channel. The other gene, which is responsible for Dent disease 2, is *OCRL* (also called *OCRL1*; short for oculocerebrorenal syndrome of Lowe), which encodes a phosphatidylinositol 4,5-bisphosphate (PIP2) 5-phosphatase. Some researchers think that Dent disease 2 may be a mild variant of Lowe syndrome, which is also caused by mutations in the *OCRL* gene, and which is also characterized by kidney dysfunction and visual impairments. The major difference between Dent disease 2 and Lowe syndrome is the presence of behavioral disorders, an increased risk of epilepsy, and mild to severe intellectual impairment in the latter.

In 60% of cases, Dent disease is caused by inactivating mutations in the *CLCN5* gene. *CLCN5* is a member of the chloride channel (CLC) family of chloride ion channels and ion transporters (*CLCN1*–*CLCN7*, and *CLCKa* and *CLCKb*). These CLCs play important roles in the control of volume, migration, proliferation, and differentiation of cells, along with the regulation of acidity levels. *CLCN5* is located on the short arm of the X chromosome at Xp11.22; has a coding sequence of 2238-bp, which consists of 12 exons that span approximately 30 kilobases of genomic DNA (deoxyribonucleic acid); and encodes a 746 amino acid protein (CLC-5).

In 15% of cases, the disorder is associated with mutations in the *OCRL* gene, located on the long arm of the X chromosome at Xq25. In the remaining 25% of cases, the genetic cause of the disorder was unknown as of 2021.

Demographics

Dent disease is an extremely rare disorder. About 250 cases of Dent disease 1 and 25 cases of Dent disease 2 have been reported in the medical literature since the disorder was identified in 1964. One estimate is that Dent disease affects one male in every 500,000. It is thought that the disease may be underdiagnosed because its symptoms are similar to those of other kidney disorders and because some patients have relatively mild symptoms.

As far as is known, Dent disease appears in all races and ethnic groups worldwide. It is possible, however, that symptom profiles may vary somewhat between Western and Asian populations. A group of Japanese researchers reported in 2014 that their patients diagnosed with Dent 2 as well as Dent 1 disease showed a wider range of symptom severity than their counterparts in European and American case reports.

Signs and symptoms

Symptoms in males may appear at any time from early childhood through the early adult years. Early

KEY TERMS

End-stage renal disease (ESRD)—A potentially fatal condition that occurs when the kidneys can no longer effectively filter urine and excrete waste products from the body.

Hypercalciuria—Abnormally high levels of calcium in the urine.

Idiopathic—Referring to a disease of unknown origin or arising spontaneously.

Ion channel—A transmembrane protein that transports ions across a plasma membrane in the direction of their concentration (electrochemical) gradient; also called ion pump.

Ion transporter—A transmembrane protein that transports ions across a plasma membrane against the direction of their concentration (electrochemical) gradient.

Kidneys—A pair of body organs whose primary function is to produce urine.

Lowe syndrome—A rare X-linked recessive disorder characterized by congenital eye disorders as well as renal tubular dysfunction, and caused by mutations in the same gene as Dent disease 2.

Nephrocalcinosis—An abnormal increase in calcium levels in kidney tissue.

Nephrolithiasis—The medical term for the process of kidney stone formation.

Osteomalacia—The medical term for bone softening in adults due to inadequate levels of dietary calcium or phosphate, or the resorption of calcium from the

bones by excessive secretion of parathyroid hormone.

Peritoneal dialysis—A form of therapy for kidney disorders that involves using the patient's abdomen (peritoneal cavity) as the site of treatment. Fluid is infused into the abdomen through a catheter and remains in the abdomen for several hours while waste products diffuse into the fluid from the abdominal blood vessels. The fluid is then removed and replaced with fresh fluid four to six times per day.

Renal—Relating to or affecting the kidneys.

Renal calculus (plural, calculi)—The medical term for a kidney stone. Kidney stones are formed from minerals dissolved in the urine.

Renal tubular disorders—Various defects in the renal tubular transport processes and their regulation.

Rickets—Defective calcification or mineralization of bones in children due to lack of vitamin D in the diet, defective metabolism of vitamin D, or insufficient calcium in the diet. The equivalent condition in adults is called osteomalacia.

Serum—The liquid part of blood.

Voltage-gated calcium channel—A type of voltage-gated (voltage-dependent) ion channel found in excitable cells (such as muscles, neurons) that are permeable to the calcium ion.

X-linked disorder—Any disorder caused by genes located on the X chromosome.

symptoms of Dent disease are similar to the indicators of rickets or calculi (stones that form in an organ or duct). In the more serious cases of Dent disease, kidney dysfunction can be an early symptom.

Although females only carry the disease rather than developing the full-blown syndrome, they may have abnormal test results on laboratory urine tests. Female carriers of Dent disease do not, however, develop kidney stones or kidney dysfunction.

The most common clinical features of the disorder in males include the following:

- **Proteinuria:** High serum proteins are present in the urine. Half the cases also result in low-molecular-weight (LMW) proteins.
- **Aminoaciduria:** Elevated levels of amino acids appear in the urine.

- **Glycosuria:** Also called glucosuria, high levels of glucose are present in excreted urine.
- **Kaliuresis:** High levels of potassium are present in excreted urine.
- **Hyperuricosuria:** Excessive levels of uric acid are present in the urine. Impaired urinary acidification: Inability to secrete acidic urine occurs.
- **Hypercalciuria:** Modest amounts of calcium are present in the urine.
- **Serum calcium:** Normal levels of calcium are present in the blood.
- **Oxalate and citrate:** Urinary oxalate and citrate levels are normal.
- **Hypophosphatemia:** Low levels of phosphorus appear in the blood.

- Low levels of parathyroid hormone (PTH) are present.
- Vitamin D: Increased levels of 1,25 vitamin D are present; medically known as calcitriol (1,25-Dihydroxycholecalciferol), which is the active form of vitamin D found in the body.
- Nephrocalcinosis: Deposits of calcium may accumulate in kidney tissue.
- Calcium nephrolithiasis: Kidney stones composed of calcium oxalate, calcium phosphate, or both, are present in about half of patients with Dent disease. The stones form from minerals dissolved in the urine.
- Osteomalacia: Indications of weak bones are present in adults with the disorder.
- Rickets: Inadequate mineralization of bones in children, which can result in fractures and limb deformities.
- Thirst. Constant and excessive thirst is often exhibited, along with frequent urination. Dehydration often results.
- Loss of appetite and unintended weight loss.

Diagnosis

Because it occurs only rarely, Dent disease is often misdiagnosed as idiopathic hypercalciuria (IH), an excess of urinary calcium without any obvious cause. It can, however, be diagnosed definitively by a combination of laboratory tests and molecular genetic testing.

Examination

During an office examination, young patients may be suspected of having Dent disease on the basis of clinical symptoms, particularly short stature, frequent urination, dehydration, anemia, fatigue, loss of appetite, weight loss, and weakened and/or painful bones and joints.

Laboratory tests

Numerous laboratory tests can be performed to help diagnose Dent disease. For instance, if the disease is present, then serum proteins in the urine will range from one to two grams per day, with the probability that low-molecular weight proteins of less than 30,000 daltons are also present. In addition, elevated levels of amino acids, glucose, potassium, and uric acid are likely to be present in the urine. The urine will often have relatively low acidity. In addition, calcium levels in the urine will range from four to six milligrams per kilogram body weight (while at the same time kidney function and serum calcium levels are normal). Oxalate and citrate levels should appear normal in the urine. However, low levels of parathyroid hormone (PTH) are present, while increased levels of vitamin D should be found.

The appearance of low-molecular-weight proteins in the urine is identified by measuring levels of two

common proteins: α 1 microglobulin and retinol binding protein.

Genetic testing

Genetic testing is often performed to identify gene mutations that are specific to Dent disease. Patients are tested for mutations within the genes *CLCN5* (Dent disease 1) and *OCRL* (Dent disease 2). Molecular testing for mutations in both genes is readily available. When a person is diagnosed with Dent disease on the basis of genetic testing, such testing may be recommended for other family members following consultation with a genetic counselor.

Treatment and management

Because the mechanisms that cause kidney scarring and eventual kidney failure are poorly understood, the treatment for Dent disease is primarily supportive, limited to reducing damage to kidney tissue and preventing or at least minimizing kidney failure. There were no standard guidelines for therapy as of 2021 because the disease was so rare that a sufficiently large sample of patients could not be recruited for clinical trials.

Reducing levels of calcium in the urine is one goal of therapy because high calcium levels are assumed to cause kidney stones and kidney calcification. Because nephrolithiasis (the formation of kidney stones) and nephrocalcinosis (calcification of kidney tissue) appear to be related to hypercalciuria (high levels of urinary calcium), treatment typically includes a thiazide diuretic (such as hydrochlorothiazide, commonly abbreviated HCTZ) to stimulate renal calcium reabsorption and reduce the amount of calcium excreted in urine. In some cases, this treatment works. However, little data have been collected as to whether thiazide diuretics reduce the numbers of kidney stones or minimize kidney problems. In addition, the use of thiazide diuretics is known to cause low levels of potassium in the blood (hypokalemia).

For osteomalacia (weak bones), vitamin D or related derivative compounds can increase bone strength. However, the use of vitamin D must be carefully monitored because its use increases the risk of high levels of urinary calcium.

For idiopathic hypercalciuria, the potassium-sparing diuretic amiloride is used. This drug increases distal tubular calcium reabsorption.

Patients with ESRD may benefit from hemodialysis, peritoneal dialysis, or kidney transplantation. Peritoneal dialysis is less efficient than hemodialysis but is a useful option in many developing countries. When patients with Dent disease undergo a kidney transplant, it has been found that nephrocalcinosis does not reoccur. Kidney

QUESTIONS TO ASK YOUR DOCTOR

- Because the disease is so rare, which professionals are most knowledgeable in the treatment of Dent disease?
- Should I or other family members undergo genetic testing for Dent disease?
- What are the optimal treatment options available?
- If my kidneys fail, will a kidney transplant help me?
- Where can I go for the latest information about research on Dent disease?

transplantation may therefore be an effective option for some patients.

Prognosis

The prognosis of Dent disease 1 is generally poor; in one study of patients diagnosed with Dent disease, 9 out of 15 men developed ESRD by age 47. In addition, decreased renal function is believed to be caused in part by infection and obstruction due to kidney stones.

Because Dent disease is so rare, most physicians have no experience with it. Consequently, in order to familiarize the medical community worldwide about Dent disease, an international registry was established at the Mayo Clinic in Rochester, Minnesota. The registry, called the Dent Disease Registry (or the International Registry for Calcium Stone Diseases), helps to increase understanding of the disease and eventually to establish guidelines for the diagnosis and treatment of the disease. In addition, this concerted effort is providing valuable information concerning Dent disease, which helps biomedical researchers and clinicians to increase knowledge.

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ORGANIZATIONS

American Association of Kidney Patients, 14440 Bruce B. Downs Blvd., Tampa, FL 33613, (800) 749-2257, (813) 636-8100, <http://www.aakp.org>

Lowe Syndrome Association, 7025 CR 46A Ste. 1071 #434, Lake Mary, FL 32746-4753, (216) 630-7723, <http://www.lowsyndrome.org>

National Kidney Foundation, 30 E. Thirty-third St., New York, NY 10016, (800) 622-9010, info@kidney.org, <http://www.kidney.org>

William Arthur Atkins BB BS, MBA
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Dentatorubral-pallidoluysian atrophy

Definition

Dentatorubral-pallidoluysian atrophy (DRPLA) is a disorder of ataxia (loss of balance), choreoathetosis (involuntary rapid, irregular, jerky movements or slow, writhing movements that flow into one another), and dementia (inability to clearly think; confusion, poor judgment; failure to recognize people, places, and things; personality changes) in adults, and ataxia, myoclonus (involuntary spasms of a muscle or muscle group), epilepsy (seizures), and loss of intellectual function (intellectual disability) in children.

The name of the disorder is derived from the names of several anatomical structures in the cerebellum and basal ganglia of the brain: "dentato-" refers to the dentate nucleus in the cerebellum, "rubral" to the red nucleus in the mid-brain, "pallido-" to the globus pallidus in the basal ganglia, and "luysian" to the subthalamic nucleus in the basal ganglia. The subthalamic nucleus is sometimes called the corpus Luysi or Luys' body, after the French anatomist Jules Bernard Luys, who first described it in 1865.

Description

DRPLA is also known as Haw River syndrome, Natito-Oyanagi disease, and myoclonic epilepsy with choreoathetosis. The typical age of onset of DRPLA is 30 years, but it can present in people as young as one year of age and

as old as 62 years of age, with differences in presentation between children and adults. In patients under the age of 20, DRPLA presents as seizures, ataxia, and myoclonus, as well as progressive (worsening) mental deterioration. In patients over the age of 20, DRPLA is suspected when a person develops ataxia, choreoathetosis, dementia, and psychiatric disturbances (delusions, hallucinations). A positive family history (a relative with similar symptoms or one already diagnosed) confirms the diagnosis.

DRPLA is sometimes initially thought to be Huntington's disease. A possible diagnosis of DRPLA can be devastating for a family to experience—their once healthy child, or young adult, will begin to have seizures, involuntary movements, loss of control over voluntary movement, and delusions—perhaps no longer being able to identify family members. Diagnosing DRPLA is complicated and requires a knowledgeable physician with expertise in both neurology and genetics. Usually an individual diagnosed with DRPLA already has a parent with the disease; however, if the disorder had not been diagnosed properly, the parent died prior to the onset of symptoms, or the parent has very late onset of the disease, there may not be a documented family history of DRPLA.

Genetic profile

DRPLA is an autosomal dominant condition, which means that both males and females are equally likely to have the disease, and an individual with the variant gene has a 50/50 chance to pass the condition to any child. The gene associated with DRPLA is known as the atrophin-1 gene or *ATN1*, and is located on the short arm of chromosome number 12 at 12p13.31. The gene has a section of DNA in which the DNA alphabet is repeated in triplets called CAG (cytosine-adenine-guanine) repeats. Normally a person has 6 to 35 CAG repeats in the *ATN1* gene. In patients with DRPLA, there are 49 to 88 repeats that cause the gene's protein product, atrophin 1, to be toxic to cells. Although scientists do not understand the exact mechanism, the number of repeats expands when the gene is transmitted from parent to child. The length of the repeat transmitted to the next generation depends upon the length of the parent's repeat and the sex of the transmitting parent.

There is an inverse correlation between the age of onset and the size of the expanded CAG repeats. In other words, the younger the age of onset, the larger the number of CAG repeats:

- Onset before age 21—repeat range of 63–69 (average of 68)
- Onset from 21 to 40 years—repeat range of 61–69 (average of 64)

- Onset after 40 years—repeat range of 54–63 (average of 63)

Although there is significant overlap, the inverse correlation exists.

DRPLA exhibits a phenomenon known as anticipation, which is found in other genetic conditions. Anticipation means that the disease increases in severity and presents at a younger age of onset with each successive generation. For example, when the CAG repeat is inherited from the father, DRPLA can manifest itself 28 years earlier in the offspring than the age at which the father began having symptoms. If transmitted from the mother, DRPLA can present 15 years earlier than in the previous generation.

Demographics

DRPLA has been reported to occur most often in the Japanese population, although it has been described in other ethnic groups, including those in Europe and North America. The prevalence of DRPLA in the Japanese population is estimated to be 2–7 in 1,000,000, which is similar to the prevalence of Huntington's disease in this population. A CAG repeat size of 17 or higher (usually 20–35) is more common in healthy Japanese individuals than in Caucasians, which may explain why DRPLA is more common in the Japanese. In other words, a larger repeat size in a parent increases the possibility that the DNA will become unstable and expand when transmitted to the next generation. Even though DRPLA is rare in the United States, five generations of an African-American family in North Carolina, where the condition is also called the Haw River syndrome, have suffered from DRPLA.

Signs and symptoms

The cardinal features of DRPLA are involuntary movements (usually in the face, neck, tongue, and hands) and dementia (inability to clearly think; confusion; poor judgment; failure to recognize people, places, and things; personality changes) regardless of the age of onset. A history of ataxia, epilepsy, and intellectual disability in children, combined with a positive family history, are often the presenting signs of this condition in an individual under 20 years of age. Seizures are always present in patients under 20, but they are not as common in patients aged 20–40 and rarely seen in patients with onset after 40. Adult-onset DRPLA (after age 20) presents with ataxia, choreoathetosis, dementia, and psychiatric disturbances. Other symptoms that have been reported include degeneration of the cornea of the eye and obstructive sleep apnea that does not respond to surgical treatment.

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman’s abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Amniotic fluid—The fluid that surrounds a developing baby during pregnancy.

Anticipation—Increasing severity in disease with earlier ages of onset in successive generations; a condition that begins at a younger age and is more severe with each generation.

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Autosomal dominant—A pattern of genetic inheritance in which only one abnormal gene is needed to display the trait or disease.

Basal ganglia—A group of small compact groups of nerve cells (called nuclei) located at the base of the forebrain. The various nuclei govern such functions as control of voluntary movements, routine behaviors, cognition, and emotion.

Cerebellum—The portion of the human brain that lies underneath the cerebral hemispheres at the back of the brain overlying the brain stem. It is responsible for the control and coordination of movement.

Choreoathetosis—Involuntary rapid, irregular, jerky movements or slow, writhing movements that flow into one another.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted through either the mother’s vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Dementia—A condition of deteriorated mental ability characterized by a marked decline of intellect and often by emotional apathy.

DNA repeats—A three-letter section of DNA called a triplet, which is normally repeated several times in a row. Too many repeats often cause the gene to malfunction, resulting in disease.

DRPLA—Dentatorubral-pallidolysian atrophy; also called Haw River syndrome and Natito-Oyanagi disease. DRPLA is a disorder of ataxia, choreoathetosis, and dementia in adults, and ataxia, myoclonus, epilepsy, and intellectual disability in children.

Epilepsy—A seizure disorder.

Myoclonus—Twitching or spasms of a muscle or an interrelated group of muscles.

Sporadic—Isolated or appearing occasionally in a population with no apparent pattern.

Diagnosis

A diagnosis of DRPLA is made when there is a positive family history of the disease, characteristic clinical findings, and DNA testing that reveals an expansion in the CAG repeat of the *ATN1* gene. Genetic testing to examine the CAG repeats in the *ATN1* gene can be performed from a small blood sample. A few reports have described DRPLA as sporadic (occurring by chance) in some families. Upon closer examination, the asymptomatic fathers had a mildly expanded CAG repeat size. Therefore, it is always important to evaluate both parents of an affected individual even if they appear to have no symptoms of DRPLA. Testing of asymptomatic children is not appropriate since it takes away the child’s right to want to know or not know this information. It also raises the possibility of stigmatization (labeling someone a certain way and making assumptions about them) within a

family, as well as the threat of educational and employment discrimination. Children *with* symptoms, however, usually benefit from having a diagnosis established.

For pregnancies at 50% risk, prenatal diagnosis is available via either CVS (chorionic villus sampling) or amniocentesis. CVS is a biopsy of the placenta performed in the first trimester of pregnancy under ultrasound guidance. Ultrasound is the use of sound waves to visualize the developing pregnancy. The genetic makeup of the placenta is identical to that of the fetus (developing baby), and therefore the *ATN1* gene can be studied from this tissue. There is approximately a 1 in 100 chance for miscarriage with CVS. Amniocentesis is a procedure done under ultrasound guidance in which a long, thin needle is inserted into the mother’s abdomen, into the uterus, to withdraw a couple of tablespoons of amniotic fluid (fluid surrounding the developing baby) to study. The *ATN1*

QUESTIONS TO ASK YOUR DOCTOR

- At what stage of a person's life do the symptoms of dentatorubral-pallidoluysian atrophy first appear?
- What treatments are available for this condition, and does the plan of treatment differ for various age groups?
- If I have an older sister with dentatorubral-pallidoluysian atrophy, what are the chances that I might develop the disorder also?
- How long does a person live after a diagnosis of dentatorubral-pallidoluysian atrophy, and what are the usual causes of death for this disease?

gene can be studied using cells from the amniotic fluid. Such other genetic tests as a chromosome analysis may also be performed with either CVS or amniocentesis. A small risk of miscarriage (1 in 200 to 1 in 400) is associated with amniocentesis.

Treatment and management

There is currently no cure for DRPLA; treatment is supportive. Epilepsy is treated with antiseizure medications. Psychiatric disturbances can be treated with appropriate psychotropic medications. Children diagnosed with DRPLA may benefit from special education programs tailored to their individual needs.

Prognosis

The prognosis for DRPLA is poor, as there was no cure as of 2021. Patients with DRPLA have progressive disease, which means symptoms become worse over time. The average duration of the disease is 13 years, followed by death due to difficulty swallowing and bronchopneumonia following increasingly severe seizures. The patient's lifespan is reduced by the disease, although a few patients have been reported to live as long as 60 years.

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ORGANIZATIONS

National Ataxia Foundation (NAF), 600 Highway 169 South, Suite 1725, Minneapolis, MN 55426, (763) 553-0020, naf@ataxia.org, <http://www.ataxia.org>

National Institute of Neurological Disorders and Stroke (NINDS), PO Box 5801, Bethesda, MD 20824, (301) 496-5751, (800) 352-9424, <http://www.ninds.nih.gov>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

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Deoxyribonucleic acid see **DNA (deoxyribonucleic acid)**

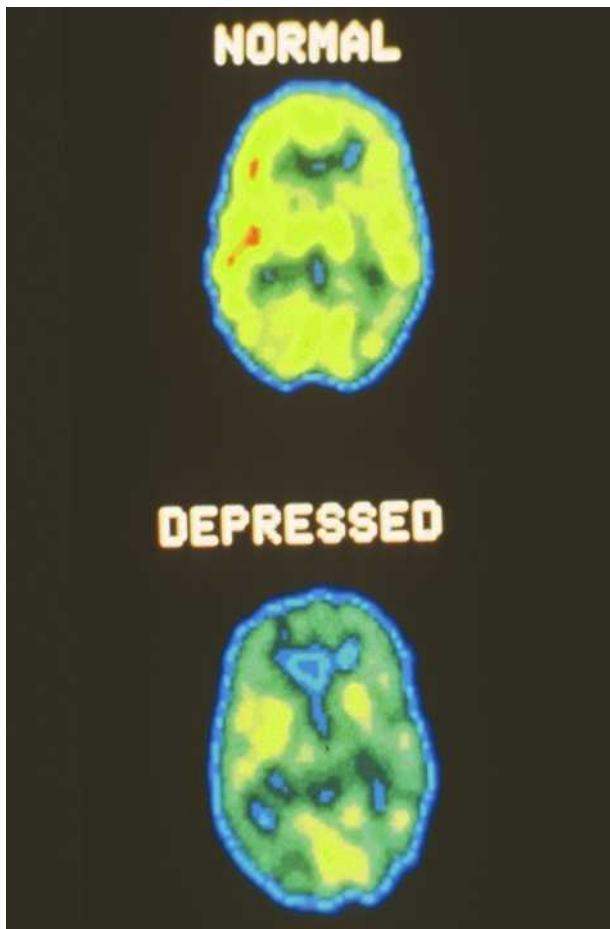
Depression

Definition

Depression is the general name for a family of illnesses known as depressive disorders. It affects not only the mood and thoughts but also the physical functions of affected individuals. Depressive disorders usually result from a combination of genetic, environmental, and psychological factors. The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, text revision (DSM-V) defines a major depressive episode (MDE) as a period of two weeks or longer during which there is either depressed mood or loss of interest or pleasure (anhedonia), and at least four other symptoms that reflect a change in functioning, such as problems with sleep, eating, energy, concentration, and self-image.

Description

Everyone feels sadness, grief, or despair at some point in their lives. However, unlike these normal, transient emotional states, a depressive disorder is not a temporary bout of "feeling down" but rather a serious illness



PET scans comparing a normal human brain (top) to the brain of a person suffering from depression. (*Science Source*)

that should be recognized and treated as a medical condition. Without treatment, a depressive disorder can persist, and its symptoms can go on for weeks, months, or years. The three most common types of depression are dysthymic disorder, major depression, and bipolar disorder.

Depression is quite widespread and one of the leading causes of disability in the world. Commonly recognized symptoms of all types of depressive disorders are recurring feelings of sadness and guilt, such changes in sleeping patterns as insomnia or oversleeping, changes in appetite, decreased mental and physical energy, unusual irritability, the inability to enjoy once-favored activities, difficulty in working, and thoughts of death or suicide. If only these “down” symptoms are experienced, the individual may suffer from a unipolar depressive disorder such as dysthymia or major depression. If the depressed periods alternate with extreme “up” periods characterized by unusual energy levels, the individual may have a bipolar disorder.

Dysthymic disorder is a relatively mild depressive disorder that is characterized by the presence of two or more of the symptoms listed above. The symptoms are not severe enough to disable the affected individual, but they are long-term (chronic) and may last for several years. Individuals affected by dysthymic disorder often experience episodes of major depression at some point in their lives.

In cases of major depression, the affected individual has five or more symptoms and experiences one or more prolonged episodes of depression that last longer than two weeks. These episodes can render the person unable to function. Individuals experiencing an episode of major depression often entertain suicidal thoughts, which make this disorder very serious. Some individuals affected by major depression may experience only a single bout of disabling depression in their lifetimes. More commonly though, affected individuals experience recurrent disabling episodes throughout their lives.

Bipolar disorder, formerly called manic depression or manic-depressive illness, is not nearly as common as major depression and dysthymia. It is associated with alternating periods of extreme excitement (mania) and periods of extreme sadness (depression). The rate of the transition between cycles is usually gradual, but the mood swings may also be severe and dramatically rapid. When in the depressive state, affected individuals may show any or all of the common symptoms of depression. In the manic state, they may feel restless and unnaturally elated, have an overabundance of confidence and energy, and be very talkative. Mania can distort social behavior and judgment, causing the affected individual to take excessive risks and perhaps make imprudent decisions that can have humiliating or damaging consequences. Without medical treatment, bipolar disorder may progress into psychosis.

One subset of depressive disorder is seasonal affective disorder (SAD), in which the person loses energy, sleeps a great deal, tends to overeat, and shows other symptoms associated with depression during a specific season (most often the winter, but there are also patients who experience SAD during the summer months) but has consistent mental health the rest of the year. SAD is also called the winter blues, summer sadness, or seasonal depression.

Depressive disorders are believed to be related to imbalances in brain chemistry, particularly in relation to the chemicals that carry signals between brain cells (neurotransmitters), as well as the hormones released by parts of the brain. Serotonin and norepinephrine are two important neurotransmitters. Disruption of the brain’s circuits in areas involved with emotions, appetite, sexual drive,

and sleep is a likely cause of the dysfunctions associated with depressive disorders. Thus, some treatments for depression are drugs that are known to have an effect on brain chemistry.

Genetic profile

Depression is known to be genetically linked, because it often runs in families and has been studied in identical twins, but only a few specific risk genes for depression have been identified. In 2003, a group of researchers in Salt Lake City identified a gene known as *MDD1* (for major depressive disorder type 1) on the long arm of chromosome 12 at 12q22-q23.2, but little is known about this gene. In 2004, a second gene, known as *MDD2* (for major depressive disorder type 2), was identified on the long arm of chromosome 15 at 15q25.3-q26.2, but as with *MDD1*, little is known about this gene, and there are no molecular genetic tests for it.

Other genes that have been linked to susceptibility to depression include the *TPH2* gene on the long arm of chromosome 12 at 12q21.1, which codes for a protein primarily active in the brainstem and may be linked to bipolar disorder as well as major depressive disorder, and the *FKBP5* gene on the short arm of chromosome 6 at 6p21.31, which codes for a protein involved in regulating the immune system. Molecular genetic testing is available for both of these genes. A third gene, *HTR2A*, is located on the long arm of chromosome 13 at 13q14.2. *HTR2A* encodes one of the receptors for the neurotransmitter serotonin, and mutations in this gene have been linked to susceptibility to seasonal affective disorder as well as susceptibility to major depression. Molecular genetic testing is also available for this gene.

There is some evidence for convergence of linkage findings across studies, but more data are needed. Research directions include more intensive, systematic studies of linkage candidate regions and of the whole genome for accurate genetic association. According to the National Institute of Mental Health (NIMH), genetic studies of depression are now focusing on the common biological pathways (processes) that are shared by such different disorders as depression, bipolar disorder, and schizophrenia—particularly disorders that have a common age of onset. These pathways include communication between neurons and changes in the immune system. Researchers think that a better understanding of the common biological pathways affected by risk genes for various mental illnesses may yield more effective treatments than focusing on identifying and characterizing the risk genes themselves.

Genome-wide association studies (GWASs) have identified more than 80 loci associated with depression,

eight of which are unique to depression, do not overlap with other mental health disorders, and have been independently replicated. As with other complex, polygenic medical and psychiatric disorders that are phenotypically heterogeneous (they present differently), the challenge is to identify the genetic variants that are causally related to major depressive disorder. The challenge is further compounded by the observations that depression has many different causes and that many people who suffer from depression also have co-occurring mental conditions. Pleiotropy, when a genetic variant influences two or more phenotypes, also makes it harder to pinpoint specific genetic variants. GWASs have found considerable genetic overlap between depression and other mental disorders.

There are also many non-genetic factors that cause depression, including stressful environmental conditions and life events, certain illnesses, maladaptive coping patterns, and such precipitating conditions as persistent unemployment, exposure to major disasters or other traumatic events, and the loss of a close relationship. Alcohol abuse and the use of sedatives, barbiturates, narcotics, or other drugs can cause depression due to the effects of these substances on brain chemistry.

Demographics

Worldwide, depression affects more than 300 million people, and it is the most common cause of disability in people under age 60. According to the most recent (2019) statistics available from the Centers for Disease Control and Prevention (CDC), nearly 5% of the American population over the age of 18 report current depression. In every age group, women report higher rates of depression than men. Although the average age at onset of a major depressive episode is 32, the highest rates of depression for both sexes are in the 40–59 age bracket (12% for women and 7% for men), with both older and younger adults reporting somewhat lower rates. On average, eight million Americans per year receive a primary diagnosis of major depressive disorder when they seek treatment from primary care physicians, hospital emergency departments, and outpatient mental health clinics.

The National Institute of Mental Health (NIMH) confirms that many people suffer from more than one mental disorder at a given time. Nearly half (45%) of those with any mental disorder meet criteria for two or more disorders.

That women experience depression at a rate that is almost twice that of men may be partially explained by the greater willingness of women to seek psychological treatment, but this factor does not explain the entire discrepancy. Many physical events specific to women, such

as menstruation, pregnancy, miscarriage, the postpartum period, and menopause, are recognized as factors contributing to depression in women. Women in the United States may face environmental stressors with a higher frequency than men. For example, most single-parent households are headed by women; women still provide the majority of child and elder care, even in two-income families; and women are generally paid less than men, so their financial concerns may be greater.

Particular demographic problems associated with the disorder include depression in the elderly, children, and adolescents. One common belief is that depression is normal in older adults. This is not so, although increasing age, the side effects of medications taken by older adults for treatment of physical problems, and the loss of interpersonal relationships are associated with depression. Because of this misconception, depressive disorders in older adults are often overlooked, undiagnosed, and untreated. Similarly, many parents often ignore the symptoms of a depressive disorder in their children, assuming that these symptoms are merely a developmental phase that the child will outgrow.

Signs and symptoms

Individuals affected with depressive disorders display a wide range of symptoms, which vary in severity from person to person and over time in a single affected individual.

Symptoms that characterize a depressive state include feelings of hopelessness, guilt, or worthlessness; a persistent sad or anxious mood; restlessness or irritability (more common in men); anhedonia (loss of interest in activities that were once considered pleasurable); difficulty concentrating, remembering, or making decisions; sleep disorders, including insomnia, early morning awakening, and/or oversleeping; constant fatigue; eating disorders, including weight loss, loss of appetite, or overeating; suicidal thoughts and/or tendencies; and persistent physical symptoms that do not respond to normal treatments of these symptoms, such as headaches, digestive problems, and chronic pain.

Symptoms that characterize a manic state include increased energy accompanied by a decreased need for sleep, a loss of inhibitions accompanied by inappropriate social behavior, excessive enthusiasm and verve, increased talking, poor judgment, a feeling of invincibility, grandiose thinking and ideas, unusual irritability, and increased sexual desire.

Symptoms that characterize seasonal affective disorder include difficulty waking in the morning; overeating, particularly heavy, carbohydrate-rich foods; weight gain; difficulty concentrating on or completing tasks; social

withdrawal; irritability; and decreased sex drive. In contrast to MDD, however, the symptoms of SAD are limited to a particular season of the year and usually remit during the rest of the year.

Diagnosis

Depression is notoriously difficult to diagnose, because its symptoms are not readily apparent to the medical professional unless the patient first recognizes and admits to them. Once the individual seeks help for his or her symptoms, the first step in the diagnosis of a depressive disorder is a complete physical examination to rule out any medical conditions, viral infections, or medications that may produce the effects also seen in depression. Laboratory tests that may be ordered include a complete blood count (CBC), liver function tests, blood urea nitrogen (BUN) and creatinine test, HIV test, tests to measure electrolyte levels, tests to measure thyroid hormone levels, and the rapid plasma reagin (RPR) test for syphilis.

Alcohol or other drug abuse as a possible cause of the observed symptoms should also be investigated; this investigation is usually accomplished with a blood and urine toxicology screen and a blood alcohol test. If the doctor suspects that an organic brain disorder may be the cause of the patient's symptoms, a CT scan or MRI may be ordered; however, imaging studies cannot be used in isolation to diagnose depression.

Once a physical basis for these symptoms is eliminated, a complete psychological exam should be undertaken. This examination consists of a mental status examination, a complete history of current and previously experienced symptoms, and a family history.

The mental status examination is used to determine the presence of a more severe psychotic condition. This mental status examination will also determine whether the depressive disorder has caused changes in speech or thought patterns or memory that may indicate the presence of a depressive disorder. The complete psychological exam also includes a comprehensive history of the symptoms experienced by the affected individual. This history includes the onset of the symptoms, their duration, and whether or not the affected individual has had similar symptoms in the past. In the case of past symptoms, a treatment history should be completed to assess whether these symptoms previously responded to treatment, and if so, which treatments were effective. The final component of the complete psychological exam is the family history. In cases in which the symptomatic individual has had similarly affected family members, a treatment history should also be completed (to the extent possible) for these family members.

Most patients suffering from depression are seen first by a primary care physician rather than a psychiatrist. There are questionnaires and self-report instruments that physicians who are not specialists in psychiatry can use to evaluate a patient who appears to have the symptoms of a mood disorder. These include the Beck Depression Inventory, the Zung Self-Rating Depression Scale, the Geriatric Depression Scale (which has also been found useful in younger adults), and the Patient Health Questionnaire (PHQ) nine-item scale for depression. The simplest screener is a two-question test: (1) During the past month, has the patient been troubled by feeling “down,” depressed, or hopeless? (2) During the past month, has the patient been troubled by losing interest or pleasure in his or her usual activities? Although these screeners and self-report inventories are not a substitute for a formal psychiatric evaluation, they can guide the patient’s primary care physician in making a needed referral to a psychiatrist.

The diagnostic criteria for a major depressive episode (MDE), according to DSM-5, are as follows:

A. Five or more of the following symptoms must be experienced for at least two weeks and must represent a change in functioning. At least one symptom is either depressed mood or loss of interest or pleasure. The doctor is instructed to exclude symptoms that are clearly related to a general medical condition, as well as delusions or hallucinations.

- Depressed mood nearly every day, as reported either by the patient or by others. In children and adolescents, this symptom may be primarily irritability.
- Marked loss of interest or pleasure in activities most of the day or nearly every day, as reported either by the patient or by others.
- Significant weight loss when not dieting, or a weight gain of more than 5% of body weight, or a noticeable decrease or increase in appetite nearly every day.
- Insomnia or hypersomnia (oversleeping) nearly every day.
- Agitation or psychomotor retardation nearly every day that is observable by others.
- Fatigue or significant loss of energy nearly every day.
- Feelings of worthlessness or guilt most days (not feelings of self-reproach or guilt for being sick). These feelings may be delusional.
- Indecisiveness or inability to concentrate on tasks, as reported either by the patient or by others, nearly every day.
- Recurrent thoughts of death (not simply fear of dying); thoughts of suicide, with or without a plan for

committing suicide; a specific plan for committing suicide; or an actual suicide attempt.

B. The symptoms cause considerable distress and impairments in social, educational, or occupational functioning.

C. The symptoms are not due to the direct effects of a substance (prescription medication, alcohol, or drug of abuse) or a general medical condition.

Treatment and management

Treatment of depression is done on a case-by-case basis and largely depends on the outcome of the psychological examination. Some mildly affected individuals respond fully to psychotherapy and do not require medication. Others with moderate or severe depression benefit from antidepressant medications. Most affected individuals respond best to a combination of antidepressant medication and psychotherapy: the medication to provide relatively rapid relief from symptoms of depression, and psychotherapy to learn effective ways to manage and cope with problems and issues that may cause the continuation of symptoms or the onset of new symptoms of depression.

Various types of antidepressant medications are available for the treatment of depressive disorders. Many individuals affected by depression will go through a variety of antidepressants, or antidepressant combinations, in a kind of trial-and-error comparison, before the best medication and dosage for them is identified. Almost all antidepressant medications must be taken regularly for at least two months before the full therapeutic effects are realized. A full course of medication is generally no shorter than six to nine months to prevent recurrence of the symptoms. In individuals affected with bipolar disorder or chronic major depression, medication may have to be continued throughout the remainder of their lives. These time-related conditions often pose problems in the management of individuals affected with depressive disorder. Many individuals who have a depressive disorder discontinue their medications before the fully prescribed course for a variety of reasons. Some experience side effects of the medications prior to feeling any benefits, and others think that the medication is not helping because of the delay between the initiation of the treatment and the feelings of symptom relief, and they many feel better prior to the full course and so cease taking the medication.

Three commonly prescribed antidepressant drug classes consist of the older tricyclics (TCAs) and two other drug classes: the selective serotonin reuptake inhibitors (SSRIs) and the monoamine oxidase inhibitors (MAOIs). The most common TCAs are amitriptyline (Elavil), clomipramine (Anafranil), desipramine (Norpramin, Pertofrane), doxepin (Sinequan, Adapin), imipramine (Tofranil, Janimine),

nortriptyline (Pamelor, Aventyl), protriptyline (Vivactil), and trimipramine (Surmontil). The most common SSRIs are citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft). The most common MAOIs are phenelzine (Nardil) and tranylcypromine (Parnate).

A fourth and newer class of antidepressant medication are the serotonin-norepinephrine reuptake inhibitors, or SNRIs. These drugs work by preventing the reuptake of norepinephrine as well as serotonin and appear to be more effective than the SSRIs, as well as having better safety profiles. The SNRIs include such drugs as venlafaxine (Effexor), duloxetine (Cymbalta), and desvenlafaxine (Pris-tiq). The SSRIs and the SNRIs have largely displaced the older tricyclics and MAOIs.

Many antidepressant medications cause such side effects as agitation, bladder problems, blurred vision, constipation, drowsiness, dry mouth, headache, insomnia, nausea, nervousness, or sexual problems. Most of these side effects subside as the treatment course progresses. The tricyclics cause more severe side effects than the newer SNRIs, SSRIs, or MAOIs.

In the most severely affected individuals, or those for whom antidepressant medications either have not worked or cannot be taken, electroconvulsive therapy (ECT) may be considered. In the ECT procedure, electrodes are put on specific locations on the head to deliver electrical stimulation to the brain. This electrical stimulation is designed to trigger a brief seizure within the brain. These seizures generally last approximately 30 seconds and are not consciously felt by the patient. ECT has been much improved in recent years; it is no longer the electroshock treatment of nightmares, and its deleterious effects on long-term memory have been reduced. ECT treatments are generally administered several times a week as necessary to control the symptoms being experienced.

Several short-term (10- to 20-week) psychotherapies have also been demonstrated to be effective in the treatment of depressive disorders. These include interpersonal and cognitive/behavioral therapies. Interpersonal therapies focus on the interpersonal relationships of the affected individual that may both cause and heighten the depression. Cognitive/behavioral therapies focus on ways in which affected individuals may be able to change their patterns of thinking or behaving that may contribute to episodes of depression. Psychodynamic therapies, which generally are not short-term psychotherapies, seek to treat the individual with a depressive disorder through resolution of internal conflicts. Psychodynamic therapies are generally not initiated until major depressive episodes have ceased or until the symptoms of depression are significantly improved by medication or one of the short-term psychotherapies.

KEY TERMS

Anhedonia—The inability to experience satisfaction or pleasure from activities or interests that the person previously enjoyed. It is a common symptom of depression.

Bipolar disorder—Formerly called manic depression, this psychological disorder is characterized by periods of mania followed by periods of depression.

Cognitive/behavioral therapies—Psychological counseling that focuses on changing the thinking and behavior of the patient.

Dysthymia—A psychological condition of chronic depression that is not disabling but prevents the sufferer from functioning at his or her full capacity.

Electroconvulsive therapy—A treatment in which a series of controlled electrical impulses are delivered to the brain in order to induce a seizure.

Grief reaction—The normal sadness felt after a traumatic major life occurrence, such as the loss of a loved one.

Interpersonal therapies—This type of psychological counseling focuses on determining how dysfunctional interpersonal relationships of the affected individual may be causing or influencing symptoms of depression.

Major depression—A psychological condition in which the patient experiences one or more disabling bouts of depression lasting two or more weeks.

Polygenic—Referring to a trait, characteristic, or condition, that depends on the activity of more than one gene for its emergence or expression.

Psychodynamic therapies—A form of psychological counseling that seeks to determine and resolve the internal conflicts that may be causing an individual to be suffering from symptoms of depression.

Psychotherapy—Psychological counseling that seeks to determine the underlying causes of a patient's depression. The form of this counseling may be cognitive/behavioral, interpersonal, or psychodynamic.

Seasonal affective disorder (SAD)—A subset of depressive disorder in which the person experiences depressive symptoms in the winter (or summer) but feels normal the rest of the year. SAD is also called the winter blues, summertime sadness, or seasonal depression.

QUESTIONS TO ASK YOUR DOCTOR

- Which medications are available for treating my family member's depression?
- Are there treatments and procedures other than medication that may be helpful in treating his or her condition?
- Are there side effects for the medications used in the treatment of depression?
- Are there changes that we can make in our loved one's lifestyle that will reduce his or her risk of depression?

Clinical trials

Clinical trials on the treatment of depression are currently sponsored by the National Institutes of Health (NIH) and other agencies. In 2021, there were more than 865 clinical trials underway for various interventions for depression in the United States alone. Some of these trials involve investigational drugs, psychological interventions using e-health and social media; the use of intermittent theta burst transcranial magnetic stimulation (iTBS); interventions that target specific subpopulations (older adults, adolescents, Hispanics, low-income patients, women in perimenopause, military personnel, women who have just given birth, people with diabetes, and cancer patients); and alternative/integrative therapies like mindfulness meditation, yoga, tai chi, and relaxation techniques.

Prognosis

More than 80% of individuals affected with a depressive disorder have demonstrated improvement after receiving the appropriate combination of treatments. However, each depressive episode increases the patient's risk of a recurrence of MDD. About half of all patients who recover from MDD will have another episode over the course of their life, and around 15% of those will develop chronic depression. The risk of recurrence is higher in patients whose symptoms did not fully resolve with treatment.

One significant tragedy associated with depression is the failure of many affected individuals to realize that they have a treatable medical condition. There have been calls for depression screening from medical professional societies, and in 2016 the U.S. Preventive Services Task Force (USPSTF) concluded, "There is a moderate net benefit to screening for depression in adults, including older adults, who receive care in clinical practices that have adequate systems in place to ensure accurate diagnosis, effective

treatment, and appropriate follow-up after screening. The USPSTF also concludes with at least moderate certainty that there is a moderate net benefit to screening for depression in pregnant and postpartum women who receive care in clinical practices that have CBT or other evidence-based counseling available after screening." Absent widespread screening for depression, only about half of patients with major depression will be identified. Some affected individuals who do not receive treatment may recover completely by themselves, but most will suffer needlessly. A small number of individuals with depressive disorder do not respond to current methods of treatment.

Resources

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ORGANIZATIONS

- American Psychiatric Association (APA), 800 Maine Avenue, SW Washington, DC 20024, (888) 357-7924, apa@psych.org, <http://www.psychiatry.org>
- Mental Health America, 500 Montgomery Street, Suite 820, Alexandria, VA 22314, (703) 684-7722, (800) 969-6642, (703) 684-5968, <https://www.mhanational.org/>
- National Alliance on Mental Illness (NAMI), 4301 Wilson Boulevard, Suite 300, Arlington, VA 22203, (703) 524-7600, (888) 999-6264, <http://www.nami.org>
- National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Bethesda, MD 20892, (866) 615-6464, (301) 443-4279, nimhinfo@nih.gov, <http://www.nimh.nih.gov>

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Diabetes

Definition

“Diabetes” is the Greek term for “passing through,” a phrase used to describe multiple distinct disorders characterized by excessive urination. Diabetes mellitus, the most common form of diabetes, is a chronic disorder of carbohydrate metabolism, characterized by the inadequate secretion or utilization of the hormone insulin and an excessive amount of sugar (glucose) in the blood and urine. Diabetes is a major cause of death in the United States and other developed countries. A multitude of different genes and gene variants (alleles) have been associated with different types of diabetes. However, the interactions of these various genes with one another and with environmental and lifestyle factors are poorly understood. Furthermore, various genes have profound effects on risk factors for diabetes, such as obesity, and on the development of various pathologies associated with diabetes. Finally, regulatory DNA sequences that turn genes

on and off, as well as modifications to individual nucleotides in DNA (known as epigenetic effects), appear to be important for the development of diabetes.

Description

The four major types of diabetes are:

- type 1 diabetes mellitus (T1D), also called insulin-dependent diabetes mellitus (IDDM)
- type 2 diabetes mellitus (T2D), also called non-insulin-dependent diabetes mellitus (NIDDM)
- gestational diabetes mellitus (GDM)
- diabetes secondary to other conditions

Diabetes mellitus

Diabetes mellitus is characterized by excessive levels of the sugar glucose in the blood, which is consequently passed through the urine. The word “mellitus” is Latin for honey. Blood glucose comes from food, the liver, and muscle cells and is used for energy by cells throughout the body. However, chronic excessive amounts of glucose in the blood cause a variety of serious health complications.

People with diabetes mellitus have excessive blood glucose because of a deficiency in the production or utilization of the hormone insulin. Insulin is made by the beta cells of the pancreas in response to elevated glucose in the blood following a meal. It binds to receptors on the body’s cells to enable the passage into the cells of glucose for energy. Insulin stimulates cells to remove glucose from the blood and stimulates the liver to metabolize glucose so that blood glucose levels remain stable. A deficiency of insulin or defective insulin utilization (called insulin resistance or insensitivity) starves cells of glucose while resulting in high blood sugar (hyperglycemia). Chronic diabetes mellitus can lead to heart disease and serious problems with the eyes, kidneys, nervous system, gums, and teeth. People with diabetes are more than twice as likely to develop heart disease or suffer strokes.

T1D was formerly called juvenile diabetes because it is usually first identified in children or young adults. It is an autoimmune disorder in which the body’s immune system attacks and destroys the beta cells of the pancreas, preventing the production and release of insulin.

T2D is the most common type of diabetes. It was formerly called adult-onset diabetes, because it usually developed in people over age 40. However, T2D is increasingly being diagnosed in children and young adults. With T2D, the body’s cells become insulin resistant and do not properly utilize the insulin being synthesized and secreted by the pancreas. In early stages, the pancreas increases insulin production in response to the increased demand. However, as the disease progresses,

the pancreas loses the ability to secrete sufficient insulin in response to meals.

GDM is a form of glucose intolerance that may develop during the late stages of pregnancy due to pregnancy hormones or insulin deficiency. It requires treatment to normalize maternal blood glucose levels and avoid complications in the infant. It usually disappears after childbirth, but women with GDM have a 20%–50% chance of developing T2D within 5–10 years. Pre-existing diabetes that is not successfully controlled before conception and during the first trimester of pregnancy may result in major birth defects in 5%–10% of pregnancies and spontaneous abortions in 15%–20% of pregnancies. If diabetes is uncontrolled during the second and third trimesters of pregnancy, dangerously high infant birth weights can result.

Prediabetes is a condition in which blood glucose levels are abnormally elevated and that may progress to T2D. It involves impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both. With IFG, the blood sugar level is elevated to between 100 and 125 milligrams per deciliter of blood (mg/dL) after an overnight fast. With IGT, the blood sugar level is

elevated to between 140 and 199 mg/dL after a two-hour oral glucose tolerance test. The risk of prediabetes progressing to T2D can be significantly reduced by moderate weight loss and physical activity.

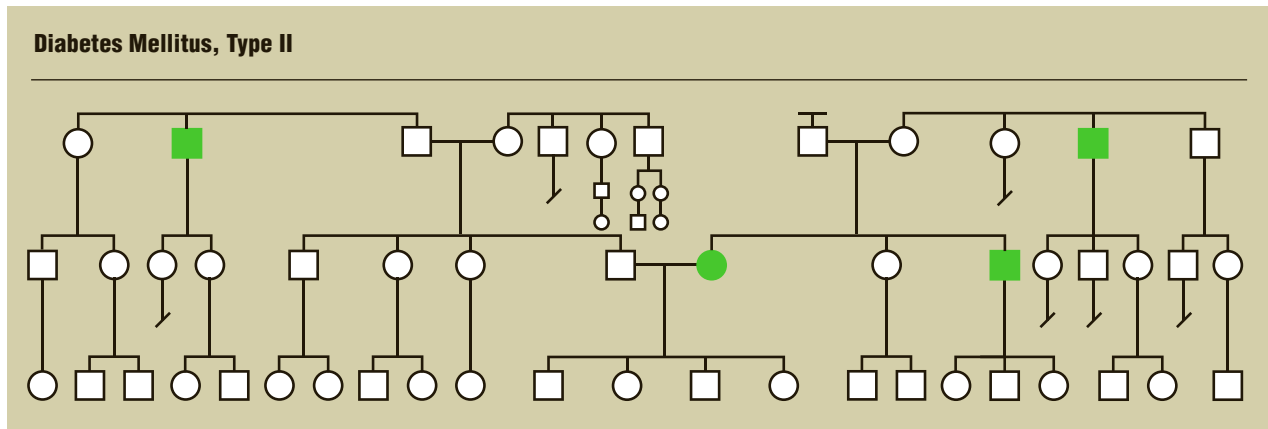
The risk of death among individuals with diabetes is approximately twice that of people without the disorder. Adults with diabetes have two to four times the increased risk for both cardiac disease and stroke. Cardiac disease and stroke are leading causes of diabetes-related mortality, responsible for 65% of deaths in people with diabetes. Approximately 73% of adults with diabetes have elevated blood pressure or use prescription medications for hypertension. Diabetic retinopathy is the leading cause of new cases of adult blindness. Approximately 60%–70% of people with diabetes have some degree of nervous system damage (neuropathy). Severe forms of diabetic neuropathy account for more than 60% of non-traumatic lower-limb amputations in the United States.

Other types of diabetes

Diabetes insipidus is caused by insufficient vasopressin (antidiuretic hormone or ADH) produced by the pituitary gland or by failure of the kidneys to respond to



Woman using a lancet on her finger to check her blood sugar level. (Bikeriderlondon/Shutterstock)



Type 2 diabetes: pedigree analysis chart (Gale)

vasopressin. This causes an abnormal amount of water to be secreted in the urine, resulting in excessive urination, thirst, weakness, and dry skin. Diabetes insipidus is often inherited, especially when it occurs in children.

Myotonic dystrophy, Friedreich's ataxia, and Wolfram's syndrome (an autosomal recessive neurodegenerative disorder that includes diabetes insipidus, diabetes mellitus, and deafness, among other problems) are a few of the other hereditary disorders that involve diabetes.

Genetic profile

Type 1 and type 2 diabetes mellitus are complex polygenic disorders, and although they have different causes, they may have genetic components in common. A combination of an inherited predisposition to diabetes and environmental factors appears to contribute to the development of both types, but genetic predisposition does not necessarily result in the development of diabetes.

T1D

Susceptibility or predisposition to T1D runs in families, and heritability is higher for individuals who have first-degree relatives with the disease. Identical twin studies have revealed that if one twin has T1D, the other twin has at most only a 50% chance of the disorder. It is believed that in most cases of T1D, risk factors are inherited from both parents. In general, a child of a man with T1D has a 1 in 17 chance of developing the disorder. A child born to a woman under age 25 with T1D has a 1 in 25 chance of developing the disorder, but the risk is only 1 in 100 if the mother was 25 or older when she gave birth. If both parents have T1D, their child's risk is 10%–25%. If a parent developed T1D before age 11, the child's risk of T1D is doubled. About 1 in 7 people with T1D also have a thyroid and adrenal gland condition called type 2

polyglandular autoimmune syndrome. Their children are at 50% risk of developing both disorders. As of 2021, hundreds of gene loci had been associated with risk for T1D. Among these are *IDDM 1* on chromosome 6, *IDDM 2* on chromosome 11, and *PTPN 22* with a mutation at LYP (lymphocyte-specific phosphatase gene) on chromosome 1.

T1D is considered to be an autoimmune disease in which immune-system cells damage insulin-producing beta cells. Certain variants of the genes *HLA-DQA1*, *HLA-DQB1*, and *HLA-DRB1* increase the risk of T1D. These genes belong to a gene family called the human leukocyte antigen (HLA) complex and produce proteins that help the immune system distinguish between the body's own proteins and foreign proteins such as those from bacteria and viruses. Researchers have, however, focused on the HLA (human leukocyte antigen) complex on chromosome 6p21, because it contributes about 50% of the genetic risk for T1D. There are many different alleles or variations in these genes, and certain combinations of these alleles are associated with an increased risk for an autoimmune response to beta cells and the development of T1D. These combinations account for about 40% of the genetic risk for T1D. Nevertheless, only about 5% of people with these combinations develop T1D. Other HLA alleles, called protective haplotypes, appear to help protect against T1D.

The *INS* gene, located on chromosome 11, produces insulin. Certain alleles in the *INS* gene may contribute to susceptibility to T1D and T2D. The associated T1D risk has been localized to a region flanking the *INS* gene that contains a short sequence of DNA that is tandemly repeated many times. The number of repeats varies among individuals, called variable number tandem repeats (VNTRs). There are three classes of VNTRs in the insulin gene. Class I includes alleles with 26–63

repeat units, class II includes alleles with approximately 80 repeats, and class III has alleles with 141–209 repeats.

Class I alleles account for 70% of the VNTR alleles. Almost all other alleles are class III. Class I VNTRs are most common in Caucasians, who have the highest rate of T1D. Class III alleles are protective against diabetes. The presence of at least one class III allele is associated with a threefold reduction in the risk of T1D. Class III VNTR alleles are associated with higher levels of insulin in the thymus. The thymus gland has an important role in training the immune system to not attack the body's own cells. Immature immune cells called T cells are presented with chains of amino acids, such as insulin, to recognize as "self." Any T cells that respond to or bind to these chains are deleted to prevent autoimmunity. Because the longer VNTRs result in more insulin in the thymus, the detection and deletion of these autoreactive T cells may be more efficient, improving immune tolerance to insulin and reducing the risk of T1D.

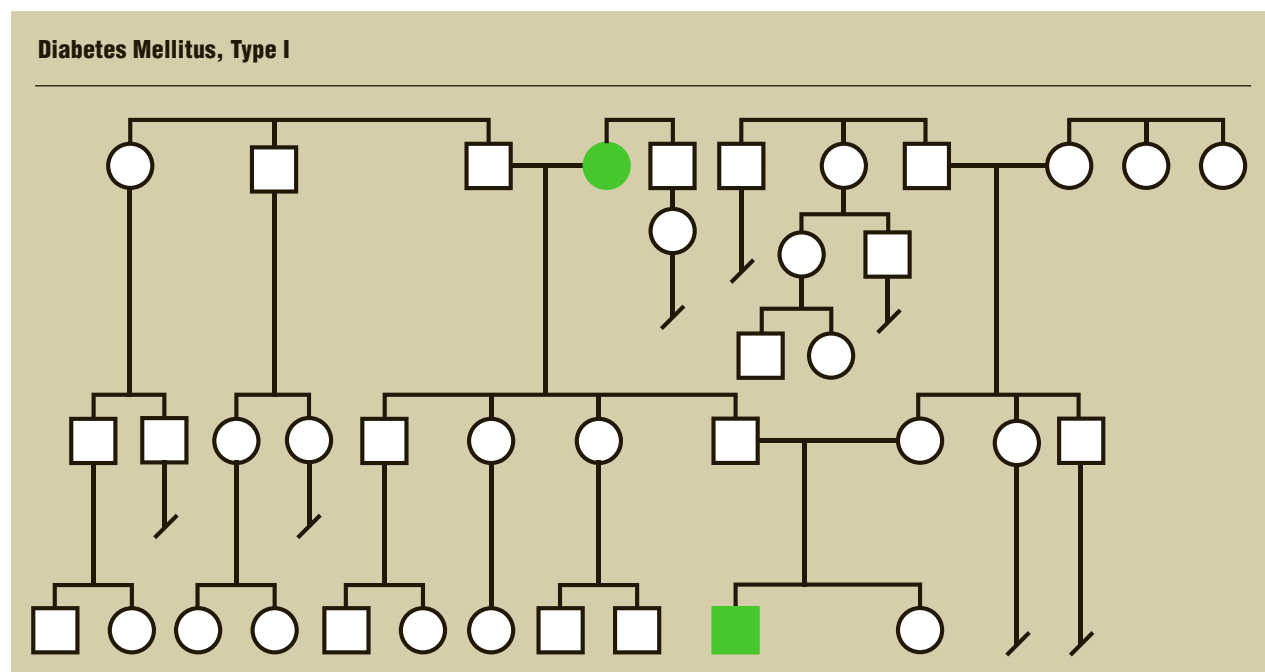
Most people who carry risk genes for T1D do not develop the disorder. Therefore, it is likely that environmental triggers are also involved. These triggers may include the following:

- cold weather, since T1D is more common in cold climates and develops more frequently during winter months
- diet in early life, since T1D is less common in children who were breastfed and started eating solid food at a later age
- viruses

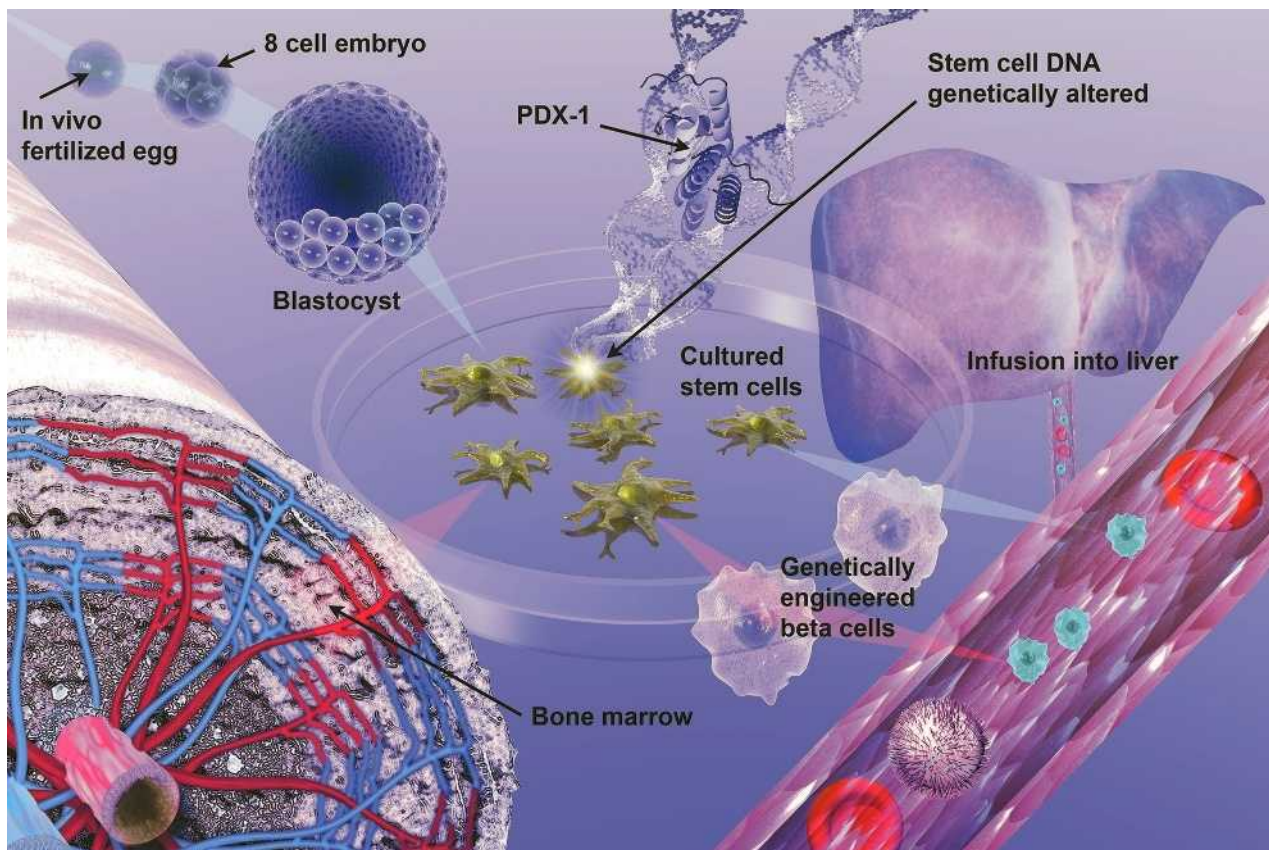
T2D

T2D is more strongly linked to genetic inheritance than T1D. T2D tends to run in families because families tend to share environmental factors such as diet and exercise. Furthermore, obesity is a major risk factor for T2D and is, at least in part, inherited. T2D can also cause obesity. If one identical twin has T2D, the other twin has a 75% chance of also developing T2D. In general, children have a 1 in 7 chance of developing T2D if a parent was diagnosed with T2D before age 50, and a 1 in 13 chance if the parent was diagnosed after age 50. If both parents have T2D—or if one parent has a rare type called maturity-onset diabetes of the young (MODY)—a child's risk of T2D is about 1 in 2.

More than 150 DNA variations have been identified as associated with T2D, but in most cases their contribution to the disorder is unknown. It is believed that each of these many gene variants may make a small contribution to the risk of developing T2D by interacting with various environmental factors. T2D-associated genes include *ABCC8*, which is involved in insulin secretion and production of glucose; *GLUT2*, which aids in transporting glucose into the pancreas; and *GCGR*, which is involved in regulating glucose. Other genes associated with T2D include *KCNJ11*, *TCF7L2*, *PPARG*, *FTO*, *NOTCH2*, *WFS1*, *IGF2BP2*, *SLC30A8*, *JAZF1*, and *HHEX*. *KCNJ11* encodes a potassium channel on the surface of beta cells, and variations in the *KCNJ11* gene



Type 1 diabetes: pedigree analysis chart (Gale)



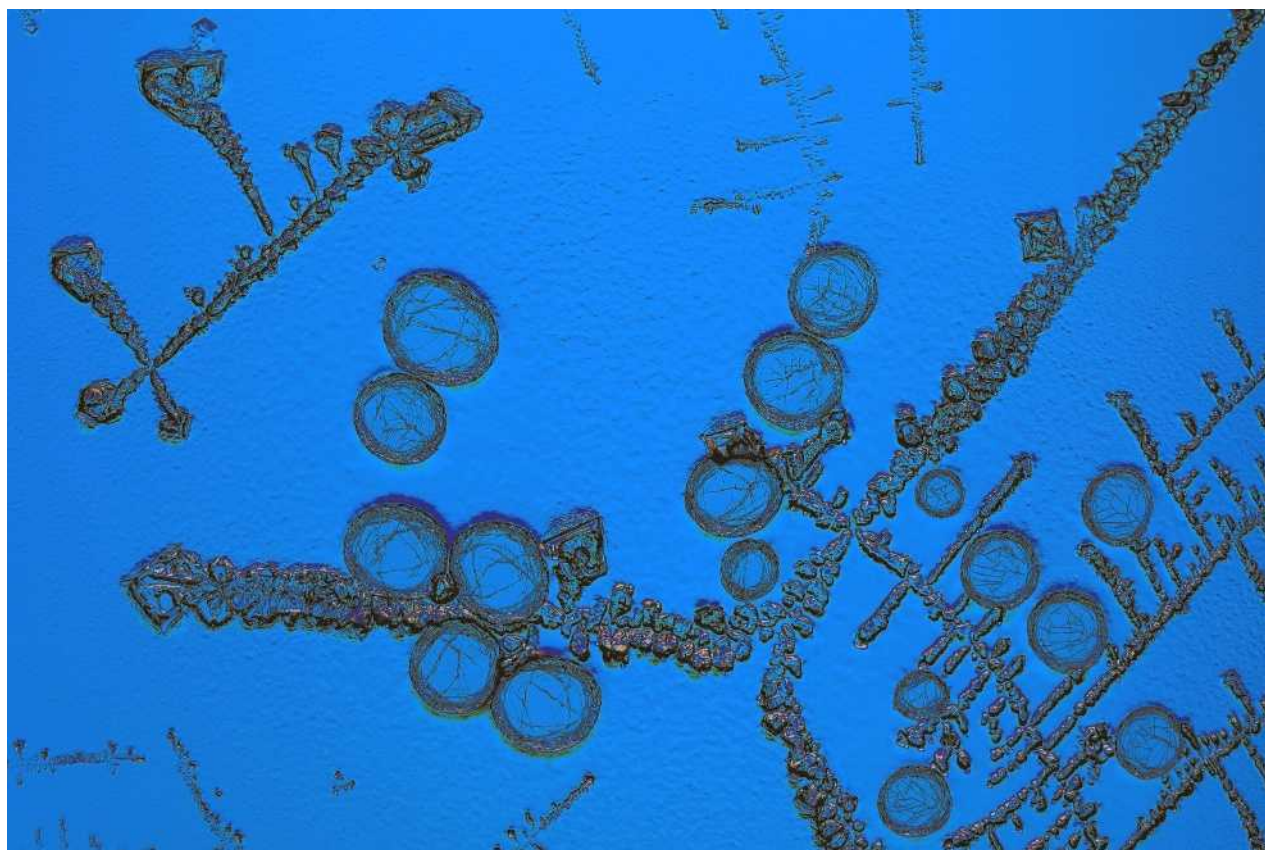
Genetic therapy for diabetes. Stem cells can be harvested from human embryonic material (upper left) or from bone marrow (lower left). Researchers engineer islet cells by adding genes that stimulate cell proliferation, but because such cell lines no longer produce insulin, the cell lines are further engineered to express the beta islet cell gene, *PDX-1*, which stimulates the expression of the insulin gene. The genetically engineered beta cells are infused into the liver where they begin to produce insulin. (Carol And Mike Werner/Science Source)

have been associated with both decreased and increased insulin release. *TCF7L2* regulates the production of glucagon-like peptide-1. T2D-associated genes may have only subtle variations called single nucleotide polymorphisms (SNPs) that are extremely common in populations, and it is very difficult to link these common gene variations with an increased risk of developing diabetes. Many of the links that have been found seem to be important in only certain ethnic or geographical populations:

- The *CAPN10* gene produces calpain-10, a calcium-activated enzyme that breaks down proteins. SNPs in part of the *CAPN10* gene are associated with a threefold increased risk of T2D in Mexican Americans. It is thought that these genetic variants of *CAPN10* may alter pancreatic beta cell survival, insulin production, insulin action, and liver glucose production. In European, Japanese, and Samoan populations, *CAPN10* does not appear to play an important role.
- Lipoprotein lipase (LPL) is an enzyme that breaks down triglycerides. It is functionally impaired or present at low

levels in many people with T2D, and evidence suggests that insulin may help regulate LPL synthesis. One common complication of T2D is protein excreted in the urine because of chronic inflammation and kidney damage. There is a correlation between the severity of this complication and genetic variation in the *LPL* gene. SNPs in the *LPL* gene are associated with insulin resistance in Mexican Americans. The same variation is associated with coronary artery disease and may provide some of the linkage between diabetes and atherosclerosis.

- PPARgamma (peroxisome proliferator activated receptor gamma) is a transcription factor that regulates fat cell development. Variations in the *PPARG* gene influence the risk of developing obesity and T2D. The Pima Indians of Arizona, a population with a high incidence of T2D, have several SNPs in the *PPARG* gene. Other SNPs in the gene confer a degree of protection against insulin resistance and obesity.
- A nonsense mutation in the *TBC1D4* gene is associated with T2D in Greenland.



Light micrograph of insulin crystals. Endogenous human insulin is a polypeptide hormone produced by the β -cells of pancreatic islets. Insulin controls the cellular uptake, use, and storage of glucose, fatty acids, and amino acids, and inhibits the breakdown of proteins, glycogen, and fats. Insulin also plays important roles in somatic growth, cell proliferation, and adiposity. The secretion of insulin to increase the blood sugar level (and of glucagon to decrease it) is the primary mechanism of glucose homeostasis. The disease diabetes mellitus occurs when regulation of glucose levels is lost due to the destruction of β -cells (type 1 diabetes) or when body tissues develop an inability to react to insulin (type 2 diabetes). To treat type 1 diabetes, several forms of insulin are synthesized using recombinant DNA technology. (Antonio Romero/Science Source)

- In 2015, researchers reported strong associations between the risk of T2D in African-American and Hispanic-American women and variations in magnesium-related ion channel genes. T2D risk varied with the amount of magnesium intake.
- Some genetic factors also affect and predict responses to diabetes treatment. For example, diabetes caused by mutations in the *HNF1A* gene responds strongly to sulfonylurea drugs.

Nevertheless, diet, weight, and other as yet unconfirmed environmental factors are very important for the development of T2D. The majority of individuals with T2D are overweight or obese. As people migrate from regions of the world where the incidence of T2D is low to regions where the incidence is high, they develop the T2D epidemiological pattern of their adopted countries. Furthermore, T2D is increasing throughout Asia with increases in wealth and the adoption of Western-style diets.

Monogenic diabetes

Cases of monogenetic diabetes are rare cases that develop because of a mutation in a single gene. Monogenic diabetes includes MODY, which accounts for 1%–5% of diabetes in young people, as well as Donohue syndrome and Rabson-Mendenhall syndrome among others. MODY is inherited in an autosomal dominant pattern, meaning that only one mutant gene, inherited from one parent, is required to develop diabetes, even when the other copy of the gene inherited from the other parent is normal. Mutations in the *INS* gene that result in abnormal insulin cause rare forms of diabetes, including a type similar to MODY caused by an abnormal insulin, called Chicago insulin, which also is inherited in an autosomal dominant pattern. A mutation in the gene encoding islet amyloid polypeptide causes an earlier-onset and more severe type of diabetes. Mutations in the *INSR* gene that encodes the insulin receptor can also cause rare types of diabetes and may be involved in susceptibility to T2D.

The *HNF4A* gene encodes a transcription factor that is found in the liver and pancreas and is associated with T2D. *HNF4A* mutations cause a rare form of autosomal dominant diabetes. SNPs in *HNF4A* have an impact on beta cell function, increasing or decreasing insulin secretion. In the British population, individuals with SNPs that cause increased insulin secretion have a reduced risk for diabetes. In Ashkenazi Jewish and Finnish populations, four SNPs near the *HNF4A* gene have been identified as associated with T2D via an unknown mechanism that may cause pancreatic beta cell malfunction.

Rarely, mutations in mitochondrial DNA cause monogenic forms of diabetes, including various forms of MODY and maternally inherited diabetes and deafness (MIDD). Mitochondrial genes are always inherited from mothers. MIDD appears to be caused by a defect in insulin secretion.

Demographics

The incidence of diabetes has been increasing at a significant rate in most parts of the world. As of 2018, an estimated 34.2 million people in the United States—10.5% of the population—had diabetes. Of these, 7.3 million—21.4%—were undiagnosed. More than one quarter (26.8%) of U.S. adults age 65 and older had diabetes. There were 88 million Americans over age 18 who had prediabetes in 2018. T2D accounts for 90%–95% of all diabetes cases.

T1D affects nearly 1.6 million American children and adults, according to the Centers for Disease Control and Prevention (CDC). Although Caucasians are at highest risk for T1D, they have a lower incidence of T2D than other ethnic groups. Native Americans and Alaskan natives have the highest diagnosed diabetes rates in the United States, at almost 15% of their populations. Diabetes affects nearly 12% of non-Hispanic blacks, 12.5% of Hispanics, 9.2% of Asian Americans, and only 7.5% of non-Hispanic whites.

Signs and symptoms

Both T1D and T2D often develop over many years without symptoms. The symptoms of T1D, however, usually come on suddenly with extreme hyperglycemia, characterized by increased thirst, especially for sweet beverages; increased urination; weight loss despite increased appetite; nausea or vomiting; abdominal pain; fatigue; and absence of menstruation in females. T2D symptoms are similar and may also include blurred vision, frequent or slow-healing infections (including urinary tract, vaginal, and skin infections), dry and itchy skin, tingling or numbness in the hands or feet, and erectile dysfunction in men.

Diabetes affects multiple organ systems and can result in many complications. Diabetic ketoacidosis (DKA) is a complication of diabetes caused by the buildup of byproducts of fat metabolism called ketones. Ketone buildup occurs when glucose is not available as a fuel source. Ketones accumulate in the blood and are present in the urine. DKA develops when ketone levels are high enough to cause the blood to acidify. In response, the liver begins releasing glucose to use as an energy source instead of fatty acids. Because the cells cannot take in this glucose in the absence of insulin, blood glucose levels are further elevated. DKA may be the first symptom of T1D or a sign that insulin doses must be increased. In T1D, DKA also can result from infection, trauma, heart attack, or surgery. DKA is less common with T2D and usually develops incidentally under conditions of severe stress. Recurrent episodes of DKA with T2D are usually the result of poor compliance with treatment or diet. The symptoms of DKA may include the following:

- fruity breath odor
- fatigue
- appetite loss, nausea, or vomiting
- rapid deep breathing
- difficulty breathing, especially when lying down
- decreased consciousness
- mental stupor that may progress to coma
- muscular stiffness or aching
- headache
- low blood pressure

Periods of hypoglycemia or low blood sugar can occur when the balance among insulin, food intake, and physical exertion is disturbed. Symptoms of mild hypoglycemia include hunger, sweating, anxiety, and increased heart rate. Severe hypoglycemia can lead to a confused mental state, slurred speech, weakness, lack of coordination, dizziness, drowsiness, and loss of consciousness. The loss of consciousness due to low levels of blood sugar is called a hypoglycemic coma.

People with diabetes are prone to infections from even simple lacerations because of decreased immune responses. Damage to the peripheral nervous system, called diabetic peripheral neuropathy, may result in decreased blood flow and loss of sensation in the limbs. A loss of sensation in the feet can cause an infection to go unnoticed. Lack of peripheral sensation, deficient oxygen supply from decreased blood flow, and reduced immune defense put patients at risk for peripheral gangrene. Small infected cuts can progress rapidly to tissue death that may require amputation of the affected limb. Poorly controlled blood sugar also predisposes people

KEY TERMS

Allele—Any of the alternative versions of a gene that are present in the population.

Autoimmune disorder—Conditions, such as type 2 diabetes, that are caused by inappropriate immune-system activity.

Autosomal dominant—Inheritance on chromosomes other than the sex chromosomes that requires only one copy of a gene for expression of the trait.

Beta cells—The insulin-producing cells of the pancreas.

Body mass index (BMI)—A measurement based on weight and height used to categorize people as underweight, normal, overweight, or obese.

Diabetes insipidus—A disorder caused by insufficient secretion of vasopressin (antidiuretic hormone or ADH) or failure of the kidneys to respond to vasopressin, with symptoms similar to those of diabetes mellitus; it may be inherited, especially in children.

Diabetic ketoacidosis (DKA)—A life-threatening complication of diabetes mellitus.

Fasting blood glucose test (FGT)—A diabetes test that measures blood glucose after an eight-hour fast.

Gangrene—Death of tissue due to deficient or absent blood supply.

Gestational diabetes mellitus (GDM)—Diabetes that develops during pregnancy and increases the risk of type 2 diabetes.

Hemoglobin—The iron-containing pigment of red blood cells that carries oxygen.

Hemoglobin A1c (HbA1c)—A blood test that indicates average blood glucose levels over the previous two or three months.

Human leukocyte antigen (HLA)—Proteins that form the major histocompatibility complex (MHC); some common HLA alleles are associated with the development of type 1 diabetes.

Hyperglycemia—High blood sugar.

Hypoglycemia—Low blood sugar.

Insulin—A hormone encoded by the *INS* gene that is required for the metabolism of carbohydrates, fats, and proteins and that regulates blood sugar levels; lack of insulin or insulin insensitivity results in high blood sugar levels and diabetes.

Maternally inherited diabetes and deafness (MIDD)—A rare type of diabetes caused by a mitochondrial gene inherited from the mother.

Maturity-onset diabetes of the young (MODY)—A rare form of diabetes inherited in an autosomal dominant fashion. It is similar to type 2 diabetes but develops before the age of 25.

Oral glucose tolerance test (OGTT)—A diabetes test that measures blood sugar at intervals after drinking a sugary solution.

Single nucleotide polymorphisms (SNPs)—Very small genetic changes (a change in a single nucleotide of DNA) that may be linked to diabetes risk.

Transcription factor—A protein that activates specific genes.

Type 1 diabetes mellitus (T1D)—An autoimmune disorder that generally develops in childhood in which the immune system attacks and destroys insulin-producing beta cells; also called insulin-dependent diabetes mellitus (IDDM).

Type 2 diabetes mellitus (T2D)—A condition in which the body does not properly utilize glucose due to insulin resistance or decreased insulin production; also called non-insulin-dependent diabetes mellitus (NIDDM).

Variable number tandem repeats (VNTRs)—Short repeated DNA sequences; VNTRs flanking the insulin gene may be involved in susceptibility to diabetes.

with diabetes to fungal infections of the skin, nails, female genital tract, and urinary tract.

Diabetic nephropathy is kidney disease that may occur early in diabetes. Patients are prone to kidney damage from severe urinary tract infections and high blood pressure. Late-stage kidney disease may cause symptoms resulting from excessive protein in the urine. These symptoms include swelling around the eyes in the morning, swelling of the legs, unintentional weight gain from

fluid accumulation, poor appetite, fatigue, headache, and frequent hiccups.

After 15 years with diabetes, 80% of patients develop diabetic retinopathy—damage to capillary blood vessels that nourish the retina of the eye—due to the effects of poorly controlled blood sugar. Signs of diabetic retinopathy include decreased visual acuity and floating spots within the field of vision. Cataracts that cloud the lens of the eye develop slowly and painlessly, causing

increasing visual problems. The signs of cataracts include cloudy vision and difficulty with night driving due to glare from bright lights. Both diabetic retinopathy and cataracts can progress to blindness. The best defenses against severe vision loss are early detection and treatment via annual eye examinations, and maintaining control over blood sugar, blood pressure, and blood cholesterol.

Diagnosis

T2D is diagnosed by positive results on any one of the three blood tests, followed by a second positive test on a different day:

- fasting blood glucose test (FGT) with values above 126 mg/dL after eight hours of fasting on two separate occasions
- random (non-fasting) blood glucose values above 200 mg/dL, accompanied by increased thirst, urination, and fatigue, and confirmed with an FTG
- oral glucose tolerance test (OGTT) with above 200 mg/dL two hours after consuming a glucose solution for a diagnosis of diabetes or prediabetes

FGT is the preferred test. This convenient test is most reliably performed in the morning after eight hours of fasting on two separate occasions.

- FGT values of 70–99 mg/dL are considered normal.
- Fasting glucose levels of 100–125 mg/dL may indicate a form of prediabetes called impaired fasting glucose (IFG). Individuals with IFG have are at increased risk of developing T2D in the future.
- A fasting glucose level of at least 126 mg/dL in conjunction with a positive OGTT on a separate testing occasion indicates diabetes.

The OGTT requires fasting for eight hours and then drinking a solution containing 2.6 oz (75 g) of glucose dissolved in water. Blood glucose levels are measured at different times over a three-hour interval. Values below 140 mg/dL are considered normal. Values from 140 to 200 mg/dL may indicate prediabetes. Values over 200 mg/dL in conjunction with a positive FGT on a separate testing occasion indicate diabetes. GDM is diagnosed with the OGTT. Glucose levels are normally lower during pregnancy, so the threshold values for diagnosis are proportionally lower. The presence of two plasma glucose values meeting or exceeding any of the following levels indicates gestational diabetes: a fasting plasma glucose level of 95 mg/dL, a one-hour level of 180 mg/dL, a two-hour level of 155 mg/dL, or a three-hour level of 140 mg/dL.

The hemoglobin A1c (HbA1c) test is used to monitor blood sugar control over a longer period of time.

Controlled blood glucose helps to minimize the development of complications caused by chronically elevated glucose levels, such as progressive damage to body organs. The HbA1c test is an overall picture of the average amount of glucose in the blood over the previous few months. HbA1c is the term for glycosylated (glucose-carrying) hemoglobin in red blood cells. HbA1c can indicate how severe blood sugar fluctuations have been in newly diagnosed patients or may indicate the need for medication or diet adjustments. HbA1c tests may be performed several times per year. The HbA1c test does not reflect temporary acute fluctuations in blood glucose. A 1% change in HbA1c reflects a fluctuation of approximately 30 mg/dL in average blood glucose. An HbA1c value of 6% corresponds to an average blood glucose level of 135 mg/dL, whereas an HbA1c of 9% corresponds to an average blood glucose level of 240 mg/dL. The closer the HbA1c can be kept to 5% or 6%, the better the control and the lower the risk of diabetic complications.

Other tests include the following:

- urinalysis followed by a blood test for ketones and pH to diagnose DKA
- insulin levels
- C-peptide (a byproduct of insulin production) levels
- antibodies against insulin, islet cells in the pancreas, or an enzyme called glutamic acid decarboxylase, which can indicate that a child is at risk for T1D

Treatment and management

The goals of diabetes treatment are to reduce symptoms, prevent diabetes-related complications, and prolong life. General diabetes treatment includes regular doctor visits for an evaluation of general health and neurological function; HbA1c measurements several times a year to evaluate overall blood glucose control; regular evaluation of blood pressure, cholesterol, and triglyceride levels; annual eye examinations; dental examinations and cleaning every six months; daily foot inspection; and current immunizations. Diabetes education is critical to the treatment plan.

The standards of diabetes management are as follows:

- a healthy diet of fruits, vegetables, and whole grains
- physical activity and regular exercise
- monitoring carbohydrate intake
- regular blood sugar monitoring with a home kit or device
- weight control or weight loss if required
- foot care

After a diagnosis of T1D, the immediate goals are to control blood glucose levels and DKA, if present. A sudden onset of severe symptoms may require hospitalization. People with T1D must take insulin daily for life. Insulin is either injected under the skin at specified times using a syringe or administered by an infusion pump that delivers the insulin continuously. Insulin is not available as an oral medication. There are different types of insulin that vary in how quickly they work and the duration of their effects. Different types of insulin are sometimes mixed in an injection. Injections are usually self-administered from one to three times daily. T1D requires that food intake be balanced by insulin intake to prevent extreme fluctuations in blood glucose. Blood sugar must be monitored regularly. Other medications may include the following:

- pramlintide (Symlin) before eating to slow movement of food through the digestive tract and prevent spikes in blood sugar
- high blood pressure medications
- aspirin to protect the heart
- cholesterol-lowering drugs

Hypoglycemia can result from too much insulin, drinking alcohol, overexertion, or eating too little. Symptoms of low blood sugar typically appear when blood glucose levels fall below 70 mg/dL. The treatment is consuming sugar, such as fruit juice. Sugar intake should be continued until blood glucose control is achieved. Only after blood glucose has returned to normal should more substantial food be eaten. Severe hypoglycemia may require a shot of glucagon at a hospital emergency room.

Ketones can be monitored using a simple urine test available at pharmacies. Left untreated, DKA can worsen and cause death. Treatment of DKA involves lowering the blood glucose level to normal and replacing fluids lost through excessive urination and vomiting. It is often possible to recognize the early warning signs of DKA and make appropriate corrections at home before the condition progresses. If severe DKA develops, hospitalization is often required.

T2D can sometimes be controlled with by weight loss, diet, and exercise alone. Medication may include the following:

- metformin—usually the first medication prescribed—to improve insulin sensitivity and lower glucose production by the liver
- sulfonylureas to increase insulin production and secretion
- meglitinides to increase insulin release by the pancreas
- thiazolidinediones to increase insulin sensitivity
- DPP-4 inhibitors to reduce blood sugar
- GLP-1 receptor agonists to slow digestion and lower blood sugar

QUESTIONS TO ASK YOUR DOCTOR

- What is the probability that I or my children will develop diabetes?
- What type of diabetes do I have?
- Which treatments are available for my type of diabetes?
- Can you recommend an organization that can provide additional information about diabetes?
- Is there genetic testing available for diabetes susceptibility genes?

- SGLT2 inhibitors to decrease glucose reabsorption by the kidneys and increase its excretion in the urine
- insulin for some patients

People with T2D and a body mass index (BMI) greater than 35 may be candidates for weight loss (bariatric) surgery. Blood sugar levels usually return to normal after surgery, even before weight loss begins.

Prognosis

Diabetes is a chronic disease for which there is not yet a cure. The prognosis varies based on the degree of blood glucose control. Good control of blood glucose can delay or even prevent the progression of complications and secondary illnesses. Complications may occur even with good blood sugar control, but good control significantly reduces the risks for heart failure, stroke, and death. A reduction of HbA1c by 1% can improve prognosis and decrease the risk of complications by 25%. Prognosis is greatly improved by maintaining a normal BMI. A BMI of 18–24.9 is considered normal and improves diabetes prognosis. A BMI of 25–29.9 indicates overweight, and a BMI of 30 or more indicates obesity and a poor prognosis. People with diabetes have increased susceptibility and a worse prognosis for illnesses such as influenza. Smoking cigarettes significantly worsens diabetes prognosis by increasing the risk of vascular complications, gangrene, and amputations.

Promising research

Although insulin is a lifesaving treatment for many people with diabetes, it is not a cure. Intensive insulin therapy is an effective treatment for the symptoms of diabetes but it also can produce undesirable side effects such as unintended weight gain and increased risk of sharp

drops in blood sugar, which are dangerous and may be life-threatening. Sensitizing beta cells in the pancreas to insulin may protect people with diabetes from beta cell failure. In January 2021, researchers at the Helmholtz Zentrum Muenchen, the Technical University of Munich and the German Center for Diabetes Research identified a novel insulin inhibitory receptor called inceptor. Inceptor is upregulated in diabetes, and by blocking insulin signaling it likely contributes to insulin resistance. In animal studies, blocking the inceptor function in beta cells in the pancreas increased insulin signaling and increased functional beta cells. The researchers hope to use the discovery of inceptor to develop drugs to promote beta cell regeneration and essentially cure diabetes.

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ORGANIZATIONS

- American Diabetes Association, 2451 Crystal Drive, Suite 900, Alexandria, VA 22202, (800) 342-2383, askada@diabetes.org, <http://www.diabetes.org>
- National Diabetes Education Program. Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333, (800) 232-4636, <http://www.cdc.gov/diabetes/ndep/index.htm>
- National Diabetes Information Clearinghouse. National Institute of Diabetes and Digestive and Kidney Diseases, <https://www.niddk.nih.gov/health-information/diabetes>
- National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD 20892-2560, (301) 496-3583, <http://www.niddk.nih.gov>

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Diamond-Blackfan anemia

Definition

Diamond-Blackfan anemia (DBA) is a very rare and potentially life-threatening blood disorder in which the bone marrow does not produce enough red blood cells to carry oxygen to the body. Generally diagnosed in the first year of life, DBA is characterized by unusually pale skin, weakness, fatigue, and irregular heartbeat. In some cases there may also be associated birth defects of the limbs, heart, and palate.

First described in 1938 by two Boston Children's Hospital doctors, Kenneth Blackfan and Louis Diamond, DBA is also known by a number of other names including the following:

- Aase-Smith syndrome II
- Aase syndrome
- Blackfan-Diamond anemia (BDA)

- Blackfan-Diamond disease (BDD)
- Blackfan-Diamond syndrome (BDS)
- chronic congenital agenerative anemia
- congenital erythroid hypoplastic anemia
- congenital hypoplastic anemia of Blackfan and Diamond
- congenital pure red cell anemia or aplasia
- erythrogenesis imperfecta
- hypoplastic congenital anemia
- inherited erythroblastopenia

Description

DBA, like other forms of anemia, results from a decreased amount of oxygen in the blood, which causes symptoms such as weakness, heart murmurs, pale skin, shortness of breath, and an increased risk of developing cancers such as acute myeloid leukemia (AML) and osteosarcoma (a type of bone cancer). While some people with DBA have no physical symptoms, others may have multiple birth defects, including triphalangeal thumb (TPT), a structural abnormality of the thumbs in which the thumbs are formed with three bones like the other fingers rather than two as seen in a typical thumb.

Several other physical abnormalities have been described in individuals with DBA, including narrow shoulders, hypoplastic radius (underdevelopment of one of the bones of the lower arm), heart defect, cleft lip/palate, and late closure of the fontanelles (soft spots on an infant's skull where the bones have not yet fused).

Genetic profile

The available evidence suggests DBA is inherited in an autosomal recessive fashion, meaning that an affected person has two copies of the abnormal gene. Parents of an affected individual carry one abnormal copy of that particular gene, but their other gene of the pair is normal. One copy of the normal gene is sufficient for the parent to be unaffected. If both parents are carriers of a gene for the same autosomal recessive condition, there is a one in four chance in each pregnancy that they will both pass on the abnormal gene and have an affected child.

Mutations in the *RPL5*, *RPL11*, *RPL35A*, *RPS7*, *RPS10*, *RPS17*, *RPS19*, *RPS24*, and *RPS26* genes are known to cause DBA. Responsible for providing instructions for producing ribosomal proteins, these genes are crucial for the creation of cellular structures called ribosomes. Ribosomes create proteins within every cell. Mutations in any of these genes affect the function and longevity of ribosomal proteins. A shortage of ribosomal proteins may cause the blood-forming cells in the bone marrow to die, resulting in anemia. This process of cell

death may also contribute to the other health problems associated with DBA.

In 40% to 50% of individuals with DBA, the exact cause is unknown, while nearly 25% of known DBA cases are caused by mutations in the *RPS19* gene. The remaining 25% to 35% of individuals with DBA have identified mutations in the *RPL5*, *RPL11*, *RPL35A*, *RPS7*, *RPS10*, *RPS17*, *RPS24*, or *RPS26* genes. Researchers suspect additional gene mutations may contribute to the cause of DBA.

Demographics

DBA is a rare condition, affecting approximately five to seven per one million live born infants worldwide. According to the Centers for Disease Control and Prevention (CDC), there are approximately 25 to 35 new cases of DBA identified each year in the United States and Canada. The disorder occurs equally in males and females and across all races and ethnicities.

Signs and symptoms

Congenital hypoplastic anemia (CHA) and abnormal thumbs (TPT) are the two classic signs of DBA. The anemia may require treatment with steroids, or possibly blood transfusions, but tends to improve over time. TPT may cause a person with DBA to have difficulty grasping and manipulating objects with their hands. A hypoplastic radius may complicate problems with appearance and movement of the hands and arms. Narrow and sloping shoulders are caused by abnormal development of the bones in that area of the body.

Slow growth in children with DBA may be partly related to their anemia but is more likely to be genetically predetermined due to the syndrome. Ventricular septal defect (VSD), a hole between the bottom two chambers of the heart, is the cardiac defect reported most often, and several cases of cleft lip and palate have occurred as well.

Diagnosis

DBA is diagnosed by physical examination and lab tests that include the following:

- **Blood tests**—Bloods tests are used to measure the number of red blood cells (reticulocytes and reticulocytes) and a blood count. Diagnosis is confirmed if the red blood cell counts are low in the presence of a normal number of white blood cells and platelets.
- **Bone marrow aspiration**—During this test, fluid is removed from the bone marrow using a long needle. Patients are given local anesthetic and a conscious sedation to help them remain calm and comfortable during the test.

KEY TERMS

Congenital hypoplastic anemia (CHA)—A significant reduction in the number of red blood cells present at birth, usually referring to deficient production of these cells in the bone marrow. Also sometimes called congenital aplastic anemia.

Fontanelle—One of several soft spots on the skull where the developing bones of the skull have yet to fuse.

Hypoplastic radius—Underdevelopment of the radius, the outer, shorter bone of the forearm.

Triphalangeal thumb (TPT)—A thumb that has three bones rather than two.

- Bone marrow biopsy—During a biopsy, the patient is given a local anesthetic and conscious sedation, and marrow cells are removed. This procedure is always performed along with marrow aspiration.
- Genetic screening—Using a blood sample, gene sequencing, gene duplication, and gene deletion testing may be performed. These tests determine whether there are mutations in the genes known to cause DBA and may be helpful in treatment planning.

Treatment and management

Some people with DBA require no medical treatment; however, for individuals who do require treatment, the most common options are oral corticosteroids, blood transfusions, and bone marrow or stem cell transplantation.

Corticosteroids

Corticosteroids are medications used to treat many medical conditions. When taken by people with DBA, corticosteroids will increase red blood cell production in approximately 80% of cases. The dosage is managed closely. Doctors will prescribe just enough corticosteroid to increase the red blood cell count. It generally takes between two to four weeks for the red blood cell count to increase. After a while, this dosage may need to be increased as the patient's body becomes accustomed to the medication.

There are long-term and short-term side effects when taking corticosteroids. Some may be serious. If side effects become a problem, other treatment options may be considered.

The short-term side effects of corticosteroid treatment include the following:

- Behavior changes, difficulty sleeping, and irritability
- Elevated blood pressure
- Increased blood sugar
- Increased risk of pneumonia, thrush (white coating in the mouth), infections, and poor wound healing
- Acne and increased hair growth
- Upset stomach, increased hunger, and water retention
- Weight gain, increased fat on the face, upper back, and stomach

Long-term side effects of corticosteroid treatment include all short-term side effects as well as the following:

- Diabetes
- Eye problems
- Fragile bones and painful hip and shoulder joints
- Muscle weakness
- Poor growth in children, sometimes severe

Blood transfusion

Another treatment for DBA is blood transfusion. In this treatment, blood from a healthy person is injected into another person through a vein or a permanent intravenous (IV) device. The healthy blood increases the number of red blood cells in the person with DBA. Individuals with DBA may need blood transfusions as often as every few weeks or only a few times a year. Some patients may require transfusions regularly for many years. After transfusion, most people with DBA will experience increased energy and will feel better. Blood transfusions for children with DBA may help prevent or treat the decreased growth rates that are a common symptom.

While problems from blood transfusions are rare, some people may experience side effects such as transfusion allergic reaction, infection, abnormal antibody development, or excess iron accumulation in various organs. Allergic reaction to blood transfusion may cause itching, hives, or rash. Very rarely this allergic reaction may be serious, causing wheezing, coughing, and difficulty breathing. If allergic reaction is suspected, patients may be treated prior to transfusion to help prevent complications.

Many people are concerned about the risk of infection from blood transfusion. Blood centers test all blood and make every effort to ensure that blood used in transfusion is safe. Donors are screened, and blood is not accepted from individuals who do not meet donation standards. All blood donations are tested for viral and bacterial infections, and in the United States infections from blood transfusions are extremely rare. In general, the blood supply in the United States is very safe.

Human blood contains traits that make it unique to each individual. When blood from a different person enters the body, the recipient's blood may produce cells, called antibodies, to fight the foreign or unknown blood. These antibodies can destroy the blood from the transfusion. To prevent these antibodies from forming, blood centers work carefully to ensure donor blood matches as closely as possible to recipient's blood.

Excessive iron may accumulate in the organs of individuals who have frequent blood transfusions. Called iron overload, it occurs when iron found in the blood from a blood transfusion enters the body. Excess iron is not easily excreted from the body, and it can accumulate in organs such as the heart, liver, and pancreas. If this condition is not treated, the organs may be damaged. To prevent iron overload, doctors carefully monitor the patient's growth, development, iron levels, hormone levels, and the state of his or her organs. Individuals with DBA who are undergoing blood transfusion should not take any medication or supplements that contain iron. Medication called chelation drugs may be prescribed to help remove excess iron.

A rare but potentially very serious complication of blood transfusion is a condition called hemolysis. Hemolysis occurs when the blood cells from the transfusion begin to die. Antibodies from the recipient's own body may attack and kill the donated blood cells. Symptoms may begin shortly after the transfusion or up to ten days later and may include:

- Fever
- Back or flank pain
- Dark urine
- Pale skin
- Yellow-tinted skin
- Dizziness and/or fainting

If any of these symptoms occur, call a doctor immediately.

Stem cell (bone marrow) transplantation

Stem cell transplant, also called a bone marrow transplant, is a procedure in which healthy stem cells are taken from a donor and given to a person with DBA. Much like a blood transfusion, stem cells enter the body through an IV. Over the course of several weeks, the stem cells migrate to the bone marrow where they begin to make red blood cells. In some cases, DBA may be cured by stem cell transplant.

Stem cells are immature blood cells and are found in bone marrow, blood cells, and umbilical cord blood from a delivered baby. Stem cells for transplantation may come from any of these sources.

QUESTIONS TO ASK YOUR DOCTOR

- What testing do you recommend?
- Which family members should have genetic testing?
- Is anemia a problem for my child?
- What type of physical therapy or exercises should my child do?

Stem cell donors and recipients must have very similar blood. Specifically, the donor's human leukocyte antigen (HLA) type must be the same as the recipient's. HLA helps the body identify blood that belongs and other substances that must be destroyed such as infections. Siblings generally have similar HLA and often make compatible donors. The sibling will have genetic testing for DBA. Siblings with DBA may not donate stem cells. HCL is inherited from each parent; therefore, each sibling has a 25% chance of being an HCL match. If there are no family members who match, a match may be found in the National Marrow Donor Program (NMDP) registry. Non-relative stem cell transplant is not as successful as transplantation from direct family members.

There are risks associated with stem cell transplant. While many patients who have stem cell transplant have few complications, other patients may experience medical problems that require treatment and even hospitalization. Prior to stem cell transplant, the patient must receive chemotherapy and/or radiation therapy to destroy the DBA affected stem cells. This process, called preparative regimen, has side effects consistent with chemo and radiation therapy and may include nausea and vomiting, hair loss, and sores of the mouth and other parts of the body.

After stem cell transplantation, there may be potentially serious side effects, including rejection, infection, and graft-versus-host disease (GVHD). The closer the donor match is to the recipient, the lower the risk of serious side effects and complications.

Rejection, or graft failure, occurs when the recipient's body rejects the donated stem cells. The recipient's immune system may attack the stem cells, killing them. The patient's own stem cells may grow back and the DBA symptoms will return.

Infection may occur, especially soon after the transplant, because the patient's immune system is weakened to help it accept the donated stem cells. Bacteria and viruses from the recipient's own body or from the

surrounding environment may pose a great risk. Infections that might normally be mild can be fatal to patients who have received stem cell transplantation.

Graft-versus-host disease (GVHD) occurs when the stem cells from the donor begin to attack the recipient's body, leading to physical symptoms such as rash, diarrhea, and liver disease. Mild GVHD may be treated with medication; however, in severe cases, it may be fatal.

Management of other features of DBA

Management of problems related to the skeletal abnormalities of DBA may require orthopedic surgery as well as physical and occupational therapy. Heart defects and cleft lip and palate are nearly always correctable, but both require surgery and long-term follow up. A genetic evaluation and counseling should be offered to any individual or couple whose child is suspected of having DBA.

Prognosis

While major medical procedures such as blood transfusions and corrective surgeries may be needed for a child with DBA, the long-term prognosis is generally good. For some patients, effective treatment may completely cure DBA. If a cure is not possible, quality of life may remain high if individuals choose a healthy lifestyle, follow treatment plans, and monitor their health closely. Rarely, treatment options, side effects, and complications may be fatal.

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ORGANIZATIONS

Diamond Blackfan Anemia Foundation (DBAF), PO Box 1092, West Seneca, New York 14224, (716) 674-2818, dbafoundation@juno.com, <http://dbafoundation.org>

Diamond Blackfan Anemia Registry, Schneider Children's Hospital, 269-01 76th Ave., Rm. 255, New Hyde Park, NY 11040, (718) 470-3610, eatsidaf@lij.edu, <http://dbar.org>

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Diastrophic dysplasia

Definition

Diastrophic dysplasia (DTD) is a rare genetic disorder of bone growth and formation that is evident at birth.

Description

Diastrophic dysplasia is one of the genetic osteochondrodysplasias, a group of disorders characterized by abnormal growth and formation of bone and cartilage. Cartilage is a tough, elastic tissue that makes up much of the skeleton during early development. The main features of DTD include: malformed ears, cleft palate, short limbs, short stature, spinal and joint deformities, and abnormalities of the bones of the hands and feet. Although children with DTD may experience delays in motor development (e.g., walking at a later age than expected), they are of normal intelligence. The syndrome derives its name from the Greek word *diastrophos*, meaning "twisted" or "crooked." Maroteaux and Lamy first used the term "diastrophic dysplasia" in 1960 to describe three of their patients and 11 other cases already reported in the literature. Since then, at least 300 cases of DTD have been described. Diastrophic dysplasia is also known as diastrophic nanism or diastrophic dwarfism.

Genetic profile

Diastrophic dysplasia is one of several skeletal disorders caused by mutations in the *SLC26A2* gene (solute carrier family 26, sulfate transporter, member 2), also called diastrophic dysplasia sulfate transporter (DTDST). This gene provides instructions for making a protein that is essential for the normal development of cartilage and for its conversion to bone. Mutations in the *SLC26A2* gene alter the structure of developing cartilage, preventing bones from forming properly and resulting in the skeletal problems characteristic of diastrophic dysplasia. DTD is inherited in an autosomal recessive manner. Affected individuals have a mutation in both copies of their *SLC26A2* gene; they inherit one mutation from each

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Cartilage—Supportive connective tissue which cushions bone at the joints or which connects muscle to bone.

Chondrocyte—A specialized type of cell that secretes the material that surrounds the cells in cartilage.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Clubfoot—Abnormal permanent bending of the ankle and foot. Also called *talipes equinovarus*.

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

DNA mutation analysis—A direct approach to the detection of a specific genetic mutation or mutations using one or more laboratory techniques.

Dysplasia—The abnormal growth or development of a tissue or organ.

Epiphysis—The growth area at the end of a bone.

Fibroblast—Cells that form connective tissue fibers like skin.

Founder effect—increased frequency of a gene mutation in a population that was founded by a small ancestral group of people, at least one of whom was a carrier of the gene mutation.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Linkage analysis—A method of finding mutations based on their proximity to previously identified genetic landmarks.

Metacarpal—A hand bone extending from the wrist to a finger or thumb.

Metaphysis—The growth zone of the long bones located between the ends (epiphyses) and the shaft (diaphysis) of the bone.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Nanism—Short stature.

Sulfate—A chemical compound containing sulfur and oxygen.

Vertebra—One of the 26 bones that compose the spine. *Vertebrae* is the plural form.

parent. Parents of affected individuals are carriers; they have a mutation in one copy of their *SLC26A2* gene and are without symptoms of the disorder.

Most bone in the body begins as cartilage and later hardens (ossifies) to form bone. In certain parts of the body such as the rib, auricle, and joints, cartilage does not ossify; it remains as cartilage and functions as load-bearing or shock-absorbing tissue. Cartilage contains sulfur-containing compounds

known as proteoglycans. It is thought that abnormal function of the sulfate transporter gene leads to insufficient sulfate uptake by proteoglycans in the cartilage. This undersulfation results in weakness and distortion of the cartilage. The exact mechanism by which this occurs is not fully understood.

Three other genetic skeletal dysplasias: recessively inherited multiple epiphyseal dysplasia (rMED), atelosteogenesis type 2 (AO-2), and achondrogenesis type IB

(ACG-IB), are also due to mutations in the *DTDST* gene. When compared to DTD, both AO-2 and ACG-1B are more severe skeletal dysplasias, with the latter being a lethal disorder. Recessively inherited MED is a relatively mild condition. This broad range in severity, from mild to fatal, is attributed to the different types and combinations of genetic mutations within the *DTDST* gene that are responsible for these four related diseases.

Demographics

Diastrophic dysplasia is a rare disorder in most parts of the world. The exact incidence is unknown; researchers estimate that it affects about 1 in 100,000 newborns, except in Finland, where the incidence is estimated at 1 in every 30,000 live births. Approximately 1%–2% of Finnish people are DTD carriers. Most Finnish DTD gene carriers possess the same ancestral mutation, known as DTDST (Fin). The high frequency of this single mutation in Finland is attributed to a founder effect.

Signs and symptoms

Diastrophic dysplasia is a variable condition that tends to become more severe with age. Many manifestations of the disorder are prenatal in onset and are therefore apparent at birth.

Growth

Diastrophic dysplasia is considered a short-limbed skeletal dysplasia because the limbs are disproportionately short for the overall height of the individual. The newborn with DTD tends to be short, with an average birth length of 16.5 in. (42 cm). This growth failure continues throughout childhood and is progressive in nature. The degree of deformity caused by orthopedic complications of this disorder can influence overall height. A wide range of final adult heights has been reported with lower limits at 2 ft. 10 in. (86 cm) and 3 ft. 5 in. (104 cm), and upper limits at 4 ft. 5 in. (135.7 cm) and 4 ft. 3 in. (129 cm) for males and females, respectively. On x-ray, the limb bones appear short and thick with broad metaphyses and flattened, irregular epiphyses.

Craniofacial

One of the most distinct features of DTD is the so-called “cauliflower ear.” In more than 80% of infants with DTD, fluid-filled cysts appear on the outer ear (pinnae) during the first few weeks of life. These cysts later calcify and may eventually ossify to form bone. In as many as 25%–60% of individuals with DTD, some form of cleft palate is present. Although individuals with DTD may have a small chin (micrognathia), the head is otherwise normal in size.

Thoracic

Occasionally there may be abnormalities of cartilage in the trachea, larynx, and bronchi, which may lead to a life-threatening complication—collapse of the airways—especially in early infancy.

Spinal

Spina bifida occulta in the neck (cervical) and upper back (thoracic) region is the most common spinal abnormality found in DTD and is present in over 50% of cases. In spina bifida occulta there is incomplete closure of bones of the spinal column. Other common spinal abnormalities include progressive curvature of the spine, either from front to back (kyphosis) or from side to side (scoliosis). Kyphosis in the neck region (cervical kyphosis) is present in at least 30% of affected individuals and is usually evident at birth. This type of spine curvature usually resolves over time without treatment. In severe cases however, cervical kyphosis can lead to respiratory problems. Scoliosis, which is generally not present at birth, may appear at an early age and become problematic in early adolescence. Nearly 50% of females and at least 20% of males will develop scoliosis.

Joints

Joint changes in diastrophic dysplasia are progressive in nature and can be a painful complication of this disorder. Individuals with DTD may experience limited mobility and/or permanent immobility (contractures), especially in the knees and shoulders. The joints in an individual with DTD are also prone to partial or complete dislocations in the shoulders, hips, kneecaps, and elbows.

Hands and feet

The hands of a child with diastrophic dysplasia are distinct. The fingers are short (brachydactyly) and there may be fusion of the joints between the bones of the fingers (sympalangism). The metacarpal bone of the thumb is short and oval-shaped; these bony deformations cause the thumb to deviate away from the hand and assume the appearance of the so-called “hitchhiker thumb,” a classic feature of DTD. The bony changes in the feet are similar to those found in the hands. The great toes may deviate outward, much like the thumbs. Clubfoot deformity (talipes), due to abnormal formation and limited mobility of the bones of the foot, is a common birth defect found in newborns with DTD.

Diagnosis

At birth, the diagnosis of diastrophic dysplasia is based on the presence of the characteristic physical and radiologic (x-ray) findings. DNA mutation analysis may be helpful in confirmation of a suspected diagnosis. In

those rarer cases where DNA mutation analysis does not detect changes, a laboratory test that measures the uptake of sulfate by fibroblasts or chondrocytes may be useful in making a diagnosis.

If there is a family history of diastrophic dysplasia and DNA is available from the affected individual, then prenatal diagnosis using DNA methods, either mutation analysis or linkage analysis, may be possible. DNA mutation analysis detects approximately 90% of *DTDST* mutations in suspected patients. In patients where the mutations are unknown or undetectable, another DNA method known as linkage analysis may be possible and, if so, it can usually distinguish an affected from an unaffected pregnancy with at least 95% certainty. In linkage analysis, DNA from multiple family members, including the person with DTD, is required. DNA-based testing can be performed through chorionic villus sampling or through amniocentesis.

If DNA-based testing is not possible, prenatal diagnosis of diastrophic dysplasia in an at-risk pregnancy may be made during the second and third trimesters through ultrasound. The ultrasound findings in an affected fetus may include: a small chin (micrognathia), abnormally short limbs, inward (ulnar) deviation of the hands, the “hitchhiker” thumb, clubfoot, joint contractures, and spinal curvature.

General population carrier screening is not available, except in Finland where the frequency of a single ancestral mutation is high.

Treatment and management

There is currently no treatment that normalizes the skeletal growth and development in a child with diastrophic dysplasia. The medical management and treatment of individuals with DTD generally requires a multidisciplinary team of specialists that should include experts in orthopedics. At birth it is recommended that a neonatologist be present because of the potential for respiratory problems. Surgery may be indicated in infancy if congenital abnormalities such as open cleft palate and/or clubfoot deformity are present. Throughout childhood and adulthood, bracing, surgery, and physical therapy are measures often used to treat the spinal and joint deformities of DTD. Such measures, however, may not fully correct these deformities.

Due to the significant short-limbed stature associated with diastrophic dysplasia, certain modifications to home, school, and work environments are necessary in order for a person with DTD to perform daily tasks. Occupational therapy may help affected individuals, especially children, learn how to use assistive devices and to adapt to various situations.

QUESTIONS TO ASK YOUR DOCTOR

- What tests are available to determine whether or not our newborn child has diastrophic dysplasia?
- If the child has the condition, what early treatments should be provided to reduce the severity of the disorder?
- As the child grows older, will he or she need to be concerned about transmitting this condition to his or her own children?
- Will our child need to be monitored for this condition throughout his or her life, and, if so, what specific conditions should we watch for?

Prognosis

In infancy there is an increased mortality rate as high as 25%, due to respiratory complications caused by weakness and collapse of the cartilage of the wind pipe (trachea) and/or the voice box (larynx), conditions which may require surgical intervention. Some forms of cleft palate and micrognathia may be life-threatening in early life as they can result in respiratory obstruction. Severe spinal abnormalities such as cervical kyphosis may also cause respiratory problems. After the newborn period, the lifespan of an individual with DTD is usually normal, with the exception of those cases where spinal cord compression occurs as a result of severe cervical kyphosis with vertebrae subluxation. Spinal cord compression is a significant medical problem that can lead to muscle weakness, paralysis, or death. In a susceptible individual, spinal cord compression may occur for the first time during surgery due to the hyperextended neck position used during intubation. Other anesthetic techniques may be indicated for such cases.

People with diastrophic dysplasia are of normal intelligence and are able to have children. Since many of the abnormalities associated with DTD are relatively resistant to surgery, many individuals with DTD will have some degree of physical handicap as they get older. They may continue to require medical management of their spinal and joint complications throughout adult life.

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ORGANIZATIONS

- MAGIC Foundation, 6645 W. North Ave., Oak Park, IL 60302, (708) 383-0808, (800) 362-4423, ContactUs@magicfoundation.org, <http://www.magicfoundation.org>
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), 1 AMS Circle, Bethesda, MD 20892-3675, (301) 495-4484, (877) 226-4267, (301) 718-6366, NIAMSinfo@mail.nih.gov, <http://www.niams.nih.gov>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Diffuse angiokeratoma see **Fabry disease**

Direct-to-consumer genetic testing

Definition

Direct-to-consumer (DTC) genetic testing, also called at-home genetic testing, consumer-initiated genetic testing, direct-access genetic testing, and home DNA testing, is an elective (optional) test marketed directly by private companies to the general public. A DTC test can be ordered online or purchased in a store, and completed by anyone over the age of 13 without having to consult a health care provider. DTC testing intended to answer questions about family history is known as ancestry or genealogy testing.

Description

History

The first DTC genetic tests were marketed within a few years after the completion of the Human Genome



A direct-to-consumer genetic testing kit. The purchaser puts a saliva sample in the plastic tube and sends it to the company for analysis. (Martin Shields/Science Source)

Project in 2003. These initial tests were expensive, costing about \$1,000 in 2007. Advances in sequencing technology led to price reductions: the average price of a DTC test dropped to \$400 by 2010; to \$99 by 2012; and as low as \$59 by 2018. In turn, the drop in price prompted growing consumer interest in these tests: the *MIT Technology Review* reported in 2019 that as many people purchased DTC genetic tests in 2018 as in all previous years combined.

By 2018, over 26 million people worldwide had purchased these tests, with the figure projected to rise to 100 million by the end of 2021. Some geneticists estimate that so many DTC tests have been completed in the United States that even people who have not taken such a test are likely to be related genetically to someone who has.

DTC marketing and regulation

Direct-to-consumer genetic tests were initially not regulated by the Food and Drug Administration (FDA) or any other federal agency, as they were marketed by private companies and so were purely commercial transactions. In 2006, however, the U.S. Government Accountability Office (GAO) began an investigation of the companies that offered DTC genetic tests, and found that the results of the tests were often misleading and marketing practices were sometimes deceptive. As a result, the FDA redefined DTC genetic tests in 2010 as medical devices requiring the agency's approval. In 2013, the FDA sent cease-and-desist letters to companies marketing DTC genetic tests. By 2015, however, the largest companies began to redefine their tests and sought FDA approval for them as medical devices. As of 2021, the only company with FDA approval for its DTC genetic tests is 23andMe. The

FDA has approved the company's tests for genetic health risk (GHR) testing, carrier screening, and cancer predisposition tests. The FDA does not currently regulate ancestry tests or low-risk general health tests.

How the tests work

People who are interested in a DTC genetic test can purchase most brands over the counter in drugstores or they can order their kit online from a test company's website. As of 2021, the two largest DTC genetic test companies by far are Ancestry and 23andMe; others include Orig3n, HomeDNA, MyHeritage, and African Ancestry.

To use the kit, the person provides a saliva sample or a buccal swab (skin cells obtained by wiping the inside of the cheek with a Q Tip) and then returns the kit to the company for analysis. A few companies ask the consumer to submit a blood sample drawn at a health clinic. To keep costs down, DTC testing companies use automated analysis of a preplanned number of single-nucleotide polymorphisms (SNPs), which are genetic variants characterized by a substitution of a single nucleotide at a specific position in a person's genome. SNPs can be used to identify a person's susceptibility to such genetic disorders as sickle cell anemia or cystic fibrosis. However, the SNP arrays used by the company can identify only the particular gene variants included on its array.

After performing the analysis, the company typically notifies the consumer in the form of an online report on the company website, although some companies will also notify consumers by a telephone call or by mail. DTC genetic companies vary as to whether their fee includes a genetic counselor's explanation of the test results or answers to the consumer's questions. Some companies provide these services; others do not, and it is up to each consumer to find out the specific services offered before purchasing and using a kit.

If the company does not offer explanation of test results as part of the cost of its kit, consumers have the option of consulting so-called third-party interpretation (TPI) services online to obtain an analysis of their genomic data. They can also consult their primary care physician or a qualified genetic counselor for guidance in understanding the data.

Purpose

People may be interested in DTC genetic testing for several reasons:

- Curiosity about their family's history, ethnicity, and countries of origin.
- Concern about susceptibility to various diseases. Some DTC tests offer estimates of a person's risk of such disorders as Alzheimer's, Parkinson's, or celiac disease.

- Carrier risk. In genetics, a carrier is a person who has a mutation for a specific disease and is capable of passing it on to descendants. The carrier will not necessarily have symptoms of the disease in question.
- Paternity testing.
- Kinship identification. Some people are interested in finding out whether they have previously unknown relatives or are related to a famous person. Adoptees and people conceived by in vitro fertilization (IVF) are increasingly interested in locating their biological parents, including sperm donors. According to recent studies, women are four times more likely than men to look for relatives identified by DTC genetic testing.
- Desire to improve one's overall health and fitness by making lifestyle changes on the basis of genetic test results.
- Pharmacogenomic information. Some DTC genetic tests offer information about the ways in which a person's genome may affect his or her response to prescription drugs.

Although most DTC genetic testing companies focus only on human DNA, HomeDNA offers three genetic testing kits for dogs and cats: a mixed-breed dog identification test; a dog DNA health screen, and a cat DNA health screen. Each test costs \$125 as of 2021.

Limitations

The chief limitation of DTC genetic testing is that it cannot be used to definitively diagnose or treat a specific disease or condition. Consequently, most insurance companies will not pay for DTC tests, and the results of DTC genetic testing cannot be used as evidence in a court of law. As noted earlier, these tests offer only restricted sets of SNPs for analysis; DTC tests may include only some of the genes, regions of genes, or variants relevant to a specific disease.

In addition, the genes sampled by DTC tests are not the only factors contributing to a person's health risks. Such factors as genetic variations that were not tested by the company; environmental, occupational, and climate-related issues; and lifestyle choices like diet, exercise, drug use, and sexual behavior also influence a person's risk of developing diseases.

Risks

There are several risks associated with DTC genetic tests:

- Potentially inadequate oversight of the company's laboratory. The Clinical Laboratory Improvement Amendments (CLIA) of 1988 is a set of federal standards regulating laboratory testing in the United

KEY TERMS

Autosome—Any chromosome that is not a sex chromosome. The human genome has 22 pairs of autosomes.

Buccal—Related to the cheek.

Carrier—In genetics, a person who has a genetic mutation associated with a disease and is capable of passing it on. A carrier may or may not display the symptoms of the disease.

Clickwrap agreement—An online agreement between a user and a company in which users must click a box or button and read the agreement before they download content, make a purchase, or use a website.

Clinical Laboratory Improvement Amendments (CLIA)—A set of regulations passed in 1988 that establish federal standards applicable to all laboratories or sites that test human specimens for health assessment or to diagnose, prevent, or treat disease.

False negative—A test result that indicates that a disease or condition is not present when it really is; sometimes called a type II error.

False positive—A test result that indicates that a person has a disease or condition when they do not; it is sometimes called a type I error.

Forensic—Pertaining to the use of science or medicine in the investigation and establishment of evidence in a court of law.

Genealogy—The study or investigation of a person's lineage or family tree.

Genome—The total amount of genetic information within an organism's chromosomes, including its genes and DNA sequences.

Germline—The population of a complex organism's cells that pass on genetic information to offspring. Germline cells include eggs, sperm, and fertilized eggs.

Health Insurance Portability and Accountability Act (HIPAA)—A 1996 federal statute that includes a privacy rule regulating the use and disclosure of protected health information (PHI). DTC genetic testing is not subject to HIPAA privacy regulations.

In vitro fertilization (IVF)—A form of assisted reproduction technology in which a human ovum (egg) is combined with sperm outside the body in a laboratory container ("in vitro" means "in glass").

Pharmacogenomics—The study of the ways in which a person's genetic makeup affects his or her response to drugs.

Single nucleotide polymorphism (SNP)—A germline substitution of a single nucleotide (any of a group of molecules that form the building blocks of DNA or RNA) at a specific position in a person's genome.

Third-party interpretation (TPI) service—An online tool that analyzes the raw DNA data from a DTC genetic test and provides a genetic health risk report.

States. They require clinical laboratories to be certified by the Center for Medicare and Medicaid Services (CMS) before accepting human samples for diagnostic testing. The FDA categorizes laboratory tests as high complexity, moderate complexity, or waived. The FDA waives CLIA certification for tests approved for home use, which means that DTC genetic tests may be analyzed in laboratories that have not been certified by CMS.

- **False negatives.** A false negative is a test result that indicates that a disease or condition is not present when it actually is. Because DTC genetic tests are based on limited arrays of SNPs, it is possible for a person to have a health condition that is not detected by a particular company's SNP array.
- **False positives.** A false positive is an error in which a test result incorrectly indicates the presence of a disease that is not actually present. This type of error means that a DTC test report can show that the consumer has an

increased risk of a serious health condition when that risk really does not exist. False positives can cause considerable anxiety in consumers of DTC testing, leading to what one group of researchers considers a burden on the health care system, with clinical testing done in order to confirm that a patient does not have a clinical diagnosis of the disease associated with the reported genetic variant.

- **Disagreement among geneticists and researchers** about the significance of some genetic variants and their roles in causing disease. In regard to DTC testing, one DTC testing company may classify some SNPs as disease-causing or disease-associated variants, while another may classify them as benign.
- **Family disruption related to the exposure of secrets.** An increasing number of people are discovering that their legal father is not their biological father; that they have half-siblings that they were unaware of due to a parent's extramarital affair; or that they may have as many as a

hundred relatives as the result of IVF conception via a sperm donor. One such donor, a biochemist living in the United Kingdom, is known to have fathered over 100 children. In addition, adoptees using DTC genetic testing in order to track down their biological parents may encounter rejection rather than acceptance.

- **Personal identity issues.** Some people who had a specific self-understanding based on a particular ethnic identity or geographical origin may feel disoriented or disappointed if their DTC test does not confirm their self-image. One recent example concerns a woman who thought that she was a mixture of Scots-English and German ancestry, only to find out that she had numerous biological connections to Hispanics in the company's database.
- **Privacy concerns.** By far the greatest risk confronting people who take a DTC genetic test is the high probability that they are signing away their right to privacy of their DNA. DTC genetic testing is not covered by the Health Insurance Portability and Accountability Act (HIPAA) of 1996. Most DTC testing companies have what is known as a clickwrap agreement, in which a consumer purchasing a test kit online must press or click on a button in order to read the agreement and complete the purchase. The agreement usually spells out the company's privacy policy, such as who is the legal owner of the data; whether the company will destroy the genetic sample after analysis; whether the company shares or sells data to biotechnology companies, academic institutions, or other organizations; how the company protects consumers' information against unauthorized access; and whether the company will notify consumers of changes in, or updates to, its privacy policy. Anyone purchasing a DTC test kit should read the agreement very carefully before completing their purchase.

Alternatives

The primary alternative to DTC genetic testing is a traditional genetic test, ordered and interpreted by a physician or other health care professional for a specific medical reason. This type of testing is considerably more expensive than DTC genetic testing, costing between \$1,000 and \$2,000 as of 2021. A clinical genetic test involves a full investigation into the genetic cause of a disease, which sometimes includes using more than one sequencing method, examining the complete coding regions of the genes in question, and manual investigation rather than automated analysis of gene variants. In addition, a clinical genetic test must be performed in a CLIA-certified laboratory. In spite of the high cost, the results of such tests are considerably more likely to provide an accurate diagnosis, to be specific to the patient

QUESTIONS TO ASK YOUR DOCTOR

- What is your opinion of direct-to-consumer genetic testing?
- How many of your patients have asked you for a clinical genetic test on the basis of DTC test results?
- If I decide to purchase a DTC genetic test, will you help me interpret the results?
- Have you ever referred a patient to a certified genetic counselor on the basis of DTC test findings?

in question, and to guide treatment if a genetic disorder is revealed.

Applications

Research

The explosion of interest in DTC genetic testing and the corresponding increase in the number of consumers distressed by test results has led to one NIH-registered clinical trial of a tool to assist parents in telling children conceived by IVF about their genetic heritage. Another recently completed clinical trial is a study of how individual patients and their physicians understand and respond to uncertain genetic risk information obtained by DTC testing.

Forensic investigation

The growing popularity of DTC genetic testing has allowed for the compilation of large databases of genetic information about people living in the United States. GEDmatch is a company founded in 2010 to compare autosomal DNA data files from different testing companies in order to assist amateur genealogists as well as adoptees searching for birth parents. As of late 2020, GEDmatch held over 1.45 million DNA profiles. The company made history in 2018 when its databank was used to track the Golden State Killer, a serial rapist and murderer who had been unidentified since his crime spree began in 1973. At least 10 other cold homicide cases have been solved by using GEDmatch since 2018.

The other significant forensic application of the DNA data compiled by GEDmatch is identification of missing persons and other unknown human remains. The DNA Doe Project was established in 2017 to help identify such persons. At least 42 persons, some of whose

remains were discovered as early as 1971, have been positively identified by the Doe Project as of early 2021.

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ORGANIZATIONS

- American College of Medical Genetics and Genomics (ACMG), 7101 Wisconsin Avenue, Suite 1101, Bethesda, MD 20814, (301) 718-9603, (301) 718-9604, acmg@acmg.net, <https://www.acmg.net/>
- Federal Trade Commission Consumer Information, 600 Pennsylvania Avenue, NW, Washington, D.C. 20580, To file a complaint: (877) FTC-HELP, (202) 326-2222, <https://www.consumer.ftc.gov>
- National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, <https://www.genome.gov/about-nhgri/Contact>, <https://www.genome.gov/>
- National Society of Genetic Counselors (NSGC), 330 North Wabash Avenue, Suite 2000, Chicago, IL 60611, (312) 321-6834, nsgc@nsgc.org, <https://www.nsgc.org>
- U.S. Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, Atlanta, GA 30333, (800) CDC-INFO (232-4636), <http://www.cdc.gov/cdc-info/requestform.html>, <http://www.cdc.gov>
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) 463-6332, <https://www.fda.gov/>

Rebecca J. Frey, PhD

Disorder of cornification 10 see **Sjögren–Larsson syndrome**

Disorders of sex development (DSD)

Definition

Hermaphroditism, also called intersex, is a rare condition in which ovarian and testicular tissue exist in the same person. When the tissue is a mix of ovarian and testicular tissue it is referred to as an ovotestis. The testicular tissue contains seminiferous tubules or spermatozoa. The ovarian tissue contains follicles or corpora albicantia. The condition is the result of a chromosome anomaly.

Description

Among human beings, hermaphroditism is an extremely rare anomaly in which gonads for both sexes are present. External genitalia may show traits of both sexes, and the chromosomes show male–female mosaicism (where one individual possesses both the male XY and female XX chromosome pairs). There are two different variants of hermaphroditism: true hermaphroditism and pseudohermaphroditism. There are female and male pseudohermaphrodites. True hermaphroditism refers to the presence of both testicular and ovarian tissue in the same individual and is classified by the position and histology of the testes/ovaries. In 30% of cases there is a testis on one side with an ovary on the other, in 50% of cases there is both testicular tissue and ovarian tissue on both sides, and in the remaining 20% of cases there is an ovotestis on one side and either a testis or an ovary on the other side. The external genitalia in these individuals may range from normal male to normal female. However, most phenotypic males have hypospadias. Pseudohermaphroditism refers to gonadal dysgenesis.

Genetic profile

The most common karyotype for a true hermaphrodite is 46XX (70% of cases). DNA from the Y chromosome is translocated to one of the X chromosomes. Clinical studies have shown cases in which molecular analysis shows the sex-determining region (*SRY*) gene to be present with a microdeletion of other major regions on the Y chromosome. If this is the case, the patient is a phenotypical male but a karyotypical female. The karyotype for male pseudohermaphrodites is 46XY. Female pseudohermaphroditism is more complicated. The condition is caused by deficiencies in the activity of enzymes. The genetic basis for three enzyme deficiencies has been

identified. Deficiency of 3B-hydroxysteroid dehydrogenase type 2 is due to an abnormality on chromosome 1p13.1. Deficiency of 21-hydroxylase is due to an abnormality on chromosome 6p21.3. Deficiency of 11B-hydroxylase type 1 is due to an abnormality on chromosome 8q21.

Demographics

True hermaphrodites are extremely rare, representing only about 5% of all disorders of sexual dysmorphia, and are found more commonly in Africa. Approximately 500 individuals have been identified in the world to date. Because of the ambiguity of genitalia and difficulties in making an accurate diagnosis, the incidence of pseudohermaphroditism is not well established. The incidence of male pseudohermaphroditism has been estimated at between 3 and 15 per 100,000 people. The incidence of female pseudohermaphroditism has been estimated at between 1 and 8 per 100,000 people.

Signs and symptoms

True hermaphroditism is characterized by ambiguous internal and external genitalia. On internal examination (most often using laparoscopy), there is microscopic evidence of both ovaries and testes. Male pseudohermaphroditism is characterized by ambiguous internal and external genitalia. However, gonads are often (but not always) recognizable as testes. These are frequently softer than normal. An affected person is often incompletely masculinized. Female pseudohermaphroditism is characterized by female internal genitals. External genitals tend to appear as masculine. This is most commonly characterized by clitoral hypertrophy. Most hermaphrodites are infertile, although a small number of pregnancies have been reported.

Diagnosis

True hermaphroditism is often diagnosed after laparoscopic investigation. An initial suspicion of male pseudohermaphroditism is often made by inspection of external genitals during childhood and by MRI findings, which may show a mix of internal reproductive organs. Palpation of testicles and prostate oftentimes presents with dysmorphia or amorphia. The descent of the testis is dependent on the amount of testicular tissue present in the body, also an indicator of hermaphroditism. Hermaphroditism is confirmed by chromosomal analysis and assays of hormones such as testosterone, follicle-stimulating hormone, and luteinizing hormone. Initial suspicion of female pseudohermaphroditism is also made by inspection of external genitals. This is confirmed by analysis of chromosomes and hormonal assay.

QUESTIONS TO ASK YOUR DOCTOR

- Should I consider hormone replacement therapy?
- What are the chances that another child of mine will have this abnormality?
- Are there support groups for me/my child?
- How often should I/my child see a medical doctor?
- Am I/my child a surgical candidate?

Laparoscopic examination usually reveals nearly normal female internal genitals.

Treatment and management

Early assignment of gender is important for the emotional well-being of any person with ambiguous genitalia. A decision to select a gender of rearing is usually based on the corrective potential of the ambiguous genitalia rather than by using chromosome analysis.

Corrective surgery is used to reconstruct the external genitalia. In general, it is easier to reconstruct female genitalia than male genitalia, and the ease of reconstruction plays a role in selecting the gender of rearing. Treating professionals must be alert for stress in persons with any form of hermaphroditism and their families.

Prognosis

With appropriate corrective surgery, external genitalia may appear normal. However, other problems, such as virilization, may appear later in life. There has been some interest among persons with ambiguous genitalia at birth to reverse their gender of rearing.

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CARES Foundation, 2414 Morris Avenue, Suite 110, Union, NJ 07083, (866) 227-3737, contact@caresfoundation.org, <http://www.caresfoundation.org>

March of Dimes National Office, 1550 Crystal Drive, Suite 1300, Arlington, VA 22202, (888) 663-4637, <http://www.marchofdimes.org>

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DNA (deoxyribonucleic acid)

Definition

Deoxyribonucleic acid (DNA) is the molecule that contains the hereditary information. It is found in almost all of the cells of humans and other organisms. Most DNA is located in the nucleus of cells and is referred to as nuclear DNA. A small amount, called mitochondrial DNA (mtDNA), is in the mitochondria, the energy-producing organelles inside cells. DNA stores all the instructions required for making proteins, the fundamental components of an organism's cells, including structural proteins, enzymes, hormones, and antibodies and other immune-system proteins, that are necessary to maintain life. The complete set of nuclear DNA of a cell or organism is called its genome.

The information carried by DNA is in chemical form: DNA molecules consist of two twisting paired strands or helices. Each strand contains four types of chemical compounds called deoxyribonucleotides, consisting of a sugar, a phosphate group, and one of four bases—adenine (A), thymine (T), guanine (G), or cytosine (C). Each chain is

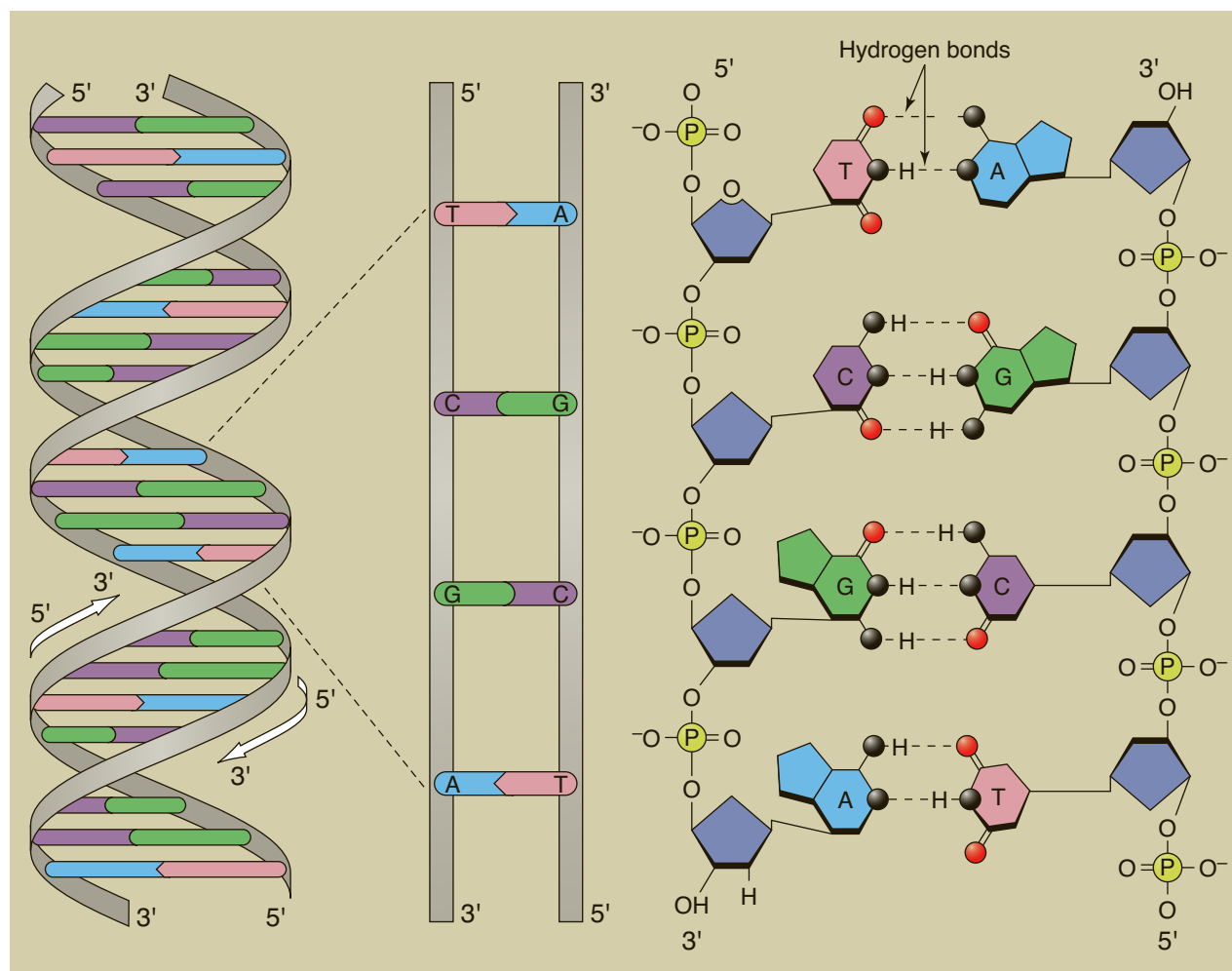
formed by the linked sugar-phosphate groups on the outside of the helix. The bases of each chain face inside of the helices and form specific base pairs joining the two chains—an A always pairs with a T, and a C always pairs with a G. The order (sequence) of these bases determines their biological instructions.

Each DNA sequence that contains a set of instructions (for example, instructions for making a specific protein) is known as a gene. The sizes of genes can vary greatly, ranging from about 1,000 paired bases to one million paired bases in humans. Altogether, the human genome contains about three billion base pairs, which are organized into the 23 pairs of chromosomes within the nuclei of almost all human cells. The DNA is tightly coiled and packaged into the chromosomes. When cells divide, the DNA unwinds and is copied (transcribed), and the copies are transferred to the new cells. DNA also unwinds when its instructions are required to make proteins and for other biological processes.

The history of DNA

Genetics is the science of heredity—the study of the structure and function of genes and the methods by which genetic information contained in genes is passed from one generation to the next. The modern science of genetics can be traced to the research of Gregor Mendel, who developed laws that mathematically describe how hereditary characteristics are passed from parents to offspring. These laws revealed that hereditary characteristics are contained in discrete units of genetic material now known as genes.

The story of genetics during the twentieth century is, in one sense, an effort to discover the gene itself. An important breakthrough came in the early 1900s with the research of the American geneticist, Thomas Hunt Morgan (1866–1945). Working with fruit flies, Morgan was able to show that genes are associated with the chromosomes in the nuclei of cells. By 1912, Hunt's student,



Structure of DNA molecule (Gale)

the geneticist Alfred Sturtevant (1891–1970), had constructed the first chromosome map showing the relative positions of different genes arranged linearly on a chromosome. Genes, therefore, had concrete physical references as positions on a chromosome.

During the 1920s and 1930s, a small group of scientists looked for a more specific description of the gene by focusing on its molecular composition. Most researchers assumed that genes were proteins, because proteins are large and complex and can occur in an almost infinite variety of structures. These were qualities expected for a class of molecules that must be able to carry the enormous variety of genetic traits.

A smaller group of researchers looked to a second family of compounds as potential candidates for the molecules of heredity—nucleic acids. Nucleic acids were first discovered in 1869 by the Swiss physician Johannes Friedrich Miescher. Miescher originally called these compounds “nucleins” because they were obtained from the nuclei of cells. One of Miescher’s students, Richard Altmann, later suggested a new name for the compounds that better reflected their chemical nature: nucleic acids.

In the 1930s, nucleic acids seemed unlikely candidates for molecules of heredity. What was known about their structure suggested that they were too simple to carry the vast array of complex information required for a molecule of heredity. Each DNA molecule consists of a long chain of nucleotides—alternating sugars and phosphates, with the sugars attached to one of the four different nitrogen bases. A fifth pyrimidine base, uracil (U), replaces thymine in ribonucleic acid (RNA). At the time, it was not clear how this relatively simple structure could assume enough different conformations to “code” for hundreds of thousands of genetic traits. In comparison, a single protein molecule contains various arrangements of about 20 fundamental units (amino acids), making it a much better candidate for the carrier of genetic information. However, in the 1940s and early 1950s, elegant experiments demonstrated unequivocally that DNA, not protein, is the genetic material.

The DNA double helix

But how could a simple molecule like DNA carry all of the necessary information? Although the building blocks of DNA—the deoxyribonucleotides—had been known for almost 100 years, their arrangement into a three-dimensional structure remained a mystery. That mystery was solved by a somewhat unusual pair: James Watson (1928–), a 24-year-old American trained in genetics, and Francis Crick (1916–2004), a 36-year-old Englishman, trained in physics and self-taught in chemistry. The two met at the Cavendish Laboratory of

Cambridge University in 1951. They were united by a passionate belief that the structure of DNA held the key to understanding how genetic information is stored in a cell and transmitted to daughter cells and subsequent generations.

The key to the structure of DNA lay in a technique known as x-ray crystallography. When x-rays are directed at a crystal of some material, such as DNA, they are reflected and refracted by the atoms that make up the crystal. The refraction pattern thus produced consists of a collection of spots and arcs. A skilled observer can determine from the refraction pattern the arrangement of atoms in the crystal. However, obtaining satisfactory x-ray patterns from crystals is often difficult. Interpreting the x-ray patterns—especially for complex structures like DNA—can be extremely difficult.

Watson and Crick were fortunate in obtaining access to some of the best x-ray diffraction patterns that then existed. These “photographs” were the result of work being done by Maurice Wilkins (1916–2004) and Rosalind Elsie Franklin (1920–1958) at King’s College in London. When Wilkins showed Watson one of Franklin’s x-ray patterns, he suddenly saw the solution to the DNA puzzle. Racing back to Cambridge, Watson convinced Crick to make an all-out attack on the DNA problem. They worked continuously for almost a week. Their approach was to construct Tinkertoy-like models of the DNA molecule, shifting atoms around into various positions, looking for an arrangement that would yield the x-ray pattern that Watson had seen in Franklin’s laboratory. A crucial clue came from rules formulated by Erwin Chargaff (1905–2002) and his colleagues at Columbia University in the late 1940s: the base composition (the numbers of As, Ts, Gs, and Cs) of DNA is always the same in cells from a given organism but varies from species to species; and most significantly, the number of As always equals the number of Ts, and the number of Gs always equals the number of Cs.

On March 7, 1953, Watson and Crick found their answer. They built a model consisting of two helices (corkscrew-like spirals) wrapped around each other. Each helix consisted of a backbone of alternating sugar and phosphate groups. To each sugar was attached one of the four nitrogen bases, A, C, T, or G. The sugar-phosphate backbones formed the outside of the DNA molecule, with the nitrogen bases tucked inside. Each nitrogen base on one strand of the molecule faced another nitrogen base on the opposite strand of the molecule. The base pairs were not arranged at random, however, but in such a way that each A was paired with a T and each C with a G. The Watson-Crick model immediately suggested how DNA could function as the carrier of genetic information. The sequence of the nitrogen bases along

the molecule could act as the genetic code. A sequence, such as A–T–A–C–G–C, and so on, might tell a cell to make one kind of protein (such as one that makes red hair), whereas another sequence, such as G–C–T–C–T–C, and so on, might code for a different protein (such as one that makes brown hair). Furthermore, the double helix could be unwound to allow for the exact copying of the complementary strands when the chromosomes were duplicated at cell division. At their local pub that night, Watson announced that they had “discovered the secret of life.” Watson, Crick, and Wilkins shared the 1962 Nobel Prize in Physiology or Medicine (Franklin had died in 1958).

Over the next decade, Marshall Nirenberg and his colleagues demonstrated that the sequence of each three bases in DNA coded for a specific amino acid in a protein—known as the “triplet code.” It was further demonstrated that DNA in the nucleus of a cell acts as a template for the formation of mRNA. The mRNA then leaves the nucleus, migrating to the cytoplasm where it acts as a template for the production of protein. The information contained in the mRNA molecule is translated into the “language” of amino acids, the building blocks of proteins, telling the cell’s protein-making machinery the precise order in which to link the amino acids to produce a specific protein.

Forms of DNA

DNA can exist in different forms. The Watson-Crick double helix is a right-handed helix known as the “B” form: the helix makes a turn every 3.4 nanometers (nm), and the distance between two neighboring base pairs is 0.34 nm, yielding about ten base pairs per turn of the double helix. The intertwined strands make two grooves of different widths, called the “major groove” and the “minor groove,” which facilitate the binding of specific proteins. In a solution with higher salt concentrations, DNA can change to the “A” form, which is still right-handed but makes a turn every 2.3 nm, with 11 base pairs per turn. The “Z” form of DNA derives its name from its zigzag shape. It forms a left-handed helix. Although Z–DNA was first identified in synthetic DNA prepared in the laboratory, it has since been found to occur naturally in cells in small amounts. Its biological role in cells is still being elucidated.

Complementary DNA (cDNA) is generated from mRNA in a reaction catalyzed by reverse transcriptase enzymes that come from RNA viruses. These are viruses that have RNA as their genetic material instead of DNA, and they use reverse transcriptase to make DNA to incorporate into the genome of host cells. Using mRNA as a template, scientists can use reverse transcriptase to make cDNA, which can be cloned to create a cDNA library that

KEY TERMS

Amino acids—Building blocks of proteins; 20 different amino acids are coded for by human DNA.

Complementary DNA (cDNA)—DNA that is transcribed (copied) from messenger RNA using the enzyme reverse transcriptase.

Epigenome—All of the molecules that are added to DNA molecules to regulate the activity of genes without changing the DNA sequence.

Genome—The entire DNA sequence of a cell or organism.

Human Genome Project (HGP)—An international collaboration begun in 1990 and completed in 2003 that sequenced the entire DNA sequence of the human genome.

Messenger RNA (mRNA)—The nucleic acid that is transcribed from the DNA of genes and used as the blueprint for proteins.

Mitochondrial DNA (mtDNA)—A small set of genes within mitochondria (the powerhouses of cells) that are maternally inherited.

Nucleotides—The building blocks of nucleic acids (deoxyribonucleotides in DNA and ribonucleotides in RNA), consisting of a sugar, phosphate, and nitrogen base—adenine (A), guanine (G), cytosine (C), or thymine (T)—in DNA.

Polymerase chain reaction (PCR)—A method for making millions of copies of (amplifying) a DNA sequence.

Proteins—The enzymes and structural components of the human body, made up of amino acids; DNA sequences encode the instructions for making proteins.

Single nucleotide polymorphisms (SNPs)—Common variations in single nucleotides in a DNA sequence.

represents the DNA that has been converted into mRNA and protein in cells, tissues, or organisms. This is important because only about 1% of the DNA in the human genome encodes proteins, and only a small percentage of these proteins are produced in a given type of cell or tissue.

A scientific revolution

The discovery of the structure and function of DNA ushered in scientific advances unprecedented in human

history. In 1977, Frederick Sanger developed a method of rapidly determining DNA sequences from various organisms, including humans. In 1981, the first complete genome sequence, other than viral sequences, was announced—the complete human mitochondrial genome sequence. By 1983, scientists had located the DNA that caused Huntington’s disease—the first genetic disorder to be mapped. Another technological advance in 1983, the invention of the polymerase chain reaction (PCR), enabled scientists to make millions of copies of DNAs for sequencing and cloning. By 1989, the first DNA mutation (change) that caused cystic fibrosis had been identified.

The Human Genome Project (HGP) began in 1990. This international collaboration set out to determine the sequence of all three billion base pairs of DNA in the human genome. The first draft of the human genome was published in 2001, and the project was completed in 2003, several years ahead of schedule, due to the development of new sequencing methods (next-gen sequencing). The HGP brought many surprises. For example, instead of the predicted 50,000–140,000 genes in the human genome, there were only about 20,500. In part, this is because the hypothesis that each gene coded for one enzyme (or protein), first proposed by George Beadle (1903–1989) and Edward Tatum (1909–1975) in 1941, turned out to be a gross oversimplification. Modifications to DNA, mRNA, and proteins, as well as numerous regulatory factors, can result in single genes producing different proteins. Furthermore, before the HGP, it was assumed that most of the 99% of the human genome that did not code for proteins is “junk DNA.” The ENCODE Project, an international follow-up to the HGP, has revealed that more than 80% of this non-protein-coding or non-gene DNA is essential for regulating gene expression (protein production by genes).

The HGP and next-gen sequencing have made it relatively simple to identify genes and mutations that cause genetic disorders or that make people susceptible to specific diseases, as well as to screen for mutations and diagnose disorders. These advances have also enabled researchers to study genetic variations among individuals and populations. Another scientific collaboration, the International HapMap Project (for “haplotype map”) is cataloging common genetic variations called single nucleotide polymorphisms (SNPs). These are changes in the nucleotides (A, C, T, or G) at specific locations in the human genome that can be used to identify populations and individuals. The genome contains about ten million SNPs. The HapMap Project is accelerating knowledge of the relationships between genetic differences and human diseases. Yet another large

QUESTIONS TO ASK YOUR DOCTOR

- How does DNA become damaged?
- Will my children inherit all of my DNA?
- Can my DNA be used to diagnose my disorder?
- Can my DNA tell what diseases I might develop in the future?
- What other information can my DNA provide?

collaboration has mapped human epigenomes. The epigenome is a collection of modifications to DNA that do not change the DNA sequence but that can affect the protein-producing activity of genes in health and disease. In February 2015, researchers published 111 different epigenomes from different human cell types. One goal of these studies is to discover how genetic differences affect individual responses to drugs (pharmacogenomics) and environmental factors such as toxins. It is hoped that this will lead to precision medicine, in which disease treatments are tailored to an individual’s genetic makeup, as well as environmental and lifestyle factors.

In addition to rapidly sequencing the DNA of people from around the world, scientists have learned to obtain and sequence ancient DNA from humans who lived tens of thousands of years ago. This has had a dramatic effect on ideas about the evolution of modern humans and their migration around the world. For example, it is now clear that modern humans interbred with Neanderthals and possibly other early humans, with 3%–6% of the human genome inherited from Neanderthals.

The synthesis of DNA in the laboratory also has important ramifications. Scientists have been able to design and synthesize new forms of living bacteria. DNA structures are being used to produce various synthetic products, and DNA information-coding functions are being exploited for new methods of data storage.

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DNA methylation

Methyl groups (CH₃) are enzymatically added to DNA molecules naturally in the process of methylation without changing the genetic code or genetic sequence of the DNA molecule. This methylation represses transcription of nearby promoters and can change transcriptional patterns between individuals, tissue types, cell types, or health states. Methylation is essential in animal development, and DNA methylation signatures change over time. The X chromosome inactivation in females is a response in part to DNA methylation. Cancer, immune disease, or birth defects can occur when the methylation process becomes chronically disrupted or faulty.

DNA's bases are enzymatically methylated

In addition to cytidine methylation at carbon 5, adenine methylation is seen in bacteria, mammals, and plants. A methyl (CH₃) group is added enzymatically to yield N6-methyladenine, 5-methyl cytosine, or N4-Methyl cytosine. The level of methylation in DNA varies among species from 75% of all methylation targets to almost none for 5MC. In mammals, 5MC in CG sequences have the cytosine on both strands methylated. There are other sequence targets for 5MC in embryonic stem cells, neural development, and hematopoietic (blood-making) progenitor cells. However, there is no known purpose for the alternate targets of DNA methyltransferase, enzymes responsible for methylation of bare DNA.

Deamination of 5-methyl cytosine

The structure of 5MC is similar to that of thymine. Through a common phenomenon, 5MC goes through deamination that produces thymine. With thymine in place to pair with guanosine, a mismatch in base pairing is detected, and the mismatch repair system is activated. This system repairs the mismatched base pair to either C:G or to T:A. The second possibility represents a mutation, while the first does not. In the absence of methylation, the deamination of cytosine produces uracil. This error is generally repaired correctly.

Conserved function

In mammals, around 75% of CG dinucleotides are methylated in somatic cells, and DNA methylation appears as the default state. It has to be excluded explicitly from defined locations despite the high mutation rate that occurs when mismatch repair repairs the location of a 5MC.

CG islands

CG, as a dinucleotide, is about 21% less common than predicted in the mammalian genome. However, throughout the genome, there are islands with rich CG content. They are located especially in promotor regions, with 60% to 70% of mammalian promoters having one. Methylation of CG islands near promoters unambiguously linked to transcriptional repression and methylation of CG islands within the coding sequence represses transcription from alternate promoters.

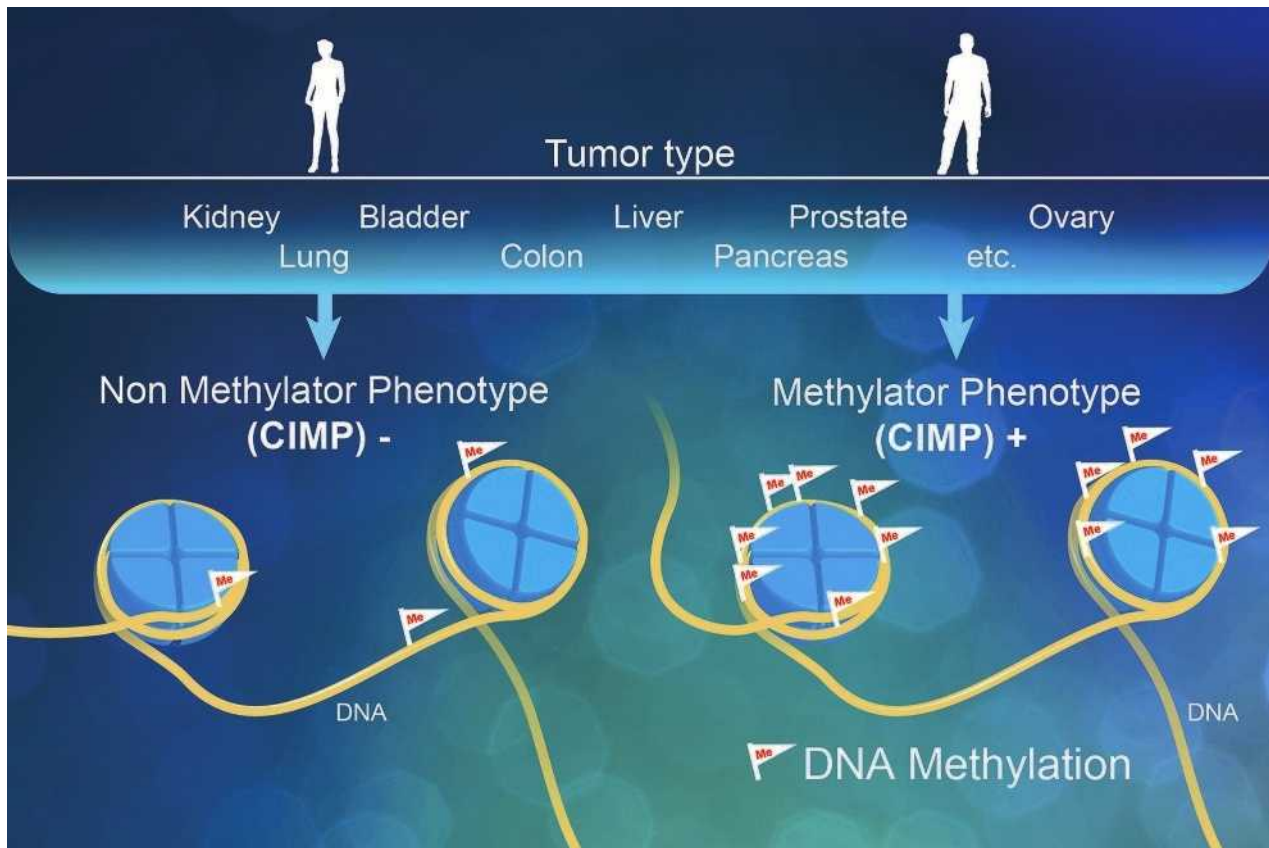
Methylation of DNA itself may physically impede the binding of the transcription complex to the gene in the promotor region. Methylated DNA can be bound by proteins that recruit additional proteins to the locus. Histones and chromatin remodeling proteins form compact, inactive DNA, termed heterochromatin. This link between DNA methylation and dense chromatin structure is very important in the control of gene expression.

Repression of transposable elements

Methylated CG sequences can permanently silence transposable elements or transposons. The significance of transposable element silencing is unknown.

Highly transcribed genes

In all species where DNA methylation occurs, there is a correlation between transcriptional activity and the density of CG in the body of their genes. Internal CG dinucleotides silence alternative promoters within the gene and transposon activity. Methylation may serve to



In every cell, DNA is tagged with chemical groups (like flags) that make up the epigenetic code. These flags help the cell's machinery know when to activate or inactivate a gene. In many tumor cells the flags are incorrectly applied. These newly added methyl groups cause the cell to act erratically, causing the cell to express genes at the wrong levels or not at all. These flags can turn off key defensive genes that help protect the cell from becoming cancerous and disrupt other processes. When this event occurs, it's called CpG island methylation phenotype, or CIMP for short. (Darryl Leja/NHGRI/Science Source)

form the platform upon which histones bind chromatin and condense the DNA.

DNA methylation in health and disease

Embryonic development

Almost all methyl groups from parents' chromosomes are erased during gametogenesis and embryogenesis. Then, methylation occurs during the implantation of the embryo, which keeps most genes except housekeeping genes repressed. After implantation, methylation patterns assume cell-type and developmental stage-specific methylation patterns that endure in differentiated cells.

Aging

DNA methylation changes with aging, with methylation status used as a molecular clock with the highest level in infants. However, some genes, like the estrogen receptor and insulin-like growth factor, become hyper-methylated over time.

Brain

Animal researchers have found changes in methylation rates in the brain following learning activities. Then, methylation returns to the native state after several weeks. The memory remains, however.

Exercise

Demethylation slows following intense exercise in some genes in skeletal muscles and leads to increased methylation levels in adipose tissue. There is also preliminary evidence that more physical activity leads to greater DNA methylation in white blood cells.

B cell differentiation

B cells are hypomethylated throughout their differentiation. The largest difference in methylation rate is seen in germinal center B cells and memory B cells. Long-lived B cells also share a methylation pattern with B cell tumors.

Cancer

Widespread hypomethylation is linked to the development of several cancers. Changes in DNA methylation are seen during cancer development, with hypomethylation linked to chromosomal instability and loss. DNA hypermethylation is associated with promoters that allow transcription of oncogene suppressors. Cancer develops readily without oncogene suppressors.

DNA methyltransferases

Methylation of DNA in mammals is mainly on the C5 position of cytosine in CG dinucleotides. DNMT1 is the proposed maintenance methyltransferase responsible for copying DNA methylation patterns to the daughter strands during replication. At the same time, DNMT3a and DNMT3b are the de novo DNA methyltransferases that set up DNA methylation patterns early in development.

Differentially methylated regions (DMRs)

DMRs are regions of the genome that are methylated in a different pattern according to tissue type, cell type, age, disease state, or between individuals. These functional regions are involved in gene transcriptional regulation. Studying them may unlock secrets to cell differentiation or disease states.

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Dolichospondylic dysplasia see **3-M syndrome**

Donohue syndrome

Definition

Donohue syndrome, also formerly called leprechaunism, is a genetic disorder caused by mutations in the insulin receptor gene. W. L. Donohue first described this rare syndrome in 1948.

Description

Donohue syndrome is a disorder that causes low birth weight, unusual facial features, and failure to thrive in infants. It is associated with the over-development of the pancreas, a gland located near the stomach. It is also considered to be the most insulin-resistant form of diabetes.

Donohue syndrome results from a mutation of the insulin receptor gene *INSR*, which prevents insulin in the blood from being processed. Therefore, even before birth the fetus exhibits insulin resistance and has high levels of unprocessed insulin in the blood. Insulin is one of two hormones secreted by the pancreas to control blood sugar (glucose) levels. Donohue syndrome is known as a progressive endocrine disorder because it relates to the growth and functions of the endocrine system, the collection of glands and organs that deliver hormones via the bloodstream.

Hormones are chemicals released by the body to control cellular function (metabolism) and maintain equilibrium (homeostasis). These hormones are released either by the endocrine system or by the exocrine system. The endocrine system consists of ductless glands that secrete hormones into the blood stream. These hormones then travel through the blood to the parts of the body where they are required. The exocrine system consists of ducted glands that release their hormones via ducts directly to the site where they are needed. The pancreas is both an endocrine and an exocrine gland. As part of the endocrine system, the pancreas acts as the original producer of estrogen and other sex hormones in fetuses of both sexes. It also regulates blood sugar through its production of the hormones insulin and glucagon. The pancreas releases insulin in response to high levels of glucose in the blood. Glucagon is released when glucose

levels in the blood are low. These two hormones act in direct opposition to each other (antagonistically) to maintain proper blood sugar levels. As an exocrine gland, the pancreas secretes digestive enzymes directly into the small intestine.

In an attempt to compensate for the high blood insulin level, the pancreas overproduces glucagon as well as the female hormone estrogen and other related (estrogenic) hormones. As excess estrogen and related hormones are produced, they affect the development of the external and internal sex organs (genitalia) of the growing baby.

Insulin mediates the baby's growth in the womb through the addition of muscle and fat. A genetic link between fetal insulin resistance and low birth weight has been suggested. Without the proper processing of insulin, the fetus will not gain weight as fast as expected. Therefore, the effects of Donohue syndrome tend to become visible during the seventh month of development, when the fetus either stops growing entirely or shows a noticeable slowdown in size and weight gain. This lack of growth is further evident at birth in affected infants, who demonstrate extreme thinness (emaciation), difficulty in gaining weight, a failure to thrive, and delayed maturation of the skeletal structure.

Genetic profile

Donohue syndrome is a non-sex-linked (autosomal) recessive disorder. In 1988, Donohue syndrome was identified as the first insulin receptor gene mutation directly related to a human disease. The gene responsible for the appearance of Donohue syndrome is the insulin receptor gene *INSR*, located on the short arm of chromosome 19 at 19p13.2. More than 40 distinct mutations of this gene have been identified. Besides Donohue syndrome, other types of non-insulin-dependent (type 2) diabetes mellitus (NIDDM) can result from mutations of this gene, including Rabson-Mendenhall syndrome and type A insulin resistance syndrome. Donohue syndrome is considered the most severe of these three *INSR*-related disorders, with Rabson-Mendenhall syndrome intermediate in severity (patients survive into their late teens or early 20s) and type A insulin resistance syndrome the mildest (it is not usually life-threatening).

Demographics

Donohue syndrome occurs in approximately one out of every four million live births. About 70 cases worldwide have been reported between 1948 and 2021, with two-thirds of reported patients being females; thus, the female: male ratio for this syndrome is 2:1. As in all recessive genetic disorders, both parents must carry the

genetic mutation in order for their child to have the disorder. Therefore, Donohue syndrome has been observed most often in cases in which the parents are related by blood (consanguineous). Parents with one child affected by Donohue syndrome have a 25% likelihood that their next child will also be affected with the disease.

Donohue syndrome appears most frequently in countries where first-cousin marriage is legally permitted. Affected families have been identified among African Americans, among First Nations tribes in Canada, in Yemen, in Israel, in Japan, in Turkey, in France, in China, and in eastern Europe. It appears, however, that the disorder can affect patients in any race or ethnic group.

Signs and symptoms

Infants born with Donohue syndrome have characteristic facial features that have been said to exhibit elfin or leprechaun-like qualities, such as a smallish head with large, poorly developed, and low-set ears; a flat nasal ridge with flared nostrils; thick lips; a greatly exaggerated mouth width; and widely spaced eyes (hypertelorism). They will be very thin and have low blood sugar (hypoglycemia) due to their inability to gain nutrition through insulin processing. They will exhibit delayed bone growth and maturation, and difficulty in gaining weight and developing (failure to thrive).

Donohue syndrome patients are prone to persistent and recurrent infections. Delayed bone growth not only leads to skeletal abnormalities but also to a compromised immune system. Many of the chemicals used by the body to fight infection are produced in the marrow of the bones. When bone maturation is delayed, these chemicals are not produced in sufficient quantities to fight off or prevent infection.

At birth, affected individuals can also have an enlarged chest, with possible breast development, excessive hairiness (hirsutism), as well as overdeveloped external sex organs because of increased estrogen production caused by an overactive pancreas. As an additional side effect of the increased sex hormones released in Donohue syndrome, these individuals often have extremely large hands and feet relative to their non-affected peer group. As the result of a lack of insulin, the infant is likely to have a relatively small amount of muscle mass, very little fat, and a distended abdomen (due to malnutrition). Additional symptoms of Donohue syndrome include pachyderma, or elephant skin, in which there is excess skin production causing large, loose folds; and abnormal coloration (pigmentation) of the skin in the folds of the body known as acanthosis nigricans. These individuals are also quite susceptible to both umbilical and inguinal hernias.

KEY TERMS

Acanthosis nigricans—A skin condition distinguished by velvety, dark patches where the skin is folded or creased.

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Chorionic villus sampling (CVS)—A procedure involving removal of a small placental sample during pregnancy to obtain fetal chromosome results.

Consanguineous—Sharing a common bloodline or ancestor.

Endocrine system—A system of ductless glands that regulate and secrete hormones directly into the bloodstream.

Fibroblasts—Cells that form connective tissue fibers like skin.

Hirsutism—The presence of coarse hair on the face, chest, upper back, or abdomen in a female as a result of excessive androgen production.

Histologic—Pertaining to histology, the study of cells and tissues at the microscopic level.

Hypoglycemia—An abnormally low glucose (blood sugar) concentration in the blood.

Insulin—A hormone produced by the pancreas that is secreted into the bloodstream and regulates blood sugar levels.

Insulin receptor gene—The gene responsible for the production of insulin receptor sites on cell surfaces. Without properly functioning insulin receptor sites, cells cannot attach insulin from the blood for cellular use.

Insulin resistance—An inability to respond normally to insulin in the bloodstream.

Insulin-like growth factor I—A hormone released by the liver in response to high levels of growth hormone in the blood. This growth factor is very similar to insulin in chemical composition, and like insulin, it is able to bring about cell growth by causing cells to undergo mitosis (cell division).

Pachyderma—An abnormal skin condition in which excess skin is produced that appears similar to that of an elephant (pachyderm).

Pancreas—An organ located in the abdomen that secretes pancreatic juices for digestion and hormones for maintaining blood sugar levels.

Serological—Pertaining to serology, the science of testing blood to detect the absence or presence of antibodies (an immune response) to a particular antigen (foreign substance).

In addition to the defect in the insulin receptor gene, Donohue syndrome is associated with problems in the epidermal growth factor receptor, which controls growth of the skin. Abnormal functioning of the epidermal growth factor receptor has been identified in three unrelated individuals affected with Donohue syndrome. This finding suggests that the probable cause of Donohue syndrome is more than just the insulin receptor. These observations may help explain the physical symptom of pachyderma in those affected with Donohue syndrome. It has also been suggested that the high concentrations of insulin close to the cell membranes lead to a lowering of growth hormone receptor activity at these locations. This lowered growth hormone activity in turn causes slowed cellular growth, which leads to systemic growth failure in affected patients.

Diagnosis

In families with a history of the disease, diagnosis in utero before birth of the fetus is possible through molecular DNA analysis of tissue samples from the chorionic

villi, which are cells found in the placenta. Molecular genetics testing for Donohue syndrome is widely available in the United States and Europe for carrier parents as well as patients.

After birth, the diagnosis of Donohue syndrome is usually made based on the blood tests that show severe insulin resistance coupled with hypoglycemia. The presence of several of the physical symptoms in addition to positive results in a test for severe insulin resistance, such as an insulin receptor defect test or a fasting hypoglycemia test, is usually sufficient for a diagnosis of Donohue syndrome. The diagnosis of Donohue syndrome may be confirmed by observed cellular (histologic) changes in the ovaries, pancreas, and breast that are not normal for the age of the patient.

Treatment and management

Genetic counseling of parents with a Donohue syndrome-affected child may help prevent the conception of additional children affected with this genetic disorder. After birth, affected infants may require treatment

for malnutrition as well as insulin-resistant diabetes. Patients with a demonstrated residual insulin receptor function may survive past infancy. In these cases, the treatment regimen must certainly include ongoing insulin-resistant diabetes care and dietetic counseling to assist with weight gain. It may also be necessary to administer growth hormone therapy to certain patients to spur growth, but this is indicated only in those individuals who show signs of functioning growth hormone receptors and no signs of higher-than-normal resistance to growth hormone.

The revolutionary impact of recombinant DNA technology, whereby scientists can mass-produce genetic material for use in medicine, has made possible another treatment method that involves the introduction of recombinant human insulin-like growth factor 1 (rhIGF-1) into the body. A case study has been reported of a female affected with Donohue syndrome and low levels of insulin-like growth factor 1 (IGF-1), which is indicative of a higher-than-normal resistance to growth hormone.

Examination of the patient's fibroblasts showed normal binding of IGF-1 and normal functioning of these fibroblasts in response to IGF-1. Fibroblasts are connective tissue cells that accomplish growth in humans by differentiating into chondroblasts, collagenoblasts, and osteoblasts, all of which are the precursor cells necessary to produce bone growth in humans. This case report indicates that if enough IGF-1 could get to the fibroblasts in the patient's body, there is every reason to believe that these fibroblasts would function normally and mature into the precursor cells needed for bone growth. This finding made the patient an ideal candidate for rhIGF-1 treatments.

In this study, the long- and short-term effects on growth patterns and glucose metabolism in the patient were studied after the treatment with rhIGF-1. The rhIGF-1 that was not immediately utilized by the patient was rapidly destroyed in the cellular conditions produced by Donohue syndrome. Therefore, to maintain the desired levels of rhIGF-1 in the blood, the patient received rhIGF-1 both in injections prior to every meal and via a continuous subcutaneous infusion method similar to that used to continuously pump insulin for some patients with diabetes. Recombinant human IGF-1 was administered to this patient over a period of six years with an observation of normal blood glucose levels and a return to normal growth patterns. Moreover, the treatment did not cause negative side effects. The results of this case study offer a promising treatment for certain individuals affected with Donohue syndrome.

A 2013 report from a group of Japanese researchers indicated that treatment with rhIGF-1 was effective for

QUESTIONS TO ASK YOUR DOCTOR

- How is my child's Donohue syndrome related to diabetes?
- Are there treatments available to cure or slow the progress of Donohue syndrome in my child?
- What clinical trials for treatments of Donohue syndrome are currently in progress?
- What is the prognosis for a child diagnosed with Donohue syndrome prenatally?

about two years in treating a male patient with Donohue syndrome but was unsuccessful in bringing about his longer-term survival. Another case study was published in 2014 of a female treated with rhIGF-1 administered through an insulin pump. The patient's progress was interrupted, however, by the development of an ovarian tumor. The authors of the study concluded that further experience with the use of an insulin pump is needed to confirm the efficacy of continuous rhIGF-1 infusion as a treatment for Donohue syndrome.

Prognosis

Individuals born with Donohue syndrome generally die in infancy from either malnutrition or recurrent and persistent infection. All individuals affected with Donohue syndrome who survive past infancy have severe intellectual disability and profound motor skill impairment. Survival into childhood is thought to be due to some remaining insulin receptor function and the ability of extremely high insulin concentrations to transmit signals through alternate pathways.

There is an additional possibility that the mutations responsible for Donohue syndrome may increase the risk of cancer in long-term survivors. The case study of the female patient who developed ovarian cancer has already been mentioned. Another case was reported in 2013 of a female patient with Donohue syndrome who survived until age 24 with rhIGF-1 therapy but then developed cancer of the endometrium (the tissue that lines the uterus). Further research will be needed to determine whether mutations in the *INSR* gene are associated with cancer as well as insulin resistance syndromes.

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ORGANIZATIONS

Endocrine Society, 2055 L St. NW, Suite 600, Washington, DC 20036, (202) 971-3636, (888) 363-6274, <http://www.endocrine.org>

National Center for Biotechnology Information, 8600 Rockville Pike, Bethesda, MD 20894, (888) 346-3656, <http://www.ncbi.nlm.nih.gov>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06813, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Paul A. Johnson
and Rebecca J. Frey, PhD

Down syndrome

Definition

Down syndrome is the most common chromosome disorder and genetic cause of intellectual disability. It occurs because of the presence of an extra copy of chromosome 21. For this reason, it is also called trisomy 21.

Description

When a baby is conceived, the sperm cell from the father and the egg cell from the mother undergo a reduction of the total number of chromosomes from 46 to 23. Occasionally an error occurs in this reduction process, and instead of passing on 23 chromosomes to the baby, a parent will pass on 24 chromosomes. This event is called nondisjunction, and it occurs in 95% of Down syndrome cases. The baby therefore receives an extra



Young girl with Down syndrome. (Design Pics/Disability Images)

chromosome at conception. In Down syndrome, that extra chromosome is chromosome 21. Because of this extra chromosome 21, individuals affected with Down syndrome have 47 instead of 46 chromosomes.

Genetic profile

In approximately 1%–2% of Down syndrome cases, the original egg and sperm cells contain the correct number of chromosomes, 23 each. The problem occurs sometime shortly after fertilization—during the phase when cells are dividing rapidly. One cell divides abnormally, creating a line of cells with an extra copy of chromosome 21. This form of genetic disorder is called mosaicism. The individual with this type of Down syndrome has two types of cells: those with 46 chromosomes (the normal number), and those with 47 chromosomes (as occurs in Down syndrome). Individuals affected with this mosaic form of Down syndrome generally have less severe signs and symptoms of the disorder.

Another relatively rare genetic accident that causes Down syndrome is called translocation. During cell division, chromosome 21 somehow breaks. The broken-off piece of this chromosome then becomes attached to another chromosome. Each cell still has 46 chromosomes, but the extra piece of chromosome 21 results in the signs and symptoms of Down syndrome. Translocations occur in about 3%–4% of cases of Down syndrome.

Once a couple has had one baby with Down syndrome, they are often concerned about the likelihood of future offspring also being born with the disorder. Mothers under the age of 35 with one Down syndrome-affected child have a 1% chance that a second child will also be born with Down syndrome. In mothers 35 and older, the chance of a second child being affected with Down syndrome is approximately the same as for any woman at a similar age. However, when the baby with Down syndrome has the type that results from a translocation, it is possible that one of the two parents is a carrier of a balanced translocation. A carrier has rearranged chromosomal information and can pass it on, but he or she does not have an extra chromosome and therefore is not affected with the disorder. When one parent is a carrier of a translocation, the chance of future offspring having

Down syndrome is greatly increased. The specific risk will have to be assessed by a genetic counselor.

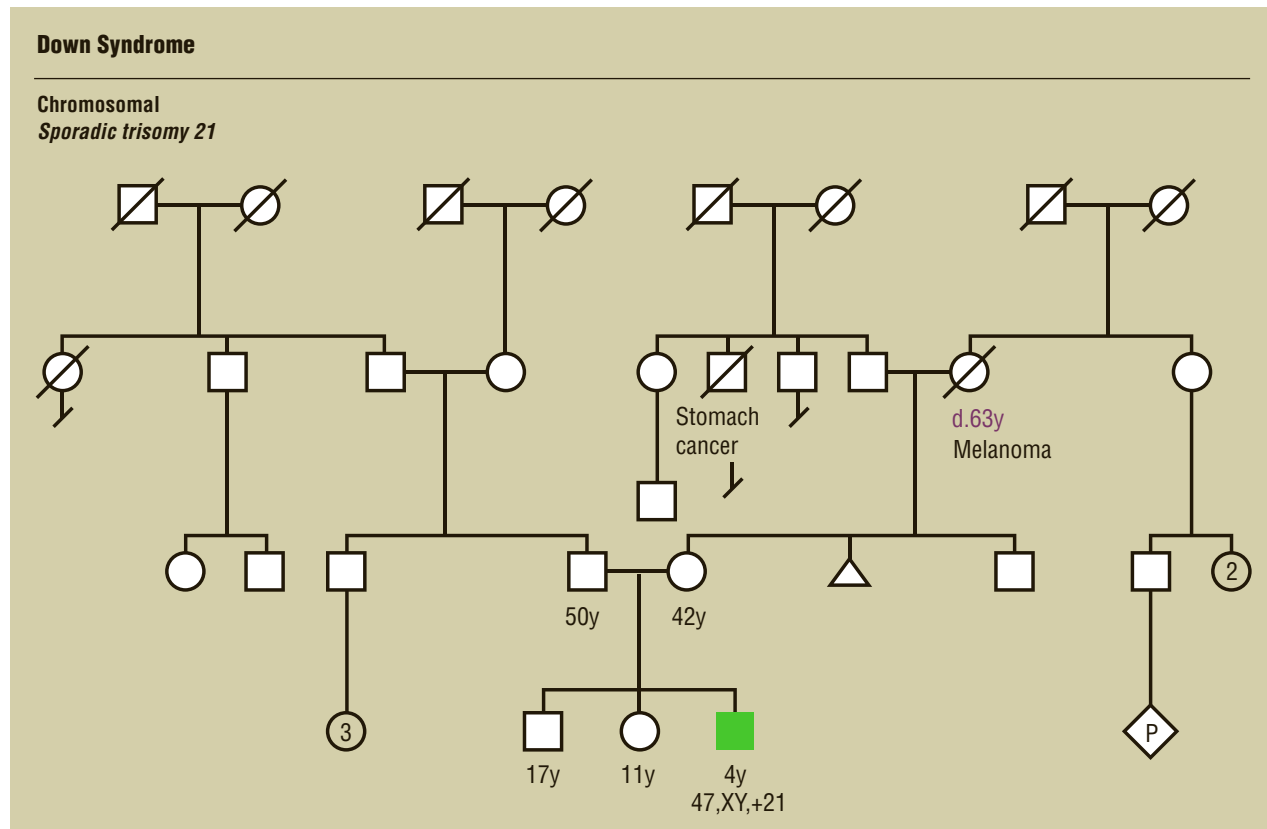
Demographics

Down syndrome occurs in about 1 in every 800 live births. It affects an equal number of male and female babies. The majority of cases of Down syndrome occur due to an extra chromosome 21 within the egg cell supplied by the mother (nondisjunction). As a woman's age (maternal age) increases, the risk of having a Down syndrome baby increases significantly. By the time the woman is age 35, the risk increases to 1 in 400; by age 40 the risk increases to 1 in 110; and by age 45 the risk becomes 1 in 35. There is no increased risk of either mosaicism or translocation with increased maternal age.

Down syndrome occurs with equal frequency across all ethnic groups and subpopulations.

Signs and symptoms

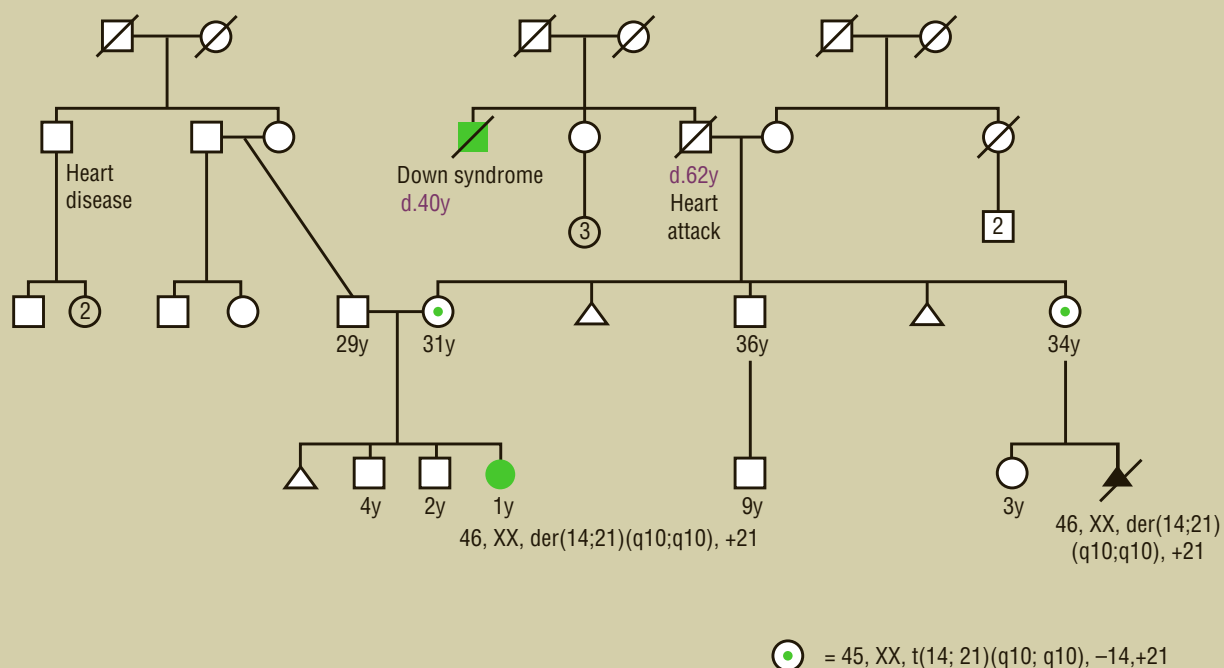
While Down syndrome is a chromosomal disorder, a baby is usually identified at birth through observation of a set of common physical characteristics. Not all affected babies will exhibit all of the symptoms discussed. There



Down syndrome: pedigree analysis chart (Gale)

Down Syndrome

Family Robertsonian Translocation



Down syndrome: pedigree analysis chart (Gale)

is a large variability in the number and severity of these characteristics from one affected individual to the next. Babies with Down syndrome tend to be overly quiet, less responsive to stimuli, and have weak, floppy muscles. A number of physical signs may also be present. These include: a flat-appearing face; a small head; a flat bridge of the nose; a smaller than normal, low-set nose; small mouth, which causes the tongue to stick out and to appear overly large; upward slanting eyes; bright speckles on the iris of the eye (Brushfield spots); extra folds of skin located at the inside corner of each eye near the nose (epicanthal folds); rounded cheeks; small, misshapen ears; small, wide hands; an unusual deep crease across the center of the palm (simian crease); an inwardly curved little finger; a wide space between the great and the second toes; unusual creases on the soles of the feet; overly flexible joints (sometimes referred to as being double-jointed); and shorter-than-normal stature.

Other types of defects often accompany Down syndrome. Approximately 30%–50% of all children with Down syndrome are found to have heart defects. A number of different heart defects are common in Down syndrome. All of these result in abnormal patterns of blood flow within the heart. Abnormal blood flow within the

heart often means that less oxygen is sent into circulation throughout the body, which can cause fatigue, a lack of energy, and poor muscle tone.

Malformations of the gastrointestinal tract are present in about 5%–7% of children with Down syndrome. The most common malformation is a narrowed, obstructed duodenum (the part of the small intestine into which the stomach empties). This disorder, called duodenal atresia, interferes with the baby's milk or formula leaving the stomach and entering the intestine for digestion. The baby often vomits forcibly after feeding and cannot gain weight appropriately until the defect is repaired.

Another malformation of the gastrointestinal tract that is seen in patients with Down syndrome is an abnormal connection between the windpipe (trachea) and the digestive tube of the throat (esophagus) called a tracheoesophageal fistula (T-E fistula). This connection interferes with eating and/or breathing because it allows air to enter the digestive system and/or food to enter the airway.

Other medical conditions occurring in patients with Down syndrome include an increased chance of developing infections, especially ear infections and pneumonia; certain kidney disorders; thyroid disease (especially low

or hypothyroid); hearing loss; vision impairment requiring glasses (corrective lenses); and a 20 times greater chance than the population as a whole of developing leukemia.

Development in a baby and child affected with Down syndrome occurs at a much slower than normal rate. Because of weak, floppy muscles (hypotonia), babies learn to sit up, crawl, and walk much later than their unaffected peers. Talking is also quite delayed. The level of intellectual disability is considered to be mild-to-moderate in Down syndrome. The degree of intellectual disability varies a great deal from one child to the next. While it is impossible to predict the severity of Down syndrome at birth, with proper education, children who have Down syndrome are capable of learning. Most children affected with Down syndrome can read and write and are placed in special education classes in school. The majority of individuals with Down syndrome become semi-independent adults, meaning that they can take care of their own needs with some assistance.

As people with Down syndrome age, they face an increased chance of developing the brain disease called Alzheimer's (sometimes referred to as dementia or senility). Most people have a 12% chance of developing Alzheimer's, but almost all people with Down syndrome will have either Alzheimer disease or a similar type of dementia by the age of 50. Alzheimer disease causes the brain to shrink and to break down. The number of brain cells decreases, and abnormal deposits and structural arrangements occur. This process results in a loss of brain functioning. People with Alzheimer's have strikingly faulty memories. Over time, people with Alzheimer's disease will lapse into an increasingly unresponsive state.

As people with Down syndrome age, they also have an increased chance of developing a number of other illnesses, including cataracts, thyroid problems, diabetes, and seizure disorders.

Diagnosis

Diagnosis is usually suspected at birth, when the characteristic physical signs of Down syndrome are noted. Once this suspicion has been raised, genetic testing (chromosome analysis) can be undertaken in order to verify the presence of the disorder. This testing is usually done on a blood sample, although chromosome analysis can also be done on other types of tissue, including the skin. The cells to be studied are prepared in a laboratory. Chemical stain is added to make the characteristics of the cells and the chromosomes stand out. Chemicals are added to prompt the cells to go through normal development up to the point where the chromosomes are most visible, prior to cell division. At this point, they are

KEY TERMS

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Intellectual disability—Significant impairment in intellectual function and adaptation in society. Usually associated with an intelligence quotient (IQ) below 70.

Karyotype—A standard arrangement of photographic or computer-generated images of chromosome pairs from a cell in ascending numerical order from largest to smallest.

Mosaic—A term referring to a genetic situation in which an individual's cells do not have the exact same composition of chromosomes. In Down syndrome, this may mean that some of the individual's cells have a normal 46 chromosomes, while other cells have an abnormal 47 chromosomes.

Nondisjunction—Nonseparation of a chromosome pair, during either meiosis or mitosis.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosome material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

Trisomy—The condition of having three identical chromosomes instead of the normal two in a cell.

examined under a microscope and photographed. The photograph is used to sort the different sizes and shapes of chromosomes into pairs. In most cases of Down syndrome, one extra chromosome 21 will be revealed. The final result of such testing, with the photographed chromosomes paired and organized by shape and size, is called the individual's karyotype. An individual with Down syndrome will have a 47 XX+21 karyotype if they are female and a 47 XY+21 karyotype if they are male.

Women who become pregnant after the age of 35 are offered prenatal tests to determine whether their developing baby is affected with Down syndrome. A genetic counselor meets with these families to inform them of the risks and to discuss the types of tests available

to make a diagnosis prior to delivery. Because there is a slight risk of miscarriage following some prenatal tests, all testing is optional, and couples need to decide whether they desire to take this risk in order to learn the status of their unborn baby.

Screening tests are used to estimate the chance that an individual woman will have a baby with Down syndrome. A test called the maternal serum alpha-fetoprotein test (MSAFP) is offered to all pregnant women under the age of 35. If the mother decides to have this test, it is performed between 15 and 22 weeks of pregnancy. The MSAFP screen measures a protein and two hormones that are normally found in maternal blood during pregnancy. A specific pattern of these hormones and protein can indicate an increased risk for having a baby born with Down syndrome. However, this is only a risk and MSAFP cannot diagnose Down syndrome directly. Women found to have an increased risk of their babies being affected with Down syndrome are offered amniocentesis. The MSAFP test can detect up to 60% of all babies who will be born with Down syndrome.

Ultrasound screening for Down syndrome is also available. This is generally performed in the mid-trimester of pregnancy. Abnormal growth patterns characteristic of Down syndrome such as growth retardation, heart defects, duodenal atresia, T-E fistula, shorter than normal long-bone lengths, and extra folds of skin along the back of the neck of the developing fetus may all be observed via ultrasonic imaging.

The only way to definitively establish (with about 99% accuracy) the presence or absence of Down syndrome in a developing baby is to test tissue during the pregnancy itself. This is usually done either by amniocentesis or chorionic villus sampling (CVS). All women under the age of 35 who show a high risk for having a baby affected with Down syndrome via an MSAFP screen and all mothers over the age of 35 are offered either CVS or amniocentesis. In CVS, a tiny tube is inserted into the opening of the uterus to retrieve a small sample of the placenta (the organ that attaches the growing baby to the mother via the umbilical cord and provides oxygen and nutrition). In amniocentesis, a small amount of the fluid in which the baby is floating is withdrawn with a long, thin needle. CVS may be performed as early as 10 to 12 weeks into a pregnancy. Amniocentesis is generally not performed until at least the 15th week. Both CVS and amniocentesis carry small risks of miscarriage. Approximately 1% of women miscarry after undergoing CVS testing, while approximately one-half of 1% miscarry after undergoing amniocentesis. Both amniocentesis and CVS allow the baby's own karyotype to be determined.

QUESTIONS TO ASK YOUR DOCTOR

- What does the term "trisomy 21" mean when speaking about Down syndrome?
- What caused my child to be born with Down syndrome?
- What is the extent of intellectual disability that my child has experienced as a result of her Down syndrome?
- Are there medical problems we should expect to see in the future as the result of our child's Down syndrome?

Approximately 75% of all babies diagnosed prenatally as affected with Down syndrome do not survive to term and spontaneously miscarry. In addition, these prenatal tests can only diagnose Down syndrome, not the severity of the symptoms that the unborn child will experience. For this reason, a couple might use this information to begin to prepare for the arrival of a baby with Down syndrome, to terminate the pregnancy, or in the case of miscarriage or termination, decide whether to consider adoption as an alternative.

Treatment and management

No treatment is available to cure Down syndrome. Treatment is directed at addressing the individual concerns of a particular patient. For example, heart defects may require surgical repair, as will duodenal atresia and T-E fistula. Many Down syndrome patients will need to wear glasses to correct vision. Patients with hearing impairment benefit from hearing aids.

While some decades ago all children with Down syndrome were quickly placed into institutions for life-long care, research shows very clearly that the best outlook for children with Down syndrome is a normal family life in their own home. This requires careful support and education of the parents and the siblings. It is a life-changing event to learn that a new baby has a permanent condition that will affect essentially all aspects of his or her development. Some community groups help families deal with the emotional effects of raising a child with Down syndrome. Schools are required to provide services to children with Down syndrome, sometimes in separate special education classrooms, and sometimes in regular classrooms (this is called mainstreaming or inclusion).

Prognosis

The prognosis for an individual with Down syndrome is quite variable, depending on the types of complications (heart defects, susceptibility to infections, development of leukemia, etc.). The severity of the retardation can also vary significantly. Without the presence of heart defects, about 90% of children with Down syndrome live into their teens. People with Down syndrome appear to go through the normal physical changes of aging more rapidly, however. The average age of death for an individual with Down syndrome is about 50 to 55 years.

Still, the prognosis for a baby born with Down syndrome is better than ever before. Because of modern medical treatments, including antibiotics to treat infections and surgery to treat heart defects and duodenal atresia, life expectancy has greatly increased. Community and family support allows people with Down syndrome to have rich, meaningful relationships. Because of educational programs, some people with Down syndrome are able to hold jobs.

Approximately 60% of women with Down syndrome are fully capable of having children. The risk of a woman with trisomy 21 having a child affected with Down syndrome is 50%.

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- "What Is Down Syndrome?" NDSS. <https://www.ndss.org/about-down-syndrome/down-syndrome/> (accessed June 1, 2021).

ORGANIZATIONS

- Down Syndrome Education USA, 18023 Sky Park Circle, Suite F, Irvine, CA 92614, (949) 757-1877, hello@dseusa.org, <http://www.dseusa.org/en-us>

National Down Syndrome Congress, 30 Mansell Court, Suite 108, Roswell, GA 30076, (770) 604-9500, (800) 232-6372, (770) 604-9898, info@ndsccenter.org, <http://www.ndsccenter.org>

National Down Syndrome Society (NDSS), 8 E 41st Street, 8th Floor, New York, NY 10017, (800) 221-4602, info@ndss.org, <http://www.ndss.org>

Paul A. Johnson

DRPLA see **Dentatorubral-pallidoluysian atrophy**

Duane syndrome

Definition

Duane syndrome (DS), also called Duane retraction syndrome (DRS), is a congenital disorder that limits the movement of the eye. It may also involve other systems of the body.

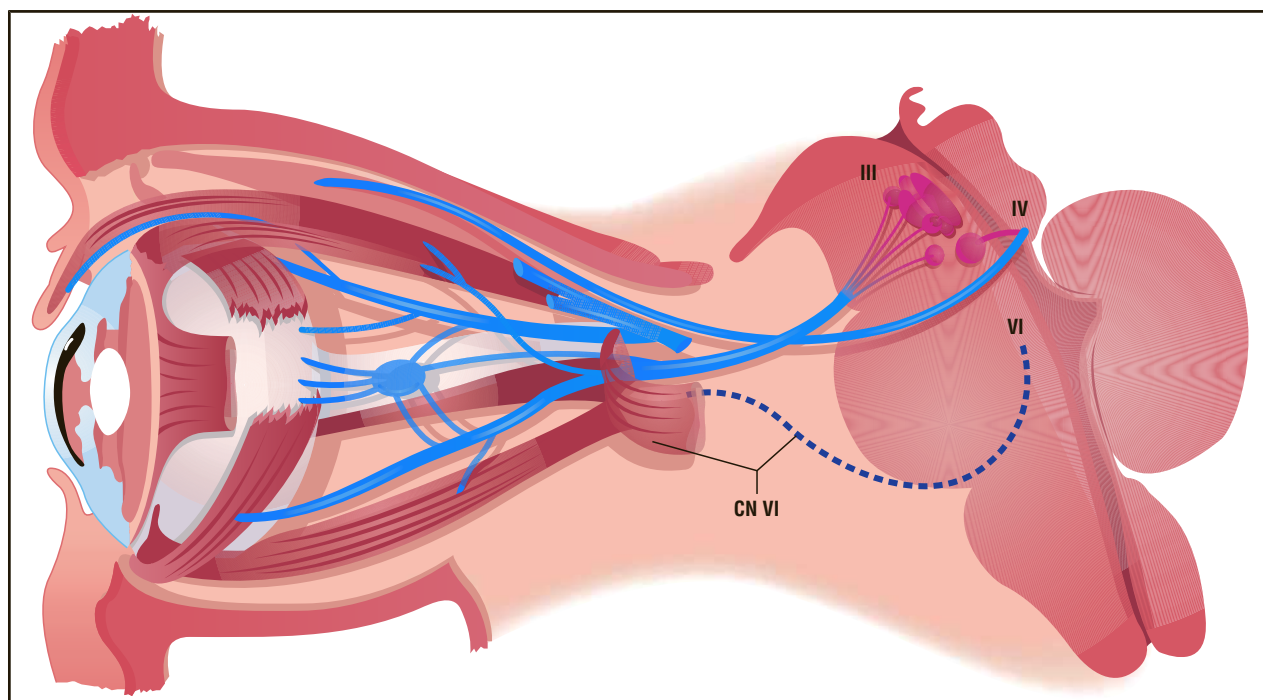
Description

Duane syndrome is an inherited disorder characterized by a limited ability to move the eye to one side or the other. DS is congenital, meaning that it is present at birth. It results from abnormal connections among the nerves that control the muscles of the eyes. About 80% of DS cases involve one eye (unilateral), and about 20% involve both eyes (bilateral). Most unilateral DS cases (72%) involve the left eye.

DS was first described in 1905 by American ophthalmologist Alexander Duane (1858–1926). It also is known as:

- Duane retraction syndrome (DUS)
- DR syndrome
- eye retraction syndrome
- retraction syndrome
- Stilling-Turk-Duane syndrome

DS is one of a group of conditions known as strabismus, or misalignment of the eye. It is classified as an incomitant strabismus because it is a misalignment of the eye that varies, depending on the direction that the eye is gazing. It is further classified as an extraocular muscle fibrosis syndrome, which means that it is a condition associated with the muscles that move the eyes. Both the active and the passive movement of the eyeball are affected in DS.



Eye diagram showing lack of the sixth cranial nerve (Gale)

Physiology

DS is believed to result from an abnormality that occurs during the development of the fetus in the womb. It may be caused by either environmental factors, genetic factors, or a combination of both. The developmental abnormality is believed to occur between the third and eighth weeks of fetal development. This is the period when the ocular muscles that rotate the eye and the cranial nerves from the brain that control the ocular muscles are forming in the fetus.

DS appears to result from the absence of cranial nerve VI, which is known as the abducens nerve. The nerve cells in the brain that connect to the abducens nerve are also missing. The abducens nerve controls the lateral rectus muscle of the eye. This muscle moves one eye outward toward the ear as a person looks toward that side. This movement is called abduction. In DS, the nerves from a branch of cranial nerve III (the oculomotor nerve) also are abnormal. The oculomotor nerve controls several eye muscles, including the medial rectus muscle. This muscle moves the eye inward toward the nose as the person looks toward the other side. This movement is called adduction.

The majority of individuals with DS have limited or no ability to move an eye outward toward the ear. Instead, the opening between the eyelids (palpebral fissure) of that eye widens, and the eyeball protrudes. In addition, individuals with DS may have only a limited ability to move

the eye inward toward the nose. Instead, when looking inward toward the nose, the medial and lateral recti muscles contract simultaneously. This causes the eyeball to retract, or pull into the skull; and it causes the opening between the eyelids to narrow as if one were squinting. Sometimes, the eye moves up or down as the individual attempts to look toward the nose. This is called upshoot or downshoot, respectively.

In some individuals with DS, the eyes may cross when looking straight ahead. Gazing straight ahead is called the primary position or primary gaze. Crossed eyes may cause the person to turn the head to one side or the other to restore binocular vision. In such individuals, this head turning may become habitual.

Associated syndromes

About 30% to 50% of individuals with DS have associated abnormalities. These may include additional eye problems, deafness, or nervous system or skeletal abnormalities. In particular, DS may be associated with abnormalities in the upper extremities, especially the hands. Sometimes DS is associated with Holt-Oram syndrome, a hereditary heart defect.

Okihiro syndrome is DS in association with other abnormalities that may include:

- flatness in the normally fleshy region between the thumb and the wrist (the thenar eminence) of one or both hands

- inability to flex the joint in the thumb
- hearing loss or deafness in one or both ears

Okiihiro syndrome also is known as:

- Duane syndrome with radial ray anomalies (as in the arms and hands)
- Duane/radial dysplasia syndrome (referring to abnormal tissue growth in the arms and hands)
- DR syndrome (the “D” refers to Duane anomaly and deafness; the “R” refers to radial and renal [kidney] dysplasia, or abnormal tissue growth in the arms, hands, and kidneys)
- Duane anomaly with radial ray abnormalities and deafness

Genetic profile

Portions of several of the 23 pairs of human chromosomes may be associated with DS. A gene that is involved in DS has been localized to a region of chromosome 2. Deletions of portions of chromosomes 4 and 8 have also been associated with DS. The presence of an additional small chromosome, thought to be broken off from chromosome 22, has been associated with DS. It is possible that these chromosome rearrangements and abnormalities may account for the wide range of symptoms and syndromes that can occur with DS. Three genes firmly associated with for DS and the associated syndromes have been identified. These are *CHN1*, *MAFB*, and *SALL4*. It is possible that DS arises from a combination of environmental factors and defects in one or more of these genes.

About 90% of cases of DS arise spontaneously. Among the other 10% that are familial, the inheritance of DS is autosomal, meaning that the trait is not carried on either the X or Y sex chromosomes. The most common type of DS, DS1, is inherited as an autosomal dominant trait. This means that only a single copy of a DS gene, inherited from one parent, can result in the condition. The offspring of a parent with DS is expected to have a 50% chance of inheriting the disorder. Some forms of DS are inherited in a recessive pattern. This requires the individual to inherit two copies of a gene, one from each parent.

Family members may exhibit different types of DS, indicating that the same genetic defect may be expressed by a range of symptoms. The severity of DS also may vary among family members. Furthermore, the majority of individuals with DS do not appear to have a family history of the disorder. There are very few reports of single families with a large number of affected individuals. However, close relatives of individuals with DS often

KEY TERMS

Abducens nerve—Cranial nerve VI; the nerve that extends from the midbrain to the lateral rectus muscle of the eye and controls movement of the eye toward the ear (abduction).

Abduction—Turning away from the midline of the body.

Adduction—Movement toward the midline of the body. In Duane retraction syndrome, turning the eye inward toward the nose.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Congenital—Referring to a disorder that is present at birth.

Downshoot—Downward movement of the eye.

Dysplasia—The abnormal growth or development of a tissue or organ.

Extraocular muscle fibrosis—Abnormalities in the muscles that control eye movement.

Head turn—Habitual head position that has been adopted to compensate for abnormal eye movements.

Holt-Oram syndrome—An inherited disorder characterized by congenital heart defects and abnormalities of the arms and hands; may be associated with Duane retraction syndrome.

Lateral rectus muscle—The muscle that turns the eye outward toward the ear (abduction).

Medial rectus muscle—The muscle that turns the eye inward toward the nose (adduction).

Oculomotor nerve—Cranial nerve III; the nerve that extends from the midbrain to several of the muscles that control eye movement.

Okiihiro syndrome—An inherited disorder characterized by abnormalities of the hands and arms and hearing loss; may be associated with Duane retraction syndrome.

Primary position, primary gaze—When both eyes are looking straight ahead.

Recessive—Referring to a genetic trait expressed only when present on both members of a pair of chromosomes, one inherited from each parent.

Strabismus—An improper muscle balance of the ocular muscles resulting in crossed or divergent eyes.

Upshoot—Upward movement of the eye.

are affected by some of the other abnormalities that may be associated with the disorder.

Okihiro syndrome, or Duane syndrome with radial ray anomalies, and Holt-Oram syndrome are both inherited as autosomal dominant traits. However, Okihiro syndrome may skip a generation in a family or may be expressed by a range of symptoms within one family.

Demographics

DS is estimated to affect 0.1% of the general population. It accounts for 1% to 5% of all eye-movement disorders. Although it is not a sex-linked disorder, females are more likely than males to be affected by DS (60%, compared with 40%).

Signs and symptoms

Types of DS

There are three generally recognized types of DS. Type 1 DS (DS1) accounts for about 70% of cases. With DS1, abduction, the ability to move the eye toward the ear, is limited or absent. The palpebral fissure (the opening between the eyelids) widens, and the eyeball protrudes when the eye is moved outward. In contrast, adduction, the ability to move the eye toward the nose, is normal or almost normal. However, the palpebral fissure narrows and the eyeball retracts during adduction. The eyes of infants and children with DS1 are usually straight ahead in the primary position. However, some children develop an increasing misalignment in the primary position and may compensate by turning their head.

With DS type 2, adduction is limited or absent, but abduction is normal or only slightly limited. The palpebral fissure narrows, and the eyeball retracts during adduction. Type 2 accounts for approximately 7% of DS cases.

With DS type 3, both abduction and adduction are limited. The palpebral fissure narrows, and the eyeball retracts during adduction. Type 3 accounts for about 15% of DS cases.

Each type of DS is subclassified according to the symptoms that occur when the individual is looking straight ahead (primary gaze). With subgroup A, the eye turns in toward the nose when gazing ahead. With subgroup B, the eye turns out toward the ear during a primary gaze. With subgroup C, the eyes are straight ahead in the primary position.

Associated symptoms

Although many individuals with DS are healthy and have no other symptoms, other body systems that may be affected with DS include:

QUESTIONS TO ASK YOUR DOCTOR

- What is the connection between my child's Duane retraction syndrome and strabismus?
- What caused my child's DS?
- Are there surgical procedures to treat Duane syndrome?
- If my child has been diagnosed with Duane retraction syndrome, what are the chances that future children will be born with the same condition?

- skeleton
- ears and hearing
- additional involvement of the eyes
- nervous system

With Okihiro syndrome, DS can be unilateral or bilateral. In addition to a flatness at the base of the thumb, there may be difficulty with thumb movements. There also may be abnormalities or the complete absence of the radial and ulnar bones of the forearm. In extreme cases, the thumb or forearm may be absent. Okihiro syndrome may be accompanied by hearing loss; abnormal facial appearance; and heart, kidney, and spinal abnormalities.

Sometimes, Wildervanck syndrome is associated with DS; this syndrome may include congenital deafness and a fusion of the cervical (neck) vertebrae (C2 and C3).

Diagnosis

Most children with DS are diagnosed by age 10. The clinical evaluation includes a complete family history, an eye examination, and examinations for other eye involvement or other physical abnormalities.

Eye examinations include the following measurements:

- visual acuity or sharpness
- alignment of the eyes
- range of motion of the eyes
- retraction (pulling in) of the eyeballs
- size of the eye opening between the eyelids
- upshoots and downshoots
- head turns

Hearing tests are frequently conducted. The cervical (neck) and thoracic (chest) parts of the spine, the

vertebrae, the hands, and the roof of the mouth all are included in the examination as well.

Treatment and management

Special glasses with prisms can eliminate the head turning that is associated with DS. Vision therapy may help with secondary vision problems.

Surgery may be performed for the following cosmetic reasons:

- abnormalities in the primary gaze (when looking straight ahead)
- an unusual compensatory head position
- a large upshoot or downshoot
- severe retraction of the eye

The goal of surgery is to reduce or eliminate the misalignment of the eye that causes abnormal head turning, as well as to reduce the retraction of the eyeball and the upshoots and downshoots. The surgery is directed at the affected muscles of the eye.

Children with DS, as well as their siblings, require complete medical examinations to detect other abnormalities that may be associated with DS.

Prognosis

If children with DS go undiagnosed, a permanent loss of vision may occur. Surgical procedures may eliminate head turns and improve the misalignment of the eyes, particularly in the primary position. However, the absence of nerves for controlling the muscles of the eye cannot be corrected, and the prognosis for surgery is mediocre. Thus, no surgical procedure can completely eliminate the abnormal eye movements, and children with some binocular vision may do better without surgery. The condition does not worsen during the course of one's life.

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Verma, Arun. "Duane Syndrome." Medscape June 19, 2019. <https://emedicine.medscape.com/article/1198559-overview> (accessed May 10, 2021).

ORGANIZATIONS

American Association for Pediatric Ophthalmology and Strabismus, 655 Beach Street, San Francisco, CA 94109-1336, (415) 561-8505, (415) 561-8531, <http://www.aapos.org>

March of Dimes Foundation, 1550 Crystal City Drive, Suite 1300, Arlington, VA 22202, (888) 663-4637, <https://www.marchofdimes.org>

National Eye Institute Information Office, 31 Center Drive, MSC 2510, Bethesda, MD 20892-2510, (301) 496-5248, 2020@nei.nih.gov, <http://www.nei.nih.gov>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <https://rarediseases.org>

Schepens Eye Research Institute of Massachusetts Eye and Ear, 243 Charles Street, Boston, MA 02114, (617) 523-7900, <https://masseyeandear.org/research/ophthalmology/seri>

Margaret Alic, PhD

Revised by Tish Davidson, AM

Dubowitz syndrome

Definition

Dubowitz syndrome is a genetic disorder defined by slow growth, a characteristic facial appearance, and a small head.

Description

Dubowitz syndrome was first described in 1965 by English physician Victor Dubowitz. This genetic disorder causes growth retardation both before and after birth. It is primarily diagnosed through the distinctive facial features of affected individuals, including a small triangular-shaped face with a high forehead and wide-set, slitted eyes. A number of other symptoms, most commonly irritation and itching of the skin (eczema), may be present in infants born with Dubowitz syndrome.

Genetic profile

Dubowitz syndrome is passed on through an autosomal recessive pattern of inheritance. "Autosomal" means that the syndrome is not carried on a sex chromosome, while "recessive" means that both parents must carry the gene mutation in order for their child to have the disorder. Parents with one child affected by Dubowitz syndrome have a 25% chance that their next child will also be affected with the disorder.

The specific gene mutation responsible for Dubowitz syndrome has not yet been identified, although some individuals diagnosed with the syndrome have mutations in the *NSUN4* and *LIG4* genes.

KEY TERMS

Eczema—Inflammation of the skin with redness and other variable signs such as crusts, watery discharge, and itching.

Microcephaly—An abnormally small head.

Ptosis—Drooping of the upper eyelid.

Demographics

Cases of Dubowitz syndrome have been reported from many different regions of the world, with the majority coming from the United States, Germany, and Russia. There does not appear to be any clear-cut ethnic pattern to the incidence of the syndrome. Dubowitz syndrome appears to affect males and females with equal probability. The overall incidence of the disorder has not been established since it is very rare. As of 2021, approximately 200 cases had been reported worldwide.

Signs and symptoms

Physical characteristics

The symptoms of people diagnosed with Dubowitz syndrome vary considerably. However, the most common physical characteristics associated with Dubowitz syndrome are growth retardation, characteristic facial appearance, and a very small head (microcephaly). A wide variety of secondary physical characteristics may be present.

Growth retardation

Children born with Dubowitz syndrome usually have a low birth weight. Slower than normal growth continues after birth. Even if the infant is born in the normal range, the height and weight gradually falls toward the low end of growth curves during childhood. However, Dubowitz syndrome is not a form of dwarfism because affected individuals have normally proportioned bodies.

Facial appearance

The characteristic facial appearance of people with Dubowitz syndrome is the primary way in which the disorder is recognized. The face is small and often triangular in shape with a pointed, receding chin. The nose is broad with a wide or rounded tip. The eyes are set far apart and sometimes appear slitted due to a decreased distance between the top and bottom eyelids or a drooping top eyelid. The forehead is high, broad, and sloping.

Eyebrows and hair are thin or absent. The ears may be abnormally shaped or placed.

Microcephaly

Infants born with Dubowitz syndrome have primary microcephaly, or a small head size at birth. By definition, in microcephaly the circumference of the head is in the second percentile or less, meaning that 98% or more of all infants have a larger head circumference than an infant with microcephaly.

Other physical characteristics

There are many other physical characteristics that have been observed in the majority of cases of Dubowitz syndrome, although they are not present in all affected individuals. These include the following:

- A soft or high-pitched cry or voice
- Partial webbing of the toes
- Cleft palate or less severe palate malformations
- Genital abnormalities, including undescended testicles
- Gastroesophageal reflux
- Inflammation and itching of the skin (eczema)

Mental and behavioral characteristics

Despite the small head size of children born with Dubowitz syndrome, developmental delay is not observed in all cases. Estimates of the incidence of developmental delay in cases of Dubowitz syndrome range from 30% to 70%, and in most cases the level of the intellectual disability is rather mild.

A number of behavioral characteristics have been described by parents of children with Dubowitz syndrome, as well as in the medical literature. These include the following:

- Extreme hyperactivity
- Temper tantrums, difficulty in self-calming
- Preference for concrete thinking rather than abstract thinking
- Language difficulties
- Shyness and aversion to crowds
- Fondness for music and rhythm

Diagnosis

Since the genetic cause is not known, there is no specific medical test that can definitively assign the diagnosis of Dubowitz syndrome. The diagnosis is usually based on the characteristic facial appearance of the affected individual as well as on other factors such as growth data and medical history. The diagnosis is easily

QUESTIONS TO ASK YOUR DOCTOR

- What physical and mental features are characteristic of Dubowitz syndrome?
- By what other names is this condition known?
- What kinds of treatments, lifestyle conditions, and other factors will contribute to a positive prognosis for a child born with Dubowitz syndrome?
- How is Dubowitz syndrome diagnosed?

missed if the physician is not familiar with genetic pediatric conditions.

Treatment and management

A number of chronic medical conditions are associated with Dubowitz syndrome. These include the following:

- Inflammation and itching of the skin (eczema)
- Susceptibility to viral infections
- Allergies
- Chronic diarrhea or constipation
- Feeding difficulties and vomiting

These conditions need to be managed individually with appropriate treatments. For example, skin creams containing corticosteroid drugs are used to treat eczema.

Other physical problems caused by Dubowitz syndrome, such as drooping eyelids (ptosis) or cardiovascular defects, can be corrected through surgery.

Prognosis

The prognosis for individuals affected by Dubowitz syndrome is good, provided that management of their medical conditions is maintained. Dubowitz syndrome has not been reported to cause shortened lifespan or any degenerative conditions. People with Dubowitz syndrome can expect to survive to adulthood and lead a fairly normal lifestyle, although most have some level of intellectual disability.

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ORGANIZATIONS

Genetic and Rare Diseases (GARD) Information Center, PO Box 8126, Gaithersburg, MD 20898, (888) 205-2311, (301) 251-4911, <http://www.rarediseases.info.nih.gov/GARD>

Learning Disabilities Association of America, 461 Cochran Road, Suite 245, Pittsburgh, PA 15228, (412) 341-1515, (412) 344-0224, info@LDAAmerica.org, <http://ldaamerica.org>

Paul A. Johnson

Duchenne and Becker muscular dystrophy

Definition

The conditions called muscular dystrophies are characterized by muscle weakness and degeneration. Duchenne muscular dystrophy is a relatively common severe muscular dystrophy. Becker muscular dystrophy is less common and less severe. Duchenne and Becker muscular dystrophy were once considered to be separate conditions. In the 1990s, however, researchers showed that they have the same etiology (underlying cause). The two disorders nonetheless remain distinct based on their different ages of onset, rates of progression, and some distinctive symptoms. Duchenne muscular dystrophy is named for Guillaume-Amand-Duchenne de Boulogne, the French neurologist who first described it in 1861. Becker muscular dystrophy is named for Peter Emil

Becker, a German geneticist who identified the disorder in the late 1940s.

Description

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are both defined by progressive muscle weakness and atrophy. Both conditions are caused by a mutation in the same gene and usually affect only boys. Symptoms of DMD typically begin in childhood, and boys with DMD are often confined to wheelchairs by the age of 12 years. Symptoms of BMD begin later, and men with BMD typically do not require wheelchairs until their 20s or even later.

Boys with DMD are usually diagnosed at a young age. Boys with BMD are diagnosed much later. Both conditions are progressive, although DMD progresses more quickly than BMD. Unfortunately, no treatments exist to slow or prevent progression of either disease. Skeletal muscles are affected initially. Eventually the muscles of the heart are also affected, and both conditions are fatal. The life expectancy of males with either Duchenne or Becker muscular dystrophy is 26 years and approximately 45 years, respectively. Both conditions are caused by disorders of the muscle tissue itself, not of the nerves that control the muscle.

Genetic profile

Duchenne and Becker muscular dystrophy are both caused by mutations in the *DMD* gene on the short arm of the X chromosome at Xp21.2-p21.1. This is the largest gene found in humans, and control of its expression is complex.

Humans each have 46 chromosomes, of which 23 are inherited from the mother and 23 are inherited from the father. The sets of 23 chromosomes are complementary: each contains the same set of genes. Therefore, every human has a pair of every gene. Genes are the sequences of DNA that encode instructions for growth, development, and functioning. One of the 23 pairs of chromosomes, the sex chromosomes, may not be complementary. Boys have an X chromosome and a Y chromosome; girls have two X chromosomes.

Scientists often say that every person has the same genes and that the genes on a pair of complementary chromosomes are the same. It is true that a specific gene at a specific place on each chromosome provides the body with a very specific instruction (i.e., plays a particular functional role). However, most genes have multiple forms. Scientists call the various forms of a gene *alleles*. A given gene may have multiple alleles that function normally and multiple alleles that lead to physical problems.

Mutations (changes) in the *DMD* gene cause Duchenne and Becker muscular dystrophy. The *DMD* gene provides instructions for a protein called dystrophin, a structural protein. Mutations in the *DMD* gene associated with DMD often completely disrupt production of dystrophin, such that no or very little dystrophin is present. Mutations in the *DMD* gene associated with BMD lead to a reduced amount of dystrophin being made and/or abnormal dystrophin. Certain mutations (alleles) in the *DMD* gene lead to the symptoms of DMD, while other mutations lead to the symptoms of BMD.

Sex-linked inheritance

Because the *DMD* gene is located on the X chromosome, Duchenne and Becker muscular dystrophy usually affects only boys. Most females have two X chromosomes. Therefore, if a female inherits an X chromosome with a mutation in the *DMD* gene, she has another normal *DMD* gene on her other X chromosome that protects her from developing symptoms. Women who have one mutated gene and one normal gene are called *carriers*. Boys, on the other hand, have an X and a Y chromosome. The Y chromosome has a different set of genes from the X chromosome; it mostly contains genes that provide instructions for male development. If a boy has a mutation in the *DMD* gene on his X chromosome, he has no normal *DMD* gene, and he develops symptoms of muscular dystrophy.

If a woman has one son with Duchenne or Becker and no other family history, she may or may not be a carrier. If a woman has another family member with Duchenne or Becker muscular dystrophy *and* a son with muscular dystrophy, it is assumed that she is a carrier. The risk for a male child to inherit the mutated gene from his carrier mother is 50% with each pregnancy. Based on the family history, geneticists can determine the likelihood that a woman is or is not a carrier. Based on this estimate, risks of having a son with muscular dystrophy can be provided.

New mutations

The *DMD* gene is very large, and new mutations are fairly common. A new mutation is a mutation that occurs for the first time in the affected person. Approximately one-third of males with DMD who have no family history of muscular dystrophy have the condition because of a new mutation that is present only in themselves. In this case, the affected male's mother is not a carrier. Approximately two-thirds of males with DMD and no family history have the disorder because of a new mutation that occurred in a relative. In other words, even if the affected male is the first in his family to have DMD, his mother may still be a carrier. The new mutation could have happened for the first time in the affected male's

mother, or the new mutation could have occurred in his maternal grandmother or grandfather (or their parents, or their parents, etc.).

Sometimes a man has mutations in the *DMD* gene of his sperm or a woman in her eggs but not in the other cells of his or her body. The mutation may even be in some sperm or eggs but not in others. This situation is called *germline mosaicism*. Germline cells are the precursors of eggs and sperm. A woman or man with germline mosaicism may have more than one affected son even though genetic studies of his or her blood show that he or she is not a carrier. Geneticists can estimate the risk that a person has germline mosaicism, and provide information regarding the risk for a person with germline mosaicism to have a child with muscular dystrophy.

Demographics

DMD, the most common form, affects approximately 1 in 3,500 males. Males from every ethnicity are affected. BMD is much less common than DMD. The incidence of BMD is lower, approximately 1 in 30,000 males, or between 17 and 27 cases per million. Between 400 and 600 boys are born each year in the United States with either DMD or BMD. Cases of DMD in women are extremely rare; only two have been recorded as of 2021.

Signs and symptoms

Both Becker and Duchenne muscular dystrophy initially affect skeletal muscle. Muscle weakness is the first symptom. Both conditions are progressive, but DMD progresses more rapidly than BMD. People with DMD usually begin to use a wheelchair in their early teens, while people with BMD may not use a wheelchair until their 20s or later. In the late stages of both diseases, the cardiac muscles begin to be affected. Impairment of the heart and cardiac muscles leads to death. Some female carriers have mild muscle weakness.

People with muscular dystrophy often develop contractures. A contracture makes a joint difficult to move. The joint becomes frozen in place, sometimes in a painful position. Scoliosis (curvature of the spine from side to side) is another common problem. Most people with DMD have normal intelligence, but cognition is affected in some. Cognition is not usually affected in patients diagnosed with Becker.

Dystrophin

The *DMD* gene contains instructions for a structural protein called dystrophin. Dystrophin is part of muscle cells and some nerve cells. Its function is not entirely understood. Based on its location in the muscle cell, scientists think that it may help maintain the structural

integrity of muscle cells as they contract. People with DMD make very little or no dystrophin, and people with BMD either make less than normal amounts of the protein or make only semi-functional dystrophin. When there is not enough dystrophin in muscle tissue, it becomes weak and starts to waste away (atrophy). The muscle tissue is replaced by a fatty, fibrous tissue.

Duchenne muscular dystrophy

The first symptoms of DMD are usually noticed in early childhood. Delays in developmental milestones, such as sitting and standing, are common. The affected child's gait is often a characteristic waddle or toe-walk. The child often stumbles, and running is difficult. While parents notice these symptoms retrospectively, and may notice them at the time, muscular dystrophy often is not suspected until additional signs are apparent. By the age of four to five years, it is difficult for the child to climb stairs or rise from a sitting position on the floor. It is around this time that the diagnosis is usually made. A particular sign of the disorder called Gowers' sign appears. The sign occurs when the child has to use his hands and arms to raise himself from sitting on the floor. These motor problems are caused by weakness in the large muscles close to the center of the body (proximal).

Although some muscles, such as the calves, appear to be large and defined, the muscle is actually atrophied and weak. It appears large because deposits of fatty fibrous tissue are replacing muscle tissue. Enlarged calves are a characteristic sign of DMD and are said to have pseudohypertrophy. Other muscles may also exhibit pseudohypertrophy. These muscles feel firm if massaged.

The weakness begins at the center of the body (the pelvis) and progresses outward from the hips and shoulders to the large muscles of the legs, lower trunk, and arms. The weakness is symmetrical; that is, both sides of the body are equally weak. Such early signs of weakness as stumbling and difficulty climbing progress to the point that the affected boy is unable to walk at all. Boys with DMD usually require wheelchairs by the age of 12 years. Eventually the muscles that support the neck are affected. The muscles of the digestive tract are affected in some males in the later stages of the disease. Contractures and scoliosis develop. Some boys also have learning disabilities or mild intellectual disability.

Cardiac symptoms and life expectancy

The weakness usually affects skeletal muscles first, then cardiac muscle. Skeletal muscles are those that attach to bones and produce movement. The muscle weakness of both Duchenne and Becker muscular dystrophy

progresses to affect the cardiac muscles. Weak, abnormal cardiac muscles cause breathing difficulties and a heart problem known as cardiomyopathy, which eventually leads to heart failure. Breathing difficulties lead to such lung infections as aspiration pneumonia. These problems are fatal in DMD and are often fatal in BMD. The life expectancy for a boy with DMD is the late teens or early 20s. The average life expectancy of males with Becker muscular dystrophy is the mid-40s.

Becker muscular dystrophy

The initial signs of BMD may be subtle. The age at which symptoms become apparent is later and more variable than in DMD. The progression of BMD is slower than that of DMD. Like DMD, boys with BMD develop symmetrical weakness of proximal muscles. The calf muscles often appear especially large. Boys with DMD develop weakness in the muscles that support their necks, but boys with BMD do not. The incidence and severity of learning disabilities and mild intellectual disability is less in BMD than in DMD.

The first symptoms of BMD usually appear in the 20s and may appear even later. Weakness of the quadriceps (thigh muscle) or cramping with exercise may be the first symptom. The age of onset and rate of progression are influenced by how much dystrophin is made and how well it functions. Not all males with BMD become confined to wheelchairs. If they are, the age at which they begin to use the wheelchair is later than in DMD. Many males with BMD are still ambulatory (able to walk) in their 20s. However, many males with BMD eventually develop cardiac problems, even if they do not have a great deal of skeletal muscle weakness. Cardiac problems are typically fatal by the mid-40s. Some men with BMD, however, remain ambulatory (and alive) into their 60s.

Since Duchenne and Becker muscular dystrophy are caused by a mutation (change) in the same gene, the two conditions are usually distinguished based on age of onset and rate of progression. Males with DMD usually require wheelchairs by the age of 12 years, and males with BMD usually do not require wheelchairs until after the age of 16. However, some males with muscular dystrophy develop symptoms at an intermediate age. Similarly, some males have elevated creatine kinase and abnormal muscle biopsies but do not develop most of the symptoms typical of muscular dystrophy. Some doctors would classify these males with very mild symptoms as having mild BMD. Some individuals who have BMD with mildly affected skeletal muscles still develop abnormalities of their cardiac muscle.

Many other forms of muscular dystrophy exist and are part of the diagnoses considered when a person

develops signs of Duchenne or Becker muscular dystrophy. The symptoms of BMD, in particular, may be caused by many other conditions. However, diagnostic studies can definitively confirm whether an individual has BMD.

Affected females

Although it is unusual, a few females have some or all of the symptoms of muscular dystrophy. Assuming that the diagnosis is correct, the symptoms can happen for various reasons. If a woman has Turner syndrome, in which she has one X chromosome instead of two, she could also develop Duchenne or Becker muscular dystrophy because she has no second X chromosome with a normal *DMD* gene to protect her. Alternatively, a woman may have muscular dystrophy because of random unfavorable X inactivation or because she has a chromosomal translocation. Rarely, she may also have inherited both X chromosomes from the same parent.

Diagnosis

The diagnosis of muscular dystrophy is based on physical symptoms, family history, muscle biopsy, measurement of creatine kinase, and genetic testing. Creatine kinase (CK) may also be called creatine phosphokinase or CPK. It is a protein present in skeletal muscle, cardiac muscle, and the brain.

Creatine kinase is released into the blood as muscle cells die. The level of CK in the blood is increased when a person has muscular dystrophy. The level of CK in a male with DMD is often more than ten times the normal level, and the level in a male with BMD is often at least five times more than the normal level. The level of CK in the blood of female carriers is variable. Approximately 50% of DMD carriers have slightly to greatly elevated serum creatine kinase levels. Only about 30% of carriers of BMD have elevated creatine kinase. Therefore, the measurement of creatine kinase is not an accurate predictor of carrier status.

If a muscle biopsy is performed, a small piece of muscle tissue is removed from the patient. Special studies are performed on the tissue. Early in the course of the disease, the muscle shows general abnormalities. Later in the disease, the muscle tissue appears more abnormal. The fat and fibrous tissues that are replacing the muscle fibers are clearly visible.

Another specialized test of muscle function, the electromyogram (EMG) may be performed. The EMG records the electrical activity of a muscle. This test is used to determine whether the symptoms are the result of an underlying muscle problem or a nerve problem. Nerves stimulate muscles to contract. A nonfunctioning muscle

KEY TERMS

Cardiac muscle—The muscle of the heart.

Cardiomyopathy—Measurable deterioration of the heart muscle to contract normally, eventually leading to heart failure.

Chromosome—A microscopic thread-like structure found within each cell of the body and consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Dystrophin—A protein that supports muscle strength. Its absence or insufficiency is one of the basic causes of muscular dystrophy.

Germline mosaicism—A condition in which the precursor cells of male sperm or female ova are a mixture of two or more cell lines that are genetically different.

Gowers' sign—An indication of weakness in the proximal muscles of the legs. The child has to use his hands and arms to rise from a squatting or kneeling position.

Mutation—An inherited or *de novo* change in the DNA sequence of the genome.

Scoliosis—Abnormal curvature of the spine, usually defined as greater than ten degrees to the right or left as the doctor faces the patient.

Skeletal muscle—Muscles under voluntary control that attach to bone and control movement.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosomal material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

X inactivation—Sometimes called dosage compensation; a normal process in which one X chromosome in every cell of every female is permanently inactivated.

due to a nerve problem often causes the same symptoms as a nonfunctioning muscle caused by a problem with the muscle.

Genetic testing

Genetic testing is a useful diagnostic tool because the diagnosis can be made without an invasive muscle biopsy. Blood from the person suspected to have muscular dystrophy is analyzed at a specialized laboratory. Genetic testing will confirm that the *DMD* gene is abnormal in most males affected with muscular dystrophy (70% with DMD and 85% with BMD). The disease-causing mutation will be unidentifiable in some males who have muscular dystrophy. Therefore, an abnormal test result is definitive, but a normal test result is not. In these cases, muscle biopsy may be necessary to confirm the diagnosis. Muscle biopsy may be helpful to determine whether a young person with mild symptoms has DMD or BMD even when the diagnosis of muscular dystrophy is established by genetic testing.

The severity of the mutation is correlated to the severity of the disease. For example, mutations that completely eliminate the dystrophin protein are associated with DMD much more often than they are associated

with BMD. Particular mutations have been associated with intellectual impairment. The severity of symptoms can be somewhat predicted by the mutation present.

Even when a mutation in the *DMD* gene has been identified in the affected family member, genetic testing to determine whether or not the females are carriers may not be straightforward.

In some families, a special form of genetic testing called linkage testing may be helpful. Linkage genetic testing can be performed when the diagnosis of Duchenne or Becker muscular dystrophy is certain in more than one family member but no mutation is identified in the *DMD* gene. Linkage testing requires the participation of multiple family members. Unique DNA sequences within the gene and flanking the gene are analyzed to determine whether the sequences are those associated with the deleterious gene or with the normal gene. This method is not 100% accurate.

If a woman knows that she is a carrier, prenatal and preimplantation diagnoses are available. If the specific DMD or BMD mutation has been identified in a family member, genetic testing can be performed on the fetus. The procedures used to obtain fetal cells are chorionic villus sampling (CVS) and amniocentesis. CVS is usually

performed between 10 and 12 weeks of pregnancy, and amniocentesis is usually performed after 16 weeks. Whether amniocentesis or CVS is performed, chromosomal analysis of the fetal cells will show whether the baby is male or female. Linkage testing may also be performed prenatally.

Treatment and management

There is no cure for muscular dystrophy. However, doctors are getting better at treating the symptoms. Many researchers are searching for preventive measures and for a cure. Therapies focus on treating the associated symptoms.

Preventive measures

Exercise and physical therapy help to prevent joint contractures and maintain mobility, although exercise should not be prolonged to the point of exhaustion, as it will lead to increased muscle damage. Swimming and other forms of exercise in water are ideal. Although there is no special diet that will relieve the symptoms of DMD or BMD, calorie restriction may be necessary, as avoiding obesity is important.

Orthopedic devices like standing frames and braces may delay the age at which an affected boy begins to use a wheelchair, and they are often used to treat scoliosis. Motorized wheelchairs and other devices help an affected person who has become disabled to maintain his independence as long as possible. When the cardiac muscles become affected, respiratory care may be necessary. Cardiac function should be evaluated in adult males with BMD even when skeletal muscles are only mildly affected. Some women who are carriers of DMD develop heart disease related to changes in their cardiac muscle. Therefore, surveillance for heart disease should be a consideration for these women.

Experimental therapies

Some researchers are trying to deliver normal dystrophin protein to the muscle. If this were done by gene therapy, a normal copy of the *DMD* gene would be inserted into the muscle cells. This research is in the early stages, but the possibilities give researchers hope that in the future there may be a cure.

A drug developed in Europe called ataluren (Translarna), which is a small-molecule agent, was tested as a treatment for DMD in the European Union in 2010, but phase 2 trials showed that patients did not derive significant improvement from the drug. Nonetheless, the European Medicines Agency approved the drug for sale in Europe in the summer of 2014. Ataluren has not yet been

QUESTIONS TO ASK YOUR DOCTOR

- How is Duchenne muscular dystrophy different from other kinds of muscular dystrophy?
- What muscles are most likely to be affected by this disorder in my son's case?
- Are there medications or treatments that will help retard the progress of my son's muscular dystrophy?
- What resources are available for parents of children with Duchenne muscular dystrophy?

approved for use in the United States by the Food and Drug Administration (FDA).

Researchers have also experimentally transferred healthy muscle cells into the tissue of individuals with muscular dystrophy; however, this is not a standard treatment. It provides another hope that in the future an effective treatment will be developed.

Claims have been made that a class of medications called corticosteroids slows the progression of muscle destruction in muscular dystrophy. The use of these drugs is controversial. Corticosteroids have not been proven to have a long-term effect. Also, corticosteroids have many serious side effects. Cortisone is a corticosteroid, and prednisone is similar to cortisone.

Discovering the *DMD* gene allowed researchers to create animal models for muscular dystrophy. They have created mice and other animals that have DMD in order to more effectively study the disease and test the efficacy of treatments. Gene therapy has been found effective in mice with DMD and is presently being scaled up for trials in dogs. This development also provides hope for the future.

Prognosis

The prognosis of DMD is confinement to a wheelchair by the age of 12 years and usually death by the early 20s; the average age at death for boys with DMD in the United States is 25. Life expectancy for these patients has been extended into the early 30s for some, however, by recent advances in noninvasive ventilation and careful monitoring of heart-related symptoms. Death usually results from cardiopulmonary problems.

The prognosis for BMD varies. Some individuals with BMD require a wheelchair after 16 years of age, but others remain ambulatory into middle adulthood.

Some mildly affected individuals never require a wheelchair. The average life expectancy for BMD is the mid-40s, although some men diagnosed with BMD have lived into their early 60s. Both conditions are progressively debilitating.

Because DMD is a relatively common and severe condition, many people very actively promote further funding, research, and support of affected individuals. Associations to help families with muscular dystrophy have chapters all over the world. Families and researchers are hopeful that the genetic discoveries of the 1990s will lead to new treatments and cures in the new millennium. However, the obstacles between understanding the pathogenesis of a disease and creating an effective treatment are large. This is especially true of muscular dystrophy.

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ORGANIZATIONS

- Muscular Dystrophy Association, 161 N. Clark, Suite 3550, Chicago, IL 60606, (800) 572-1717, <http://www.mdausa.org>
- Muscular Dystrophy Family Foundation, P.O. Box 776, Carmel, IN 46032, (317) 615-9140, <http://www.mdff.org>
- Muscular Dystrophy UK, 61A Great Suffolk Street, London, SE1 0BU, United Kingdom, 0800 652 6352, info@muscular dystrophyuk.org, <http://www.muscular dystrophyuk.org>
- Parent Project Muscular Dystrophy (PPMD), 1012 14th Street, NW, Suite 500, Washington, D.C. 07601, (201) 250-8440, (800) 714-5437, info@parentprojectmd.org, <http://www.parentprojectmd.org>

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Dyschondrosteosis

Definition

Dyschondrosteosis (DCO) is a genetic form of dwarfism characterized by short forearms, short lower legs, normal-sized torso, normal-sized head, and a wrist and arm bone abnormality called Madelung deformity.

Description

DCO was first described by doctors André Léri and Jean Weill in 1929. Léri and Weill described patients with dwarfism characterized by short lower legs, normal-sized torso, and a specific wrist and arm bone abnormality called Madelung deformity. Other names for DCO include Léri-Weill dyschondrosteosis (LWD), Léri-Weill syndrome (LWS), Léri-Weill disease, mesomelic dwarfism-Madelung deformity, Lamy-Bienefeld syndrome, Langer's syndrome, Langer's mesomelic dwarfism, and Langer's mesomelic dysplasia.

Genetic profile

DCO is a pseudoautosomal dominant condition caused by a change or mutation in one of two genes called *SHOX* and *SHOY*. The *SHOX* gene is located on the short arm of the X chromosome in the pseudoautosomal region (Xpter-p22.32). *SHOY* is located on the Y chromosome in the pseudoautosomal region (Ypter-p11.2). Chromosomes are the structures found in all cells that contain genes. In each cell, there are 46 chromosomes, which come in 23 pairs. One member of each pair comes from the mother, and the other comes from the

father. The first 22 pairs are called autosomes and are the same in males and females. The last pair of chromosomes is the sex chromosomes, X and Y. Females have two X chromosomes, and males have one X chromosome and one Y chromosome. On the sex chromosomes, there are regions that contain the same genes. These regions are called the pseudoautosomal regions because the genes in those regions behave as if they were on an autosomal chromosome and are the same in males and females. Seventy percent of families affected by DCO have a mutation in the *SHOX* gene. The remaining families have a mutation in the *SHOY* gene, or possibly another gene related to the *SHOX* and *SHOY* genes that leads to problems in bone development.

When DCO is caused by a mutated *SHOX* or *SHOY* gene, it is inherited through the family in a pseudoautosomal dominant pattern. In a pseudoautosomal dominant condition, only one nonworking copy of the gene for a particular condition is necessary for a person to experience symptoms of the condition. If a parent has a pseudoautosomal dominant condition, there is a 50% chance for each child to have the same or similar condition. DCO can also appear in an individual for the first time and not be found in the affected individual's parents. An individual who is the first member of the family to be affected by DCO passes DCO to his or her children in a pseudoautosomal dominant pattern of inheritance. Accordingly, the individual who has *de novo* (new) DCO has the same 50% chance to have affected children.

Individuals inheriting the same nonworking gene in the same family can have very different symptoms. For example, some family members affected by DCO may be affected by proportional dwarfism with no visible arm bone deformity, while other family members may have very short (mesomelic) arms and legs and severe Madelung deformity. The difference in physical findings within the same family is known as variable penetrance, or intrafamilial variability.

Studies have suggested that another form of severe dwarfism called Langer mesomelic dysplasia is the result of inheriting two copies of the mutated gene that causes DCO. Langer mesomelic dysplasia is characterized by severe short stature with underdeveloped or missing arm bones.

Demographics

DCO is a rare genetic condition. The ethnic origins of individuals affected by DCO are varied, and DCO is not more common in any specific ethnicity. There are more females than males affected by DCO, and females affected by DCO appear to be more severely affected than males.

Signs and symptoms

Most individuals affected by DCO have short stature, short lower legs and forearms (mesomelia), normal head size, normal torso size, and a specific form of arm bone abnormality called Madelung deformity. Madelung deformity occurs when one of the bones of the forearms (the radius) is short and bends toward the shortened and partially dislocated and bent ulna (subluxation), which causes the wrist to be shifted toward the thumb. Affected individuals may also exhibit abnormalities of the large bone of the upper arm (humerus); abnormal bony growths projecting outward from the surface of the shin bones (exostoses of the tibia); unusually short, broad bones in the fingers and toes; and abnormalities of the hipbones. One study found that some males have overdeveloped muscles (or muscular hypertrophy). There is also some evidence that conductive hearing loss may be found as a symptom in some individuals. Depending on the individual, DCO can result in severe to very mild symptoms (variable expression). Females affected by DCO tend to have more severe symptoms, including a more frequent occurrence of Madelung deformity.

Some individuals affected by DCO can also be affected by other symptoms not usually considered part of the DCO features. These features, such as intellectual disability, Hodgkin's lymphoma, kidney disease, and skin disorders, are believed to be caused by errors in genes close to the mutated *SHOX* or *SHOY* gene. Based on a finding of two sisters with dyschondrosteosis who both developed Hodgkin's lymphoma in late adolescence, it was suggested that a gene that increased the risk to develop Hodgkin's lymphoma may be located very near to the *SHOX* and *SHOY* genes. Individuals affected by Hodgkin's lymphoma, or other unusual symptoms, and DCO are most likely affected by an Xp22.3 contiguous gene syndrome. The name refers to a syndrome caused by the deletion or incorrect working of several genes found side-by-side on the X chromosome.

Diagnosis

Diagnosis of DCO is usually made from physical examination by a medical geneticist and x-rays of the legs and arms. The characteristic Madelung deformity of the arms is generally not identified in children through physical exam, but the first signs of the Madelung deformity, like forearm bone bowing, can be identified by x-rays in children aged two to five years. The condition's characteristic bone abnormalities become more pronounced during adolescence. Clinical genetic testing for DCO is now available to examine portions of the *SHOX* or *SHOY* genes to look for a mutation that would cause the gene not to work correctly. Although clinical testing is

KEY TERMS

Madelung deformity—A forearm bone malformation characterized by a short forearm, an arched or bow-shaped radius, and dislocation of the ulna, resulting in wrist abnormalities.

Mesomelia—Shortness of the portion of arm connecting the elbow to the wrist or forearm.

Pseudoautosomal dominant inheritance—The pattern of inheritance for a disorder caused by genes in the pseudoautosomal regions of the sex chromosomes. Individuals only require one mutated or nonworking copy of a gene to have signs and symptoms of the disorder. Affected individuals have a 50% chance to have an affected child with each pregnancy.

Pseudoautosomal region—Genes found on the sex chromosomes that contain the same genetic information whether they are on the X or Y chromosome.

available, testing cannot identify all mutations causing DCO. Physical exams and x-rays may diagnosis an individual without an identifiable mutation *SHOX* or *SHOY*. In families in which a mutation is identified, prenatal diagnosis through amniocentesis is available.

Treatment and management

DCO is a genetic disorder and does not have a specific therapy that removes, cures, or fixes all signs of the condition. Treatment and management of DCO focuses on treatment of specific symptoms of the disorder. Some progress in increasing height has been made by growth hormone (GH) supplementation in affected children. However, hormone supplementation causes disproportionate growth, leading to longer arms and trunk and shorter legs. The Madelung deformity found in many individuals with DCO can be treated surgically by addressing the deforming bone ligaments, correcting the abnormal position of the lower arm bones, and equalizing the length of the arms' radius and ulna bones. Operative treatment for the Madelung deformity is indicated for pain relief and appearance of the arm and wrist but may not greatly improve the wrists' range of motion. Individuals with conductive hearing loss may wish to consider surgery or hearing aids to improve hearing.

Prognosis

The symptoms of individuals affected by DCO can be severe or mild, and prognosis depends on the severity

of the symptoms. Severe Madelung deformity may cause pain in adolescence that is most often relieved through surgery. Individuals affected by DCO are of short stature and may need adjustments in their living space to optimize their living conditions.

Resources

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ORGANIZATIONS

- Human Growth Foundation, 997 Glencove Ave., Suite 5, Glen Head, NY 11545, (800) 451-6434, (516) 671-4055, hgf1@hgfound.org, <http://www.hgfound.org>
- Little People of America, 617 Broadway #518, Sonoma, CA 95476, (888) LPA-2001, info@lpaonline.com, <http://www.lpaonline.org>
- MAGIC Foundation, 6645 W. North Ave., Oak Park, IL 60302, (708) 383-0808, (800) 362-4423, contactus@magicfoundation.org, <http://www.magicfoundation.org>

Dawn Jacob Laney

Dysplasia

Definition

"Dysplasia" comes from the Greek *dys*, meaning "difficult" or "disordered," and *plassein*, meaning "to form." Dysplasia is the abnormal or disordered organization of cells into tissues. All abnormal tissue formations



A baby girl wearing an apparatus for hip dysplasia, lying on her sister. (Anastasia Tveretina/Shutterstock)

are classified as dysplasias, including a large number of genetic disorders.

Description

Dysplasias—or dysplastic tissues—have an abnormal cellular organization. Dysplasias can be caused by an underlying genetic disorder due to a mutation (change) in a gene or result from injury, infection, toxins, or other environmental factors. Some dysplasias develop into cancer. Dysplasias can be localized, with the tissue abnormality confined to a single area or body part, or generalized, affecting multiple parts of the body. There are several hundred genetic dysplasias resulting from inherited or acquired gene mutations. In many cases, the responsible genes and mutations are known. Genetic dysplasias tend to be generalized, with malformations or abnormalities throughout the body, depending on the particular tissue organization defect and the organs that arise from the dysplastic tissue, since structural problems associated with generalized dysplasias usually begin during embryonic development. Two major types of dysplasias—skeletal and ectodermal—are caused by underlying genetic disorders. There are no specific treatments for most forms of genetic dysplasia.

Skeletal dysplasias

Skeletal dysplasias affect the growth, organization, and development of the bony skeleton. They are always genetic disorders, but their effects vary greatly. A mild skeletal dysplasia may cause short stature with no other complications. Other skeletal dysplasias may severely reduce height, causing dwarfism with disproportion and other bone deformities. The most severe skeletal dysplasias are fatal before or soon after birth. The many types of skeletal dysplasias include achondroplasia, hypochondroplasia, thanatophoric dysplasia, achondrogenesis,

diastrophic dysplasia, atelosteogenesis, spondyloepiphyseal dysplasia, Kniest dysplasia, Stickler syndrome, pseudoachondroplasia, and metaphyseal dysplasia.

Achondroplasia. Achondroplasia, the most common form of short-limbed dwarfism, is a highly recognizable skeletal dysplasia that occurs in 1 in 15,000–40,000 newborns. Although “achondroplasia” means literally “without cartilage formation,” the disorder is caused by the failure of cartilage to be converted into bone, especially in the long bones of the arms and legs. In addition to short stature, achondroplasia causes a large head, characteristic facial features, and disproportionately short arms and legs. It is caused by a mutation in a single gene called fibroblast growth factor receptor 3 (*FGFR3*). The *FGFR3* gene produces a protein that is important for the development and maintenance of both bone and brain tissue. Almost all cases of achondroplasia are caused by one of two mutations in the *FGFR3* gene. These mutations appear to cause an overactive *FGFR3* protein that disrupts skeletal development. These are called “gain-of-function” mutations. Gain-of-function mutations in *FGFR3* are also responsible for other skeletal dysplasias, such as hypochondroplasia and thanatophoric dysplasia.

Achondroplasia is an autosomal dominant condition, meaning that a mutation in just one of the two copies of the *FGFR3* gene is sufficient to cause the disorder. Although some cases of achondroplasia are inherited from one or both parents, about 80% of cases are caused by sporadic, or *de novo*, mutations that occur in the father’s sperm cell, the mother’s egg cell, the fertilized egg or embryo, or during early fetal development. These new mutations are observed more frequently in children born to older fathers. Children who inherit two altered *FGFR3* genes, one from each parent, typically have a severe form of the disorder with extremely short bones and an underdeveloped rib cage. They are usually still-born or die of respiratory failure shortly after birth.

Hypochondroplasia. Hypochondroplasia is a short-limbed dwarfism similar to achondroplasia, but it is typically less severe. It results in varying degrees of short stature, a long torso, and disproportion of limbs. It is believed to occur with about the same frequency as achondroplasia, but people with mild symptoms may never be diagnosed. About 70% of cases are, like achondroplasia, caused by mutations in the *FGFR3* gene that appear to cause the production of an overactive protein. Like achondroplasia, hypochondroplasia is an autosomal dominant disorder. Most children with hypochondroplasia have average-sized parents. A few cases are inherited from one or both parents, but most cases result from a new sporadic mutation in the *FGFR3* gene.

Thanatophoric dysplasia. Thanatophoric dysplasia is a severe disorder resulting in extremely short limbs and extra folds of skin on the arms and legs. The chest is narrow, the ribs are short, and the lungs are underdeveloped. The head is enlarged, the forehead is large, and the eyes are wide-spaced and prominent. Most babies with thanatophoric dysplasia are stillborn or die shortly after birth of respiratory failure. The disorder occurs in 1 in 20,000–50,000 newborns, and type I is more common than type II. Thanatophoric dysplasia is not known to be inherited; rather, it is caused by new sporadic gain-of-function mutations in the *FGFR3* gene.

Ectodermal dysplasias

Ectodermal dysplasias affect the growth and development of tissues derived from the early outer layer of embryonic tissue known as the ectoderm. Tissues derived from the ectoderm include hair, nails, skin, sweat glands, and teeth. People with ectodermal dysplasias display abnormalities in at least two ectoderm derivatives. The effects of ectodermal dysplasia (ED) range from mild to severe. There are more than 150 different types of ED because so many tissues in the body are derived from the ectoderm. ED is divided into two major groups based on the presence or absence of normal sweating. Sweat production is normal in hidrotic types and reduced in hypohidrotic types. Hypohidrotic types with reduced or absent sweating are generally more severe disorders. Many different gene mutations are known to cause ED.

Hypohidrotic ED. Hypohidrotic ED is the most common form of ED, affecting at least 1 in 17,000 people worldwide. Most people with this disorder have fewer than normal sweat glands or sweat glands that do not function properly. They are not able to control their body temperature well due to reduced sweating. They may also be unable to form tears normally. They often have small or missing teeth, eyebrows, and eyelashes. Head hair is usually sparse, but fingernails are normal.

Hypohidrotic ED is caused by mutations in the *EDA*, *EDAR*, and *EDARADD* genes, which produce proteins that work together during embryonic development, forming part of a signaling pathway that is essential for proper interactions between the ectoderm and the mesoderm (the middle layer of embryonic tissue below the ectoderm). Although hypohidrotic ED has several different inheritance patterns, most cases are caused by mutations in the *EDA* gene, which is on the X chromosome and is inherited in an X-linked recessive pattern. This means that it usually affects males because they have only one X chromosome. Females, who have two X chromosomes, do not develop hypohidrotic ED unless they inherit a mutated *EDA* gene on the X chromosome from each parent. The presence of a normal *EDA* gene on one X chromosome

KEY TERMS

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a nonsex chromosome is required for a disease or inherited trait to develop in an individual.

Cartilage—A tough elastic tissue that is a building block for bone.

De novo mutation—A genetic mutation that is seen for the first time in the affected person, not inherited from the parents.

Ectoderm—The outermost of the three embryonic cell layers, which later gives rise to the skin, hair, teeth, and nails.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein and is made up of a molecular sequence found on a section of DNA. Each gene is found at a precise location on a chromosome.

Mutation—An inherited or *de novo* change in the DNA sequence of the genome.

Skeletal dysplasia—A group of syndromes consisting of abnormal prenatal bone development and growth.

Tissue—A group of similar cells that work together to perform a particular function. The four basic types of tissue are muscle, nerve, epithelial, and connective tissues.

Vertebra—One of the 23 bones that comprise the spine. Vertebrae is the plural form.

X-linked recessive inheritance—The inheritance of a trait by the presence of a single gene on the X chromosome in a male, passed from a female who has the gene on one of her X chromosomes. She is referred to as an unaffected carrier.

is sufficient to prevent the disorder. However, some females with one mutated *EDA* gene have mild symptoms of the disorder. Mutations in the *EDAR* and *EDARADD* genes that cause hypohidrotic ED affect males and females equally because the genes are located on autosomal chromosomes rather than the X sex chromosome. Hypohidrotic ED is also known as Christ-Siemens-Touraine syndrome (CST).

Clouston syndrome. Clouston ectodermal dysplasia is a hidrotic (sweating) ED that causes hair, nail, and skin abnormalities. The teeth and sweat glands are normal. People with this form of ED have partial to total baldness, severely abnormal fingernails and toenails, and darkly

QUESTIONS TO ASK YOUR DOCTOR

- What type of dysplasia does my child have?
- Is my child's dysplasia a genetic disorder?
- Did my child inherit dysplasia or is it the result of a *de novo* mutation?
- Is genetic testing available for this type of dysplasia?
- Will my grandchildren inherit dysplasia?

pigmented areas of skin, especially over the joints. They have underdeveloped eyebrows and eyelashes and may be born with teeth. They may also have thickened skin on the soles of their feet and the palms of their hands. Intelligence is usually normal, but some cases involve intellectual disability and strabismus (unbalanced eye muscles that affect binocular vision). The prevalence of Clouston syndrome is unknown, although it has been reported in many different populations and is particularly common in people of French Canadian descent.

Clouston syndrome is caused by mutations in the *GJB6* gene that produces a protein called gap junction beta 6, usually known as connexin 30. Connexin proteins form channels between cells called gap junctions. Nutrients, ions, and signaling molecules move between cells via gap junctions. Connexin 30 forms gap junctions that transport potassium ions and some small molecules. It is involved in the growth and development of various tissues in the body, especially the skin on the palms of the hands and soles of the feet, hair follicles, and nail beds. Clouston syndrome-causing mutations in the *GJB6* gene change single amino-acid building blocks in the connexin 30 protein, which leads to abnormal growth, division, and maturation of skin, nail, and hair follicle cells. These mutations are inherited in an autosomal dominant pattern, meaning that only one altered gene, usually inherited from an affected parent, is sufficient to cause Clouston syndrome. Each child of an affected person has a 50% risk of inheriting the mutated gene and having Clouston syndrome. Some cases result from new sporadic mutations in the *GJB6* gene in people with no family history of the disorder.

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ORGANIZATIONS

- Children's Craniofacial Association, 13140 Coit Rd., Suite 517, Dallas, TX 75240, (214) 570-9099 or (800) 535-3643, (214) 570-8811, contactCCA@ccakids.com, <http://www.ccakids.com>
- FACES: The National Craniofacial Association, PO Box 11082, Chattanooga, TN 37401, (423) 266-1632, (800) 332-2373, faces@faces-cranio.org, <http://www.faces-cranio.org>
- Little People of America, Inc. 617 Broadway #518, Sonoma, CA 95476, (888) LPA-2001, info@lpaonline.org, <http://www.lpaonline.org>
- National Foundation for Ectodermal Dysplasias, 6 Executive Dr., Suite 2, Fairview Heights, IL 62208-1360, (618) 566-2020, (618) 566-4718, <http://www.nfed.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Dysplasia giantism syndrome X-linked (DGSX) see **Simpson-Golabi-Behmel syndrome**

Dystonia

Definition

Dystonia is a group of complex disabling neurological movement disorders. While the disorders vary in their symptoms, causes, progression, and treatment, the dystonias are characterized by involuntary muscle contractions

and spasms that result in abnormal postures and movements. Focal dystonias—which affect a single part of the body, such as the face, arms, or vocal chords—are the most common.

Description

Dystonia is generally considered to be a group of movement disorders with a variety of symptoms. The most common characteristic of dystonia is twisting, repetitive, and sometimes painful movements that affect specific parts of the body, such as the arms, legs, trunk, neck, eyelids, face, or vocal cords. The term “dystonia” was first coined in 1911 by Hermann Oppenheim, an eminent German neurologist, in reference to a childhood-onset syndrome he termed dystonia musculorum deformans. This condition, now known as idiopathic torsion dystonia, was noted to run in families and, although presumably inherited, was only recently proven to have a genetic cause. There is, however, considerable variability in the manifestation of clinical symptoms of dystonia, which has led to a number of different and often confusing attempts to classify the dystonias. In 2012 an international panel of experts on the dystonias was formed by the Dystonia Medical Research Foundation, the European Dystonia Cooperation in Science and Technology Action, and the Dystonia Coalition. The panel proposed a revised classification scheme in 2013 in which the dystonias are classified along two axes: clinical symptoms (age of onset, distribution in the body, temporal pattern, and associated features); and etiology or cause.

The current age-based classification has five categories: infancy (birth to two years of age), childhood (3–12 years), adolescence (13–20 years), early adulthood (21–40 years), and late adulthood (over 40 years).

“Distribution” refers to the location of the symptoms in the patient’s body. Dystonia may be described as focal (localized to one body part), segmental (involves adjacent body parts), multifocal (two or more body regions that are not adjacent are involved), generalized (symptoms begin in an arm or a leg and eventually affect the rest of the body), and hemidystonia (symptoms affect only one side of the body). Spasmodic torticollis (cervical dystonia), which affects the head and neck, is the most common adult form of focal dystonia, followed by blepharospasm (eyelids), spasmodic dysphonia (larynx), and limb dystonias (hands).

“Temporal pattern” refers to the time of day that the symptoms are most noticeable: the dystonia may be persistent (occurring throughout the day), action-specific (occurs only when the patient is performing a certain action, such as writing or playing a musical instrument), or paroxysmal (resulting from a specific trigger). The phrase “associated features” refers to whether the

disorder is an isolated dystonia (there are no other motor symptoms except tremor); combined dystonia (formerly called dystonia-plus; in combined dystonia the dystonia occurs together with another movement disorder like Parkinsonism or myoclonus); or complex dystonia (in which the dystonia coexists with other neurological or systemic illnesses). The complex dystonias include dystonia coexisting with neurodegenerative disorders (Huntington’s disease, Rett syndrome, and dentatorubral-pallidolusian atrophy), disorders of copper metabolism (Wilson’s disease), disorders of purine metabolism (Lesch-Nyhan syndrome), mitochondrial disorders, encephalopathies (Aicardi-Goutières syndrome), and many others.

When dystonia is classified by cause, it is defined as either idiopathic (of unknown origin), hereditary (inherited), or acquired. Acquired dystonia may be caused by birth injury, head trauma, environmental toxins, certain infections, or stroke.

Genetic profile

At least 25 different forms of dystonia have been traced to specific genes. Most are inherited in an autosomal dominant pattern, although at least two are inherited in an autosomal recessive pattern, and one is inherited in an X-linked pattern. The classification of the hereditary dystonias was revised by the international panel to simplify and organize what had become an unwieldy list of genetic mutations that included errors in gene identification in addition to genetic loci that were unconfirmed. The present list of monogenic (single-gene) dystonias is grouped under the general headings of isolated and combined dystonias.

Isolated dystonias

There are three dystonias in this group; all three are inherited in an autosomal dominant pattern:

- Early-onset generalized dystonia (also called early-onset torsion dystonia), caused by a mutation in the *TOR1A* gene on the long arm of chromosome 9 at 9q34.
- Adolescent-onset dystonia of mixed type, caused by a mutation in the *THAPI* gene on the short arm of chromosome 8 at 8p11.21.
- Adult-onset cranial-cervical dystonia, caused by a mutation in the *GNAL* gene on the short arm of chromosome 18 at 18p11.21.

Combined dystonias

There are three subgroups classified as combined dystonias, as follows:

- Dystonia plus Parkinsonism. There are five dystonias in this subgroup with different patterns of inheritance: (1) X-linked dystonia-Parkinsonism, caused by a mutation in the *TAF1* gene on the long arm of the X chromosome

at Xq13; (2) autosomal dominant dopa-responsive dystonia, caused by a mutation in the *GCH1* gene on the long arm of chromosome 14 at 14q22.1-q22.2; (3) autosomal recessive dopa-responsive dystonia, caused by a mutation in the *TH* gene on the short arm of chromosome 11 at 11p15.5; (4) autosomal recessive dopa-responsive dystonia and cognitive impairment, caused by a mutation in the *SPR* gene on the short arm of chromosome 2 at 2p13.2; and (5) autosomal dominant rapid-onset dystonia-Parkinsonism, caused by a mutation in the *ATPIA3* gene on the long arm of chromosome 19 at 19q12-q13.2.

- **Dystonia plus myoclonus:** This dystonia is inherited in an autosomal dominant pattern and is caused by a mutation in the *SGCE* gene on the long arm of chromosome 7 at 7q21.
- **Paroxysmal dystonia plus other dyskinesia.** There are three dystonias in this subgroup, all inherited in an autosomal dominant pattern: (1) paroxysmal non-kinesigenic dyskinesia, caused by a mutation in the *MRI* gene on the long arm of chromosome 2 at 2q35; (2) paroxysmal kinesigenic dyskinesia, caused by a mutation in the *PRRT2* gene on the short arm of chromosome 16 at 16p11.2; and (3) paroxysmal exertion-induced dyskinesia, caused by a mutation in the *SLC2A1* gene on the short arm of chromosome 1 at 1p35.

Demographics

As of 2021, dystonia affected an estimated 300,000 people in the United States and Canada, affecting both sexes, all age groups, and all races and ethnic groups. Early-onset idiopathic torsion dystonia has a higher frequency among Ashkenazi Jews—Jews of Eastern European ancestry—affecting 1 in 3,000 to 9,000 people in this population.

Dystonia is the third most common movement disorder after Parkinson's disease and tremor.

Signs and symptoms

Researchers believe that dystonia is caused by a malfunction in the basal ganglia, a group of nuclei (clumps of nerve cells) in the forebrain involved in regulating voluntary and involuntary movement. Some researchers also think that abnormalities in the level of dopamine and other neurotransmitters in the brain may play a part in causing the dystonias. Acquired dystonia may occur due to head trauma, stroke, certain infections and diseases (e.g., Wilson disease, multiple sclerosis), reactions to certain neuroleptic or antipsychotic drugs (e.g., haloperidol or chlorpromazine), birth injury, or heavy-metal or carbon monoxide poisoning. About half of dystonia cases, however, have no connection to disease or injury and are either idiopathic or hereditary.

Early symptoms of dystonia may include deterioration in handwriting or musical performance, foot cramps, tremor, voice or speech difficulties, and a tendency for

one foot to pull up or drag while walking. Initially, the symptoms may be very mild and noticeable only after prolonged exertion, stress, or fatigue. Over a period of time, the symptoms may become more noticeable and widespread. The symptoms may begin at any point in the patient's life from infancy to late adulthood. In general, the earlier the onset of symptoms, the greater the chance that the disease will progress with advancing age.

Dystonia symptoms also depend on the body part affected. Dystonia localized to the face may involve repetitive blinking (blepharospasm), tongue protrusion, or jaw clenching. Blinking can become so severe that the patient cannot see due to inability to open the eyes. Dystonia affecting the neck may lead to sustained flexion, extension, or twisting postures of the neck known as spasmodic torticollis. Some dystonias are task-specific and arise only during the performance of certain tasks like writing, typing, or playing instruments. The progression of these symptoms can lead to severe disability and inability to perform daily work. Generalized dystonia, the most severe form, can present as twisting movements of the head, trunk, and arms, completely disabling the affected individual. Dystonia can often be associated with tremor in the affected body part. All forms of dystonia impair normal movement and daily function to some degree. Dystonia can be worsened by stress and anxiety, but it may be relieved by relaxation and sleep.

Diagnosis

As of 2021, there was no specific diagnostic laboratory test for dystonia, although blood, urine, and cerebrospinal fluid tests may be ordered to rule out infections, drug reactions, or other organic disorders of the nervous system. An MRI of the brain may be performed to look for evidence of stroke or a structural abnormality in the brain causing the symptoms. Imaging studies are not, however, useful in detecting abnormal patterns of activity in the basal ganglia or abnormalities in the level of neurotransmitters in the brain.

The diagnosis is often based on clinical signs and symptoms, and its accuracy depends on the examiner's experience with movement disorders. Diagnosis is often complicated because the signs of dystonia are similar to those of other disorders; many of the dystonias have overlapping phenotypes even though they may have different genetic or other causes, and the involuntary muscle contractions are often incorrectly attributed to emotional stress, athletic injuries, stiff neck, dry eyes, tics, or psychogenic or neurological disorders. The doctor will usually take a careful patient history and family history. If the family history suggests an inherited form of dystonia, molecular genetic tests may be ordered. Genetic tests are available for most of the hereditary forms of dystonia.

KEY TERMS

Basal ganglia—An area in the forebrain that contains seven nuclei (clusters of nerve cells) responsible for initiating and controlling voluntary movement along with procedural learning and some habitual actions.

Blepharospasm—An abnormal involuntary twitching or closing of the eyelid. It is the second most common type of focal dystonia.

Chromosome—A microscopic thread-like structure found within each cell of the body and consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Dyskinesia—Impairment or difficulty in performing voluntary movements, usually resulting in jerky or interrupted movements.

Genotype—The genetic makeup of an individual organism or cell.

Idiopathic—Of unknown origin.

Levodopa—A chemical produced naturally in the body that is a precursor to such neurotransmitters as serotonin and epinephrine. It is also manufactured as

a drug and used to treat Parkinson's disease and the dopa-responsive dystonias.

Mutation—An inherited or *de novo* change in the DNA sequence of the genome.

Myoclonus—Twitching or spasms of a muscle or an interrelated group of muscles.

Parkinsonism—A symptom complex that includes tremor, abnormally slow movements (bradykinesia), difficulty maintaining one's balance, and muscle rigidity. Parkinsonism should not be confused with Parkinson's disease (PD); it can occur as a group of symptoms in neurological disorders other than PD.

Phenotype—An observable characteristic or trait of an organism as determined by its genetic makeup (genotype) and its interactions with the environment.

Spasmodic torticollis—A painful chronic neurological disorder in which involuntary contractions of the neck muscles cause the person's head to twist or turn from side to side or upward and downward. It is also called cervical dystonia.

Tremor—Involuntary rhythmic back-and-forth movements involving one or more parts of the body. Tremor is most commonly seen in the hands but can affect almost any part of the body.

One helpful characteristic in differentiating dystonic movements from those caused by other disorders is the timing of the movements. Dystonic movements tend to increase during activity, nervousness, and emotional stress, and they usually disappear during sleep.

Treatment and management

There was no cure for dystonia as of 2021. However, such symptoms as spasms and pain can usually be managed with a combination of treatments. Treatment for dystonia is usually directed toward management of the symptoms and depends on the type of dystonia. Dystonia associated with or caused by such known etiologies as drugs, Wilson's disease, or dopa-responsive dystonias may be improved by treating the underlying disease with resolution of symptoms.

Traditional

No one treatment has proven universally effective for dystonia. A physician's approach to treatment is typically three-tiered, encompassing oral medications, injections of therapeutic agents (botulinum toxin) directly into dystonic

muscle, and surgery. Surgery, which involves cutting nerves and muscles or placing a lesion in the basal ganglia to reduce movement, is usually reserved for the most severe cases.

The cause and location of a patient's dystonia will play a factor in the treatment methods chosen by the physician. Patients with focal dystonia often respond best to targeted methods—such as injections of botulinum toxin or surgery—while patients with generalized dystonia may first need to be treated with oral medications to alleviate the multiple symptoms.

Drugs

Various oral medications are available for the symptomatic treatment of dystonia; however, there is no single drug that works for all patients. Among the medications that can be tried are muscle relaxants. Some patients with symptoms of early-onset dystonia may respond dramatically to levodopa, a drug used to treat Parkinson's disease. Dystonias that respond to treatment with levodopa are called dopa-responsive dystonias. Anticholinergics, dopamine-depleting agents, benzodiazepines (particularly diazepam), baclofen, or atypical

QUESTIONS TO ASK YOUR DOCTOR

- What type of dystonia do I have?
- Are there any underlying medical conditions that require treatment?
- What are the treatment options?
- How will dystonia affect my quality of life?

antipsychotics may be tried as well. Almost all these medications have side effects, however, ranging from drowsiness and short-term memory loss to weight gain, dry mouth, and constipation.

Botulinum toxin (Botox) is effective in many patients with dystonia; however, symptom relief is only temporary (about three to six months), necessitating repeated injections. There are some risks; for example, the botulinum toxin may leak from the injection site into nearby muscle groups or cause temporary paralysis at the injection site. In addition, about 15% of patients eventually develop immunity to Botox.

Deep brain stimulation

Deep brain stimulation (DBS) is an increasingly recommended treatment for severe dystonia and for patients who cannot tolerate the side effects of medications. It involves the surgical implantation of small electrodes in the brain connected by wires to a battery-powered pulse generator located beneath the skin over the collarbone or the abdomen. The pulse generator sends electrical impulses into the electrodes implanted in the areas of the brain that control movement. DBS was approved by the FDA for the treatment of dystonia in 2003. Recent improvements in both the device and method of implantation have led to high rates of success in patients with dystonia.

DBS should be performed only under the supervision of a team of specialists, including a neurologist, a psychiatrist, and a neuropsychologist, as well as a neurosurgeon. The settings of the DBS require careful monitoring and adjustment following implantation. Like medications for dystonia, DBS also carries risks, including depression and hallucinations.

Prognosis

The prognosis of dystonia depends on the body distribution, age of onset, and the cause. The initial site of symptoms may predict the prognosis. Patients with

symptoms that start in the leg have a higher likelihood (90%) of progression to other body parts and the development of generalized dystonia. Patients with symptoms starting in the neck and that are later in onset have a much lower likelihood of spread. Most focal dystonias respond to medications or botulinum toxin. Refractory and generalized dystonias may require surgical management. Most patients have a normal life expectancy with normal intelligence and cognitive skills, although they may have ongoing disabling symptoms.

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ORGANIZATIONS

Dystonia Medical Research Foundation, One E. Wacker Dr., Suite 1730, Chicago, IL 60601-1980, (312) 755-0198, (800) 377-3978, dystonia@dystonia-foundation.org, <http://www.dystonia-foundation.org>

National Institute of Neurological Disorders and Stroke (NINDS), PO Box 5801, Bethesda, MD 20824(301) 496-5751, (800) 352-9424, <http://www.ninds.nih.gov>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Dystrophia myotonica 2 see **Myotonic dystrophy**

E

Ectodermal dysplasia

Definition

The ectodermal dysplasias (EDs) are a group of over 200 hereditary conditions characterized by abnormalities of the skin, hair, teeth, fingernails and toenails, and sweat glands. First described in 1848, the EDs were given their present name by A. A. Weech in 1929.

Description

The ectodermal dysplasias are a group of congenital nonprogressive disorders characterized by abnormalities of the skin and other tissues derived from the ectoderm. All EDs have a genetic etiology. The ectoderm is the outermost germ layer of the developing embryo, which gives rise to the nervous system, hair, teeth, nails, and skin. More than 200 different ED conditions have been described in the medical literature, and their number keeps increasing. The most common of these is hypohidrotic ED, also known as HED and Christ-Siemens-Touraine syndrome, which may account for up to 80% of all EDs.

Other EDs include ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome, hidrotic ectodermal dysplasia (Clouston syndrome), Hay-Wells syndrome, incontinentia pigmenti, Rapp-Hodgkin syndrome, tricho-dento-osseous syndrome, and tooth-nail (Witkop) syndrome. Each of these conditions appears to account for 1%–4% of all ectodermal dysplasias.

Most EDs are associated with sparse hair that has abnormal texture. The hair may appear thin, dry, and brittle. In some cases, premature balding may occur.

The teeth of patients with ED are typically abnormal and reduced in number. A characteristic conical and sharply pointed tooth shape is often present. In some cases, the majority of teeth are missing.

In some EDs, the fingernails and toenails may be absent or abnormally formed. The nails may be

thickened, thinned, brittle, or display unusual ridging or pitting.

The skin may be thin, show abnormal pigmentation, and be prone to eczema (a condition of dry skin characterized by inflammation and itching). The nasal and respiratory passages may be dry, leading to abnormal discharges and increased infections. In hypohidrotic ED, the sweat glands are reduced in number, which may lead to dangerous hyperthermia (high body temperature).

Other abnormalities that may occur in the ectodermal dysplasia conditions include amastia (absent mammary glands), cleft lip and/or palate, ectrodactyly (split hand or split foot), and abnormal bands of skin in the mouth or connecting the eyelids.

Many individuals with ED have normal cognitive function. A minority of cases, however, may involve some degree of intellectual disability. In the case of hypohidrotic ED, untreated hyperthermic episodes can lead to brain damage and cognitive impairment.

Genetic profile

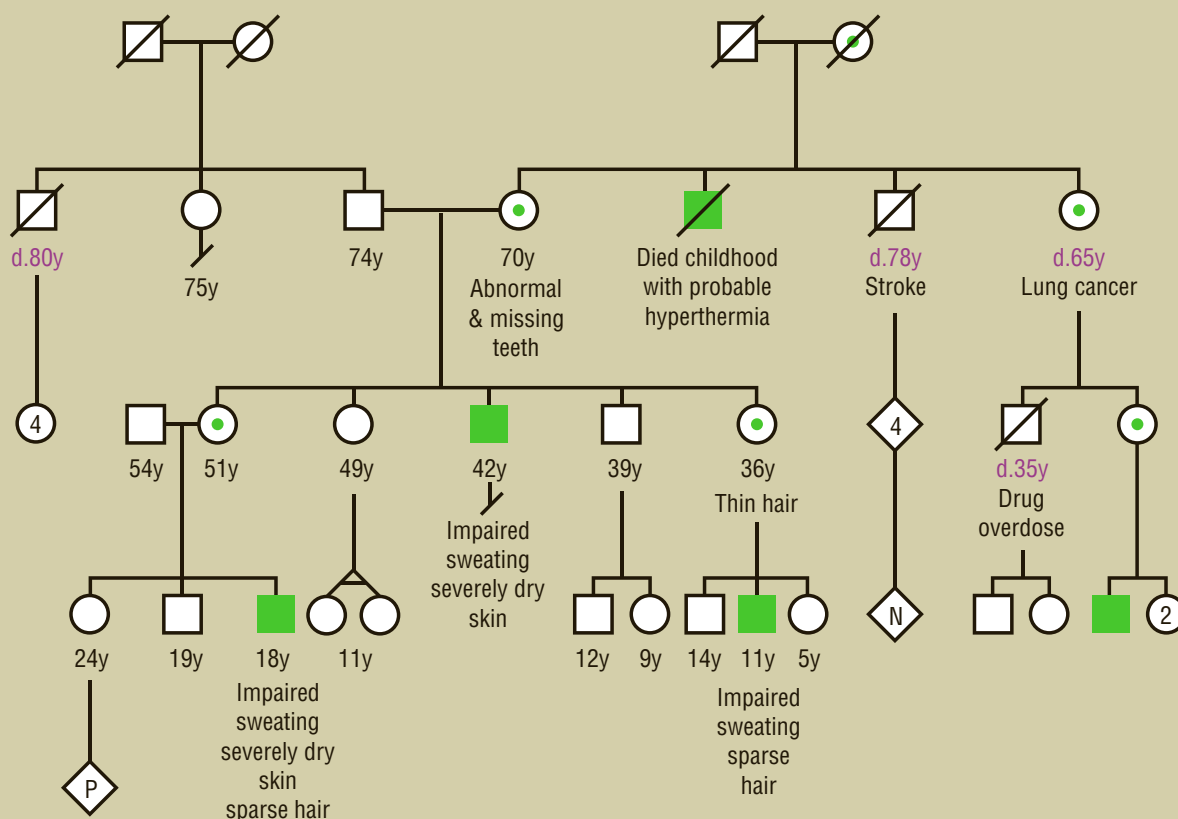
There is no inheritance pattern common to all the EDs. Some are inherited in an autosomal dominant pattern, meaning that one copy of the mutated gene in each cell is sufficient to cause the disorder; some in an autosomal recessive pattern, meaning that two abnormal genes are needed in order for a person to have the disorder. Some are X-linked dominant, some are X-linked recessive, and some result from *de novo* mutations. In addition, not all mutations that cause EDs have been identified. About 80 of the more than 200 known EDs had been traced to specific genes as of 2021.

One of the complications in understanding the genetic profiles of the EDs is that there is no universally accepted classification of the EDs, and the first classification systems were based on clinical symptoms. The earliest classification system divided the EDs into two groups according to the complete absence (anhidrotic) or severe deficiency (hidrotic) of function in the patient's eccrine

Hypohidrotic Ectodermal Dysplasia

X-Linked Recessive

60–75% of carrier females show variable manifestations



Ectodermal dysplasia: pedigree analysis chart (Gale)

glands. The eccrine glands are the glands that produce the water-based sweat that is the primary cooling mechanism in humans. In 1982 two Brazilian specialists attempted to classify the EDs into four categories according to whether their primary symptoms were related to the hair, teeth, nails, or eccrine glands. Another clinical classification system divides the EDs into two groups based on whether the ED is a pure disorder (the defects involve only ectodermal structures) or whether it is complex—that is, part of a syndrome that includes other anomalies.

Starting in 2009 with the discovery of the genetic mutations associated with EDs, some researchers suggested reclassifying them according to the underlying functional defect. One proposal suggested four groups: (1) EDs resulting from defective cell-to-cell signaling, (2) EDs resulting from faulty cell adhesion, (3) EDs associated with defects in development, and (4) EDs marked by other functional defects. Other experts suggested a

slightly different fourfold classification. One obvious difficulty with a classification based on genetics is that many of the genes associated with EDs are still unknown. In any case there was no classification system as of 2021 that was completely satisfactory, although it is expected that any forthcoming classification will combine both clinical symptoms and molecular genetic information.

Hypohidrotic ED (HED) has one of the most complicated patterns of ED inheritance, as it is caused by mutations in three different genes: *EDA*, *EDAR*, and *EDARADD*. These genes provide instructions for making proteins required for signaling between two cell layers: the ectoderm and the mesoderm. In the early embryo, these cell layers form the basis of development for many organs and tissues, including several structures required for the formation of skin, hair, nails, teeth, and sweat glands. Mutations in the *EDA*, *EDAR*, or *EDARADD* genes accordingly impair normal interactions between

the ectoderm and the mesoderm and the normal development of hair, sweat glands, and teeth, leading to the characteristic features of HED.

Most commonly, HED results from *EDA* mutations. The defective gene, located on the X chromosome (Xq12-q13.1), is inherited in an X-linked recessive pattern. Since males have only one X chromosome, one altered copy of the gene in each cell is enough to cause ED. Females, however, have two X chromosomes, so a mutation must be present in both copies of the gene to cause the dysplasia. Carriers of hypohidrotic ED experience some ED symptoms in about 70% of cases. Symptoms are usually mild, such as a few missing teeth, sparse hair, and abnormal sweat gland function. Hypohidrotic ED less commonly results from defective *EDAR* or *EDARADD* genes. The *EDAR* gene is on the long arm of chromosome 2 at 2q13, and the *EDARADD* gene is on the long arm of chromosome 1 at 1q42.3. *EDAR* mutations can have an autosomal dominant or autosomal recessive pattern of inheritance, and *EDARADD* mutations have an autosomal recessive pattern of inheritance. Autosomal dominant inheritance means that one copy of the mutated gene in each cell is sufficient to cause the disorder. Autosomal recessive inheritance means that two copies of the gene in each cell are mutated. The parents of an individual with an autosomal recessive disorder are most often carriers of one copy of the mutated gene but do not show ED symptoms.

Another ED that may be caused by mutations in two different genes inherited in two different patterns is anhidrotic ectodermal dysplasia with immune deficiency, or EDA-ID. EDA-ID may result from mutations in the *NFKBIA* gene on the long arm of chromosome 14 at 14q13, which are inherited in an autosomal dominant fashion, or from mutations in the *IKBKG* gene on the X chromosome at Xq28, which are inherited in an X-linked recessive pattern.

Incontinentia pigmenti is caused by chromosomal rearrangements disrupting the Xp11 region (type I incontinentia pigmenti) or by the *IKBKG* gene mapping to Xq28 (type II or familial incontinentia pigmenti). Both forms appear to be lethal in males, as nearly all affected living patients (97%–98%) are female.

The molecular genetics of the ED conditions are extremely challenging, due to the similar features of the many ED variants and their genetic heterogeneity (different genetic alterations producing identical physical features). An example of an ED that results from genetic mutations in any of four different genes is cranioectodermal dysplasia, an ED in which patients have abnormally shaped skulls, prominent foreheads, and other abnormal facial features, as well as the sparse hair, misshapen teeth,

abnormal fingernails, and dry skin that are found in other EDs. Cranioectodermal dysplasia may result from mutations in the *IFT43* gene on the long arm of chromosome 14 at 14q24.3, the *IFT122* gene on the long arm of chromosome 3 at 3q21, the *WDR19* gene on the short arm of chromosome 4 at 4p14, and the *WDR35* gene on the short arm of chromosome 2 at 2p24.1. Mutations in all four genes associated with the disorder are inherited in an autosomal recessive pattern.

In some cases different mutations in the same gene result in different types of ED. An example is mutations in the *TP63* gene on the long arm of chromosome 3 at 3q28. Some types of ED that were initially thought to be distinct syndromes are now known to result from different mutations in the *TP63* gene. They include Rapp-Hodgkin syndrome, Hay-Wells syndrome, ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome, and ectrodactyly-ectodermal dysplasia-cleft (EEC) syndrome.

Other EDs that are associated with identified genes include Clouston syndrome, caused by mutations in the *GJB6* gene on the long arm of chromosome 13 at 13q12 and inherited in an autosomal dominant pattern; Witkop syndrome, caused by mutations in the *MSX1* gene on the short arm of chromosome 4 at 4p16.2 and inherited in an autosomal dominant pattern; Naegeli-Franceschetti-Jadassohn syndrome (NFJS), caused by mutations in the *KRT14* gene on the long arm of chromosome 17 at 17q21.2 and inherited in an autosomal dominant pattern; oculodentodigital dysplasia, caused by mutations in the *GJA1* gene on the long arm of chromosome 6 at 6q22.31 and inherited in an autosomal dominant pattern, although some cases of this ED are *de novo* mutations; and focal dermal hypoplasia, caused by mutations in the *PORCN* gene on the short arm of the X chromosome at Xp11.23 and inherited in an X-linked dominant pattern. Focal dermal hypoplasia predominantly affects females because the genetic mutation is lethal to male fetuses.

Demographics

The exact incidence of EDs is not accurately known because there are so many different EDs, some of which have been reported in only a single family. The frequency of the different EDs in a given population is also highly variable; some, like Naegeli-Franceschetti-Jadassohn syndrome, are estimated to affect only 1 person in every 2 million. There are fewer than 1,000 cases of oculodentodigital dysplasia reported in the literature. In the United States, the prevalence of hypohidrotic ED, the most common variant, is estimated to be 1 case per 100,000 births. It is estimated that there are about 125,000 persons in the United States who are carriers of the mutations that cause the EDs.

Worldwide, the prevalence of ED is estimated at 7 cases per 10,000 births. Although the EDs can affect persons of all races and ethnic groups, some researchers think that fair-skinned Caucasians are at increased risk. Hidrotic ectodermal dysplasia appears to be more common in French Canadians than in other ethnic groups, and Witkop syndrome is associated with Mennonites of Dutch ancestry living in Canada.

Apart from the X-linked EDs, males and females are equally affected by these disorders.

Signs and symptoms

Most ED conditions cause significant dental abnormalities. In some cases, the majority of the primary (baby) and secondary (adult) teeth are missing. Teeth that are present may show a characteristic conical, pointed shape (pegteeth) or have abnormal enamel that is prone to cavities.

Hair is often thin with an abnormal texture. In hypohidrotic ED, the scalp hair is thin during childhood and ultimately shows premature balding. Although body hair, eyebrows, and eyelashes are also sparse in this condition, beard and mustache hair are normal. Hair is also sparse in EEC syndrome. In tricho-dento-osseous syndrome and Hay-Wells syndrome, the hair is sparse, coarse, and wiry. Individuals with incontinentia pigmenti may have patchy, bald areas of abnormal skin on the scalp. Frequent scalp infections occur in many of the ectodermal dysplasias.

A variety of skin abnormalities may occur in ED conditions. The skin may be dry, thin, and prone to eczema, infection, cracking, bleeding, and other problems. It may be marked by areas of uneven pigmentation, as in Naegeli-Franceschetti-Jadassohn syndrome, or by pinkish-yellow bumps on the skin, as in focal dermal hypoplasia. In hypohidrotic ED, sebaceous glands (the oil glands within the skin) are absent, causing severe dryness. Increased pigmentation may occur around the eyes (in hypohidrotic dysplasia), over the joints (in hidrotic ED), or in a linear pattern over the trunk (in incontinentia pigmenti). Hyperkeratosis, or thickened skin, occurs on the palms and soles of the feet in hidrotic ED (Clouston syndrome). Reddening and blistering of the skin may occur during infancy in incontinentia pigmenti. In Hay-Wells syndrome, abnormal bands of skin may occur between the upper and lower jaws and between the eyelids.

Decreased numbers of sweat glands and associated impaired sweating ability is an important feature of hypohidrotic ED. This characteristic can lead to life-threatening hyperthermia in hot environments or with physical exertion. Sweating is normal in most other ectodermal dysplasias.

Many EDs involve abnormalities of the mucous membranes. Production of tears and saliva may be deficient. In hypohidrotic ED, the mucous glands in the respiratory tract may be absent or decreased in number, leading to dryness, infections, and an unusual foul-smelling secretion associated with atrophy of the nasal tissues known as ozena. In some cases, dryness of the pharynx and larynx may affect the quality of the voice.

Fingernails and toenails are abnormal in many of the EDs. In EEC syndrome, the nails may be thin and brittle. Nails may be absent or abnormally formed in Hay-Wells syndrome, Rapp-Hodgkin syndrome, hidrotic ED, Witkop syndrome, and incontinentia pigmenti. Nails are normal, however, in hypohidrotic ED.

Some individuals with ED, particularly those with EEC syndrome, may have hearing impairment.

Structural birth defects may occur in some EDs. In EEC, Hay-Wells, and Rapp-Hodgkin syndromes, cleft lip and palate may occur. EEC is also characterized by split hand/split foot (or “lobster claw”) malformations and genitourinary anomalies. Amastia (absence of the breast) may occur in hypohidrotic ED, and breasts may be underdeveloped in incontinentia pigmenti and EEC syndrome. Some individuals with incontinentia pigmenti may have defects of the eye (such as congenitally crossed eyes, cataracts, or atrophy of the optic nerve) or central nervous system (such as a small head size, intellectual disability, or seizures). Cranioectodermal dysplasia is associated with deformities of the rib cage leading to breathing difficulties, as well as with disorders of the kidneys, liver, and heart.

Children with EDA-ID have defective immune systems that produce abnormally low levels of antibodies to fight off bacteria or viruses. They have frequent infections of the lungs (pneumonia), ears, skin, digestive tract, sinuses, and lymph nodes. About a quarter of these children also have chronic inflammatory conditions like rheumatoid arthritis.

Diagnosis

The diagnosis of an ED condition is typically based on clinical findings (physical examination, medical and family history), most often by a pediatrician or pediatric dermatologist. Although the EDs are congenital (present at birth), they may not be diagnosed until later infancy or early childhood, when the abnormalities in the teeth, hair, skin, and nails become apparent. With the exception of type I incontinentia pigmenti, there are no laboratory studies that are considered diagnostic. High-resolution chromosome study may be considered diagnostic for type I incontinentia pigmenti, as it can reveal the X chromosome rearrangements that appear to cause the condition.

KEY TERMS

Amastia—A birth defect involving the absence of mammary glands.

Anhidrosis—Complete inability to sweat in response to heat.

Congenital—Refers to a disorder that is present at birth.

De novo mutation—A genetic mutation that is seen for the first time in the affected person, not inherited from the parents.

Dysplasia—The abnormal growth or development of a tissue or organ.

Eccrine—Pertaining to the sweat glands located over most of the human body. Their water-based sweat is the primary mechanism of cooling in humans.

Ectoderm—The outermost of the three embryonic germ layers, which later gives rise to the nervous system, skin, hair, teeth, and nails.

Ectrodactyly—A birth defect involving a split or cleft appearance of the hands and/or feet, also referred to as a “lobster-claw” malformation.

Eczema—Inflammation of the skin with redness and other variable signs such as crusts, watery discharge, and itching.

Hyperthermia—Body temperature that is much higher than normal (above 98.6°F).

Hypohidrosis—Insufficient perspiration or absent perspiration that may be either general or localized to a specific area.

Mesoderm—The middle germ layer in the developing embryo, lying between the ectoderm and the endoderm. It gives rise to muscle, cartilage, bone, and the subcutaneous layer of the skin.

Ozena—Also called atrophic rhinitis, it is a condition in which the bony ridges and mucous membranes of the nose waste away (atrophy), resulting in a foul-smelling bacteria-infected discharge.

X-linked dominant inheritance—The inheritance of a trait by the presence of a single gene on the X chromosome in a male or female, passed from an affected female who has the gene on one of her X chromosomes.

X-linked recessive inheritance—The inheritance of a trait by the presence of a single gene on the X chromosome in a male, passed from a female who has the gene on one of her X chromosomes. She is referred to as an unaffected carrier.

The high degree of variability within and overlap between the different ED conditions can lead to difficulty identifying the specific syndrome. The presence or absence of nail and sweat gland involvement are important distinguishing features.

In hypohidrotic ED (HED), determining whether or not a female relative of an affected male also carries the *EDA* gene may be difficult. Many clinical tests based on sweat pore and dental analysis have been attempted, but they are considered unreliable. Linkage analysis by way of tracing the Xq12-13 gene locus through the family is considered to be the best way to determine carrier status. When linkage analysis is successful, it may also be used for prenatal diagnosis. Molecular diagnostic testing has made significant advances in recent years; tests are available for all the genes associated with the EDs included in this entry.

Treatment and management

Treatment of most ED syndromes requires a multi-specialty team, typically including a dermatologist (skin

specialist), dentist or oral surgeon, and ophthalmologist (eye specialist), as well as a pediatrician.

In hypohidrotic ED, males are at risk of hyperthermia and potential central nervous system damage or death. Hot environments and fevers must be avoided or managed with cooling methods, such as misting the skin with water or moving to a cool climate. Air conditioning in home, school, and work environments is considered essential. The dry nasal passages may be treated with moisturizing inhalers or other solutions. Various skin treatments may be used to prevent cracking, bleeding, and infection. Protection from exposure to direct sunlight is often necessary.

Early and extensive dental work is required in most ED conditions. In childhood, successive dentures may be used, while dental implants and bridges may be used in adults. Orthodontic treatment may also be necessary.

The abnormal hair associated with the EDs is primarily a cosmetic problem and may be managed with wigs.

In EEC, Rapp-Hodgkin syndrome, and Hay-Wells syndrome, clefting of the lip and palate requires surgical

QUESTIONS TO ASK YOUR DOCTOR

- A family member has just been diagnosed with ectodermal dysplasia. What are some of the symptoms of this disorder?
- What causes ectodermal dysplasia? Can it be prevented?
- What kinds of treatments will our family member need to deal with his ectodermal dysplasia?
- Is the condition considered to be a serious or life-threatening disorder?

correction, with treatment of any associated speech, dental, or hearing problems.

Hand and foot malformations in EEC may require orthopedic or plastic surgery and/or occupational therapy. The abnormal skin banding that may occur in the mouth and between the eyelids in Hay-Wells syndrome also requires surgical correction.

Most children with an ED require psychological counseling as they grow older in order to cope with social problems resulting from their appearance and their need for special accommodations and treatments. One European study reported in 2015 that adults with EDs suffer from higher levels of anxiety and lower quality of life than persons with other orofacial conditions.

Clinical trials

There are 36 clinical trials on EDs and related conditions being conducted in the United States as of 2021. Some are studies of investigational treatments for the EDs, one is a trial of a diagnostic method that involves imaging sweat glands in newborns, and one is a study of carriers of X-linked EDs.

Prognosis

Among males with hypohidrotic ED, unrecognized episodes of hyperthermia are a dangerous complication. The mortality rate during infancy and early childhood in affected undiagnosed males is 30% due to neurologic damage associated with hyperthermic episodes. If affected males are diagnosed and managed appropriately, a normal life expectancy and normal intelligence can be expected.

The tissue abnormalities and birth defects that occur in the EDs are usually not life threatening; however,

individuals with EDA-ID rarely survive childhood because of their susceptibility to frequent infections.

EDs typically do not cause intellectual disability, although a minority of cases of incontinentia pigmenti and EEC syndrome may involve cognitive impairment.

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ORGANIZATIONS

American Academy of Dermatology (AAD), P.O. Box 1968, Des Plaines, IL 60017, (847) 240-1280 or (866) 503-SKIN, <https://www.aad.org>

Ectodermal Dysplasia Society, Unit 1, Maida Vale Business Centre, Leckhampton, Cheltenham UK GL53 7ER, +44(0) 124 261332, info@edsociety.co.uk, <https://edsociety.co.uk/>

National Foundation for Ectodermal Dysplasias (NFED), 6 Executive Drive, Ste. 2, Fairview Heights, IL 62208, (618) 566-2020, info@nfed.org, <http://www.nfed.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

UCSF Benioff Children's Hospital, Ron Conway Family Gateway Medical Building, 1825 Fourth St., Fifth Floor, 5B, San Francisco, CA 94158, (415) 353-7800, <https://www.ucsfbenioffchildrens.org>

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Ectrodactyly-ectodermal dysplasia-clefting syndrome

Definition

Ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome is one of more than 100 ectodermal dysplasia syndromes. EEC syndrome is characterized by deformities of the hands and feet (ectrodactyly); abnormalities of the skin, hair, and nails (ectodermal dysplasia); and cleft lip and/or cleft palate (clefting). Other symptoms include dental, eye, skin, and kidney abnormalities.

Description

Ectodermal dysplasias (ED) are a group of inherited disorders that result from problems in early development of the ectodermal layer in the embryo. Problems with the ectoderm cause the hair, teeth, nail, and glands to develop and function abnormally. EEC syndrome is characterized by deformities of the hands and feet (ectrodactyly) that are sometimes referred to as lobster-claw deformities; abnormalities of the skin, hair, and nails (ectodermal dysplasia); and cleft lip and/or cleft palate (clefting). Other abnormalities include absence of the teeth and other dental abnormalities, decreased ability to sweat, absence of tear ducts, photophobia (increased sensitivity to light), and kidney abnormalities. Most individuals with EEC syndrome have some of these abnormalities, but very few individuals have all of these abnormalities.

EEC syndrome is a genetic disorder with autosomal dominant inheritance with incomplete penetrance and variable expression. It can be inherited from a parent, but many individuals are the first in their family to be affected. DNA testing is now available and may be used to clarify the diagnosis in an individual with characteristic symptoms of the syndrome.

The cosmetic concerns of EEC can have a tremendous impact on the quality of life of an individual with EEC syndrome. The facial and limb differences can be socially isolating and physically challenging. Children and adults with EEC may be socially ostracized due to their physical appearance. Many individuals erroneously assume that people with EEC syndrome have limited abilities. It is important to increase awareness with educational programs and to take proactive steps to foster self-esteem in children with EEC syndrome.

Genetic profile

EEC syndrome has autosomal dominant inheritance with incomplete penetrance and variable expression. It is caused by mutations in the *p63* gene, which is located



Mother and child with ectrodactyly-ectodermal dysplasia-clefting syndrome. (Maria Platt-Evans/Science Source)

on the long arm of chromosome 3 (3q27). The *p63* gene appears to be necessary for the normal development of the skin and limbs.

Mutations in the *p63* gene are inherited in an autosomal dominant manner. Every individual has two *p63* genes: one from their father and one from their mother. In an autosomal dominant disorder, only one gene has to have a mutation for the person to have the EEC disorder. Some individuals with EEC syndrome are born to unaffected parents. Their EEC syndrome is the result of a *de novo*, or new, mutation. No one knows the cause of *de novo* mutations or why they occur so frequently in EEC syndrome. Because individuals pass half of their genes onto their children, a person with EEC syndrome has a 50% chance that their child will also inherit EEC syndrome. If two unaffected people have a child with EEC syndrome, they have about a 4% risk to have another child with EEC syndrome. This increased recurrence risk is due to the possibility of germ-line mosaicism. Germ-line mosaicism is the presence of two cell lines in the reproductive cells (eggs or sperm cells) of an individual. Thus, a parent of a child with EEC syndrome may have one normal cell line and one cell that contains the mutation for EEC syndrome.

While EEC syndrome has autosomal dominant inheritance, it also shows incomplete penetrance. “Incomplete penetrance” is the term that is used to describe individuals with a mutation in a gene who do not have any symptoms of a particular disease. Although this is very rare, there are some large families in which this phenomenon has been documented. Because the physical findings of EEC syndrome can be so variable, it is important to carefully examine other family members to make sure that they do not have an extremely mild case of EEC syndrome.

The findings or symptoms of EEC vary from family to family and even from person to person within the same family. For example, one sibling may have cleft lip and hand abnormalities, while another sibling may have kidney and eye abnormalities. This phenomenon is referred to as variable expression. Most ectodermal dysplasias show some degree of variable expression. This can often make it very difficult for a physician to make an exact diagnosis.

Demographics

The overall incidence of ectodermal dysplasias in the United States is 7 out of 10,000 people. Because the findings of EEC syndrome overlap those seen in other ectodermal dysplasias, the exact prevalence of EEC syndrome is not known. With the advent of DNA testing, it may soon be possible to get an accurate prevalence figure for EEC syndrome, but, as of 2021, this is not yet possible.

Signs and symptoms

In order to understand the signs and symptoms of EEC syndrome it is important to understand a little about early embryonic development. Very early in pregnancy, the cells that will develop into the embryo are organized as a small round ball. These cells eventually separate into three distinct layers: the endoderm, the mesoderm, and the ectoderm. The endoderm can be thought of as the inside layer. Cells from the endoderm will eventually form the lining of the digestive tract and the respiratory tract. The mesoderm can be thought of as the middle layer, and the cells of the mesoderm will eventually become the muscles, bones, cartilage, heart, and blood vessels. The ectoderm (involved in EEC syndrome) can be thought of as the outside layer. The cells of the ectoderm will eventually become the skin, hair, nails, brain, and nervous system. Any disruption of the development of the ectoderm will lead to disruption of the organs formed from this layer.

EEC syndrome is the result of a disruption of the ectoderm layer very early in development. This

disruption causes the specific defects seen in EEC syndrome, including defects of the skin, hair, nails, and other organs. The exact nature of this disruption or problem in formation of the ectoderm is not known. Research in this area is ongoing.

EEC syndrome is a disorder that causes multiple congenital abnormalities. Although these anomalies appear to be diverse, they all arise from the same underlying defect, or insult, to the early embryonic ectodermal tissue. Ectodermal tissue is responsible for the formation of the limbs, nails, eyes, skin, hair, teeth, kidneys, glands, and face. All of these organs and systems are affected to some degree in EEC syndrome. Most individuals will have some of the EEC abnormalities, but it is very rare for one individual to have all of these abnormalities.

Abnormalities of the hands and feet of individuals affected with EEC may include:

- ectrodactyly (lobster-claw deformity) of the hands and feet
- syndactyly (webbed fingers or toes)

Abnormalities of the eyes of affected individuals may include:

- nasolacrimal duct obstruction (tear duct obstruction)
- excessive lacrimation (tears)
- blepharophimosis/blepharospasm
- corneal ulcers and scarring
- telecanthus
- photophobia

Skin abnormalities of individuals affected with EEC may include:

- dry skin
- lack of sweat pores
- thin skin/generalized skin atrophy
- hyperkeratosis (thickened skin)

Individuals affected with EEC may have hair abnormalities, including:

- dry, brittle hair
- generalized depigmentation of hair
- fine hair
- sparse hair, or alopecia areata

Teeth abnormalities in affected individuals may include:

- abnormalities in the tooth buds, resulting in missing or abnormally shaped teeth
- defective enamel
- small teeth

Abnormalities of the kidneys of affected individuals may include:

- dilated ureters or ureteral atresia
- double ureters
- hydronephrosis
- multiple renal cysts
- renal agenesis
- renal dysplasia

Gland abnormalities of individuals affected with EEC may include:

- absent or hypoplastic thymus
- hypopituitarism
- isolated growth hormone deficiency
- pituitary diabetes insipidus

Facial abnormalities of affected individuals may include:

- cleft lip
- cleft palate
- malformed ears

Additionally, individuals affected with EEC can experience nail dystrophy.

There are two other ectodermal dysplasia syndromes that closely resemble EEC syndrome: Rapp-Hodgkin syndrome (RHS) and ankyloblepharon-ectodermal defects-cleft lip and palate (AEC) syndrome (also known as Hay-Wells syndrome). These syndromes share some of the specific findings of EEC syndrome, but differ in important ways.

Rapp-Hodgkin syndrome (RHS) is another type of ED associated with cleft lip and palate. However, RHS does not share the hand and foot defects of EEC syndrome. People with RHS do have some sweating problems, and their hair grows slowly and is coarse. Some affected individuals have persistent scalp dermatitis. As a rule, individuals with RHS have more teeth than those with EEC. General health, intelligence, and lifespan are within normal expectations.

Hay-Wells syndrome (HWS), also known as ankyloblepharon-ectodermal dysplasia-cleft lip and palate syndrome, is one of several syndromes that affect both the ectoderm and structures that do not derive from the ectoderm. The scalp hair is sparse and wiry, while the eyelashes are sparse or absent. The nails may be absent or malformed, and the teeth and sweat glands may also be affected. The feature that differentiates HWS from the other ectodermal dysplasias is the fusion of the upper and lower eyelids usually by narrow bands of tissue connecting the lids (ankyloblepharon). Patients may also have inflammatory dermatitis of the scalp.

Diagnosis

The diagnosis of EEC syndrome can be complex because of the overlap of symptoms with other ectodermal dysplasia syndromes. The diagnosis of EEC syndrome is usually made through a combination of clinical exam, x-rays, kidney imaging tests, skin biopsy, and DNA testing.

To make the diagnosis of EEC, a physician must evaluate which ectodermally derived structures are involved and look for physical features that do not develop from the ectoderm. By looking at the specific pattern of defects, it may be possible to make a correct diagnosis, but because of the overlap between other ectodermal dysplasias, it can often be difficult to make a definitive diagnosis based on the clinical exam alone. DNA testing and other tests can help aid in the diagnosis.

X-rays are often helpful in establishing the diagnosis of EEC syndrome. X-rays may be taken of the jaw to look for dental abnormalities, while x-rays of the limbs may be done to look for subtle abnormalities that may not be seen with a clinical exam. The presence of dental abnormalities or limb abnormalities would add to the suspicion that a person had EEC syndrome.

Because individuals with EEC syndrome can have kidney abnormalities, it is important to assess their kidney structure. This can be done using an IV pyelogram or ultrasound. The presence of a kidney abnormality would lend credence to the diagnosis of EEC syndrome, but the absence of a kidney abnormality does not rule out the diagnosis, as not every person with EEC syndrome has every symptom.

A skin biopsy involves removing a small amount of several layers of skin to examine them under a microscope. In EEC syndrome, the skin cells themselves may be abnormal. In addition, the sweat glands may be abnormal in number or shape.

DNA testing can also be performed on blood samples from children or adults. The presence of a mutation in the *p63* gene would confirm the diagnosis of EEC syndrome. Because scientists have not yet found all of the mutations in this gene, the absence of a detectable mutation does not completely rule out the diagnosis.

The diagnosis of EEC syndrome can also be made prenatally (during pregnancy) either by ultrasound (sonogram) or by prenatal DNA testing. Sonograms use sound waves to provide an image of a fetus. The structural abnormalities of EEC syndrome, including cleft lip, kidney abnormalities, and limb abnormalities, can be detected during the second trimester of pregnancy. Because of the overlap in some of the structural

KEY TERMS

Ectoderm—Embryonic cells that are affected in EEC syndrome.

Ectrodactyly—Lobster-claw deformities of the hands and feet and missing digits on the hands and feet.

Incomplete penetrance—Absence of disease in an individual known to carry the gene for that disease.

Variable expression—Ability of the same gene to cause different symptoms in different people (with the same disorder).

abnormalities of the ectodermal dysplasias, it can be very difficult to definitively diagnose EEC syndrome by sonogram. Other ectodermal dysplasias can look very similar to EEC syndrome on a sonogram. DNA testing can clarify ambiguous ultrasound findings.

Prenatal testing can also be done using DNA testing. A sample of tissue from a fetus is obtained by either chorionic villi sampling (CVS) or by amniocentesis. CVS is generally done between 10 and 12 weeks of pregnancy, and amniocentesis is done between 14 and 18 weeks of pregnancy. CVS involves removing a small amount of tissue from the developing placenta. The tissue in the placenta contains the same DNA as the fetus. Amniocentesis involves removing a small amount of fluid from around the fetus. This fluid contains some fetal skin cells. DNA can be isolated from these skin cells. The fetal DNA is then tested to determine if it contains mutations in the *p63* gene that causes EEC syndrome. Because not all of the mutations causing EEC syndrome have been found, DNA testing is not always definitive and the interpretation of the test results is best done by a genetics professional.

Treatment and management

There is no cure for EEC syndrome, but there are many treatments available to address the symptoms. These treatments include surgery, dental care, prevention of complications from hypohydrosis (abnormal sweating), and other preventive treatments.

Individuals with EEC syndrome may need surgery to correct cleft lips, cleft palates, and abnormalities with their hands and feet. Correction of cleft lip is usually done in infancy, as is surgery for cleft palate. Correction of cleft palate is important for feeding and for speech. Surgery may be done on hand and foot abnormalities to improve the function of these limbs, to improve the appearance of these limbs, and to aid in shoe fit.

QUESTIONS TO ASK YOUR DOCTOR

- How can I help my child with EEC build self-esteem?
- What are the most effective treatments for the symptoms of EEC?
- What sort of continuing health care will my child with EEC require?

Typically, patients with EEC syndrome will need extensive dental work. X-rays may be taken to document the presence or absence of teeth. Abnormal teeth may be pulled or capped. Replacement dentures may be worn during childhood. After growth has ended, many individuals receive dental implants.

Hypohydrosis, or impaired sweating, is a major complication of EEC syndrome. Without normal sweating, the body cannot regulate temperature properly. Therefore, overheating is a common problem and can lead to seizures, coma, and death in severe cases. It is important that affected individuals with an impaired ability to sweat follow the general precautions of using air conditioning when necessary, avoiding vigorous exercise, wearing light clothing, and avoiding hot temperatures.

Abnormal development of the eye can result in dryness of the eye, cataracts, and vision defects. Artificial tears can be used to protect the eyes from corneal scarring, which can lead to blindness if left untreated.

Prognosis

The prognosis for most individuals with EEC syndrome is very good. Life expectancy ranges from slightly reduced to normal. The most life-threatening complications come from sweating problems. Individuals with an impaired ability to sweat are at risk to overheat, which can lead to seizures, coma, and death. The life expectancy of individuals with EEC syndrome without sweating problems is expected to be normal.

The prognosis for most people with EEC syndrome is very good. In general, they have minimal and manageable serious medical problems, normal IQ, and most achieve success and have a long life, regardless of their disabilities. Successful social adaptation plays an important role in the ultimate success and happiness of an individual with EEC syndrome. It is very important that the career and life choices of an individual with EEC syndrome not be limited by preconceived ideas about their abilities.

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ORGANIZATIONS

- American Cleft Palate-Craniofacial Foundation, 1504 E. Franklin St., Suite 102, Chapel Hill, NC 27514-2820, (919) 933-9044 or (800) 242-5338, (919) 933-9604, <https://acpa-cpf.org/>
- National Foundation for Ectodermal Dysplasias, 6 Executive Dr., Suite 2, Fairview Heights, IL 62208-1360, (618) 566-2020, (618) 566-4718, info@nfed.org, <http://www.nfed.org>

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Edwards syndrome

Definition

Edwards syndrome is a genetic syndrome of multiple congenital anomalies and severe-to-profound intellectual disability. It is caused by the presence of an extra chromosome 18 in some or all of the cells of the body. Babies with the condition usually do not survive past their first several months. Trisomy 18 in the embryo/fetus is also a common chromosomal cause of pregnancy loss.



The left hand of an infant with trisomy 18. One of the symptoms of the disorder is a clenched-hand posture. (Centers for Disease Control and Prevention)

Description

Chromosomes are the microscopic structures inside cells that carry the genes. The genetic material inside each cell contains all of the instructions the body needs to develop and function normally. Humans have 23 different pairs of chromosomes. Chromosomes 1–22 are numbered from largest to smallest and as a group are known as the autosomes. The last pair of chromosomes are designated X and Y and are known as the sex chromosomes—females have two X chromosomes, and males have one X and one Y. Other than sperm and eggs, each cell in the body normally has 46 chromosomes—a pair of each of the autosomes plus two sex chromosomes. In order for normal development and functioning to occur, chromosomes and genes must be present in the correct quantity and in the correct proportion to each other. Too much or too little genetic material usually causes serious problems.

The term “euploid” means “good set” and is used to designate a full set of 46 chromosomes. A cell is aneuploid (“not a good set”) if it has any number of chromosomes other than 46. A trisomy is one type of aneuploidy and refers to a cell that contains three of the same chromosome. Trisomy 18, then, refers to three chromosomes 18. After Down syndrome (trisomy 21), trisomy 18 is the most common autosomal aneuploid condition seen in live-born babies.

Edwards syndrome is made up of a specific but broad pattern of multiple congenital anomalies and intellectual disability. Babies with Edwards syndrome tend to have similar physical features and medical problems because they all have the same genetic imbalance—an extra copy of the genes on chromosome 18. The physical anomalies associated with Edwards syndrome involve nearly every organ and system of the body. However,

some anomalies occur more often than others, such as those of the heart, kidney, brain, skeleton, and craniofacial (head and face) area. The birth defects are typically serious and, combined with the large number of anomalies possible, result in a high mortality rate. About 60% of newborns with Edwards syndrome die within the first week, and 80% do not survive past the first month. Even those with Edwards syndrome who live longer will have severe to profound intellectual disability and chronic medical problems, necessitating involved care and monitoring throughout their lives.

Genetic profile

Edwards syndrome occurs in three different forms: full trisomy 18, mosaic trisomy 18, and partial trisomy 18. Before each of these is described, however, it is helpful to review the basics of normal reproduction and early embryonic development. As noted, cells in the body normally contain 46 chromosomes in 23 pairs, except sperm in males and eggs in females, which contain one chromosome of each pair, or 23 total. Meiosis is the process by which sperm and eggs, collectively known as gametes, are produced. In normal meiosis, the 46 chromosomes line up in pairs in the middle of a cell, and the cell divides down the middle separating each pair of chromosomes. When a sperm fertilizes an egg at conception, the 23 chromosomes from each gamete combine. A process of repeated chromosome duplication followed by cell division, known as mitosis, then begins. A cell that goes through mitosis produces two new cells, each with 46 chromosomes. A developing human is called an embryo during the eight weeks after conception, and a fetus for the remainder of pregnancy.

Full trisomy 18

Occasionally, chromosomes of a single pair do not separate during meiosis, an abnormal process known as nondisjunction. The result is one gamete with 24 chromosomes and another with 22. If a gamete with 24 chromosomes results in conception with a normal counterpart, an embryo with 47 chromosomes is produced. In most cases, all cells in the body will then have 47 chromosomes, a condition known as full trisomy 18 (when referring to an individual with the disorder, unless otherwise specified, the term “trisomy 18” implies a full trisomy, whereas Edwards syndrome may refer to any of the forms).

Nondisjunction of two chromosomes 18 during the formation of an egg or sperm is by far the most common cause of Edwards syndrome. Nondisjunction is a chance occurrence, with no known causative or preventive factors. The incidence of nondisjunction does increase, however, as men and women age. For anyone who has a fetus

or child diagnosed with trisomy 18, the risk for a chromosomal disorder of any type in subsequent offspring is about 1%, the exception being women over age 35, who face their age-related risk.

Mosaic trisomy 18

If the body contains a mixture of cells, some with trisomy 18 and some with a normal chromosome count, the condition is called mosaic trisomy 18. A small percentage of Edwards syndrome cases are due to mosaic trisomy 18.

Mosaic trisomy 18 occurs in one of two ways. The first involves mitotic (rather than meiotic) nondisjunction of chromosomes 18, in which a cell undergoing mitosis in a chromosomally normal embryo produces one cell with trisomy 18 and another with monosomy 18. The cell with monosomy 18 cannot survive, but if the trisomic cell survives, all cells in the body derived from it will have trisomy 18. These trisomic cells, combined with the normal cells that continue to develop, result in mosaic trisomy 18. The other cause of mosaicism involves an embryo with full trisomy 18. In this case, however, one cell loses its extra chromosome during mitosis. The result is a euploid cell, which in turn produces a euploid cell line in addition to the original trisomic cell line. Since mitotic nondisjunction appears to be the cause in most cases, and is due purely to chance, the recurrence risk for subsequent offspring after the diagnosis of mosaic trisomy 18 is less than 1%.

Because they have some normal cells, individuals with mosaic trisomy 18 tend to be less severely affected than those with full trisomy 18, but not always. Much of the prognosis depends on the total percentage of trisomic cells in the body and/or the proportion of trisomic cells in specific tissues and organs. There is no way to determine exact percentages of cells and, therefore, no way to provide an accurate prognosis.

Partial trisomy 18

A third cause of Edwards syndrome is a rearrangement, or translocation, of genetic material between chromosome 18 and another chromosome. An unbalanced chromosome translocation (extra and/or missing genetic material) may result in an embryo that has an extra piece of chromosome 18, known as partial trisomy 18. If cells are trisomic for a portion of chromosome 18, the result could be a form of Edwards syndrome. However, translocations between chromosomes can be complicated, and some cases of partial trisomy 18 may result in a pattern of anomalies that does not resemble Edwards syndrome.

Unbalanced translocations can occur in an embryo for the first time (*de novo*), or they can be inherited from

a healthy parent who is a carrier of the translocation in a balanced state (no missing or extra genetic material). Normal blood chromosome tests on both parents implies the translocation was *de novo*, which means no increased risk for subsequent offspring. Detection of a balanced translocation in one parent, however, presents an increased risk for unbalanced translocations in subsequent offspring, as well as an increased risk for pregnancy loss. In cases of partial trisomy 18, genetic counseling is critical to help determine risks and available options. Chromosome translocations resulting in partial trisomy 18 make up a small percentage of Edwards syndrome cases.

Demographics

The incidence of Edwards syndrome is about 1 in 5,000 births. Two-thirds of all newborns with the condition are female, probably because males with trisomy 18 are more likely to be miscarried. The condition is not known to occur more frequently in any ethnic group or in any part of the world. Increased parental age is the only factor known to result in a greater risk for trisomy 18. In the United States, parents of babies with trisomy 18 average about 32 years of age, while 26 is the average age for parents of children without a chromosomal disorder. The risk increases with age in both sexes, but begins earlier and is more pronounced in women.

Increasing maternal age elevates the risk for chromosomal disorders due to nondisjunction in general, not just trisomy 18. For instance, a 20-year-old woman has about a 1 in 10,000 chance of having a child with trisomy 18, while the risk of having a child with *any* chromosomal disorder at that age is 1 in 800. By age 35, those same risks have risen to 1 in 2,000 and 1 in 200, respectively, and increase to 1 in 600 and 1 in 65 at age 40. Other common chromosomal disorders caused by nondisjunction that result in live birth include trisomy 21 (Down syndrome), trisomy 13 (Patau syndrome), and several conditions caused by aneuploidy of the sex chromosomes.

Signs and symptoms

Many physical anomalies and medical complications are associated with Edwards syndrome. In fact, well over 100 different anomalies have been reported in the medical literature. The more common findings are categorized and described below.

Prenatal anomalies

The majority of pregnancies in which the embryo/fetus has trisomy 18 will result in miscarriage or stillbirth. Some physical anomalies of the heart, skeleton, brain, kidneys, and body walls have the best chance of being

detected by prenatal ultrasound. Other pregnancy-related findings include intrauterine growth restriction (IUGR) of the fetus, a single umbilical artery (also called two-vessel cord), and too much (polyhydramnios) or too little (oligohydramnios) amniotic fluid. While detection of fetal anomalies by ultrasound may lead to suspicion of Edwards syndrome, the diagnosis can only be confirmed by chromosome testing. Women carrying a fetus with Edwards syndrome sometimes report they feel little movement. Cesarean sections are more common due to abnormal fetal position or fetal distress near term.

General anomalies

Of those babies with Edwards syndrome that are live-born, two-thirds are delivered several weeks earlier or later than their expected due date. Low birth weight is common, as are low Apgar scores (measurements of a newborn's activity just after birth). Newborns are frail and tend to have a weak cry and difficulty feeding. Muscles may be poorly developed and often become tight and contracted (hypertonic). Extra hair (hirsutism) on the forehead and back is sometimes seen, as is loose, redundant skin.

Abnormalities of the lungs, kidneys, pancreas, spleen, and gastrointestinal system are associated with Edwards syndrome. The thyroid, thymus, and adrenal glands may be affected. Anomalies of the breastbone, radius (bone in the forearm), ribs, pelvis, and spine (scoliosis) are the more frequent skeletal findings. An abdominal wall defect (omphalocele) or hernia in the abdominal region may be present. Genital (sex organ) anomalies in both males and females have been described.

Heart anomalies

Ninety percent of babies with Edwards syndrome have one or more heart defects. Ventricular septal defects (VSD) and atrial septal defects (ASD), holes between the lower and upper chambers of the heart, respectively, are the most common cardiac problems. Patent ductus arteriosus (open connection between the pulmonary artery and aorta) and abnormal heart valves are also typical.

Craniofacial anomalies

Small head size (microcephaly) and a prominent occiput (back of the skull) are variations in skull shape typical of Edwards syndrome. Common facial features include widely spaced and/or slanted eyes, skin folds at the inner eyelid (epicanthal folds), ptosis (drooping) of the eyelids, low-set malformed ears, a small oral opening, narrow palate or cleft lip/palate, and a small jaw (micrognathia).

Hand and foot anomalies

A specific pattern of hand and foot anomalies is seen in most infants with Edwards syndrome. Clenched hands, with the index finger overlapping the third and the fifth finger overlapping the fourth, are a classic sign. Abnormal dermatoglyphics (fingerprint pattern), underdeveloped nails, outward or inward deviation of the hand, underdeveloped or absent thumbs, and a single crease across the palm are other frequent anomalies of the hands. Abnormalities affecting the feet include so-called “rocker-bottom feet” and clubfoot.

Central nervous system anomalies

Probably the most medically significant abnormal development that occurs in Edwards syndrome involves the brain. Some anomalies, such as a small cerebellum or hydrocephalus (increased fluid within the brain), can be visualized by ultrasound or other imaging techniques. However, some neurologic problems may only be noticed through their physical effects. For example, difficulties in feeding and breathing, hypertonic muscles, a diminished response to sound, seizures, and severe intellectual disability all indicate serious neurologic deficits. Spina bifida (open spine) is an infrequent but serious problem affecting the spinal cord. Babies with spina bifida usually have some degree of paralysis below the point on the back where the spine failed to close.

Diagnosis

Prenatal

Two screening and two diagnostic procedures for trisomy 18 are available to women during pregnancy. Following are brief explanations of each of the prenatal testing alternatives.

Maternal serum alpha-fetoprotein (MSAFP)-Plus, also known as the “triple screen,” is a routine maternal blood test offered to women at 15–20 weeks of pregnancy. It screens for open defects (such as spina bifida), Down syndrome, and trisomy 18. However, the screen’s sensitivity for trisomy 18 is not as well established as it is for the other conditions. Test results provide a risk adjustment only, not a diagnosis of any condition in the fetus. Any woman who has a result showing an increased risk for trisomy 18 in the fetus is offered follow-up testing such as amniocentesis or a detailed (level II) ultrasound.

Ultrasound, also called sonography, visualizes structures inside the body using high-frequency sound waves. During a prenatal ultrasound, a technician or doctor moves an instrument (transducer) back-and-forth across the skin of a pregnant woman’s lower abdomen. The transducer emits and receives harmless high-frequency

sound waves, which the ultrasound machine then converts into images of the fetus. Today’s sophisticated ultrasound machines, used by skilled technicians and doctors, can detect a number of different physical anomalies in the fetus. An ultrasound screen for trisomy 18 has good (but not absolute) sensitivity and presents no risk to the mother or fetus. Ultrasound becomes more sensitive for trisomy 18 the later in pregnancy it is performed. A level II ultrasound is performed after 20 weeks of pregnancy by a specialist (perinatologist). An abnormal ultrasound suggesting trisomy 18 would lead to the option of amniocentesis to confirm the diagnosis.

Chorionic villus sampling (CVS) is a method used to obtain tissue (chorionic villi) from the edge of the developing placenta. CVS is typically performed at 10–12 weeks of pregnancy. Chorionic villi come from the fetal side of the placenta and thus are chromosomally the same as cells in the fetus. Guided by ultrasound, a physician inserts a needle through either the abdomen or the cervix, into the placenta, and removes a small sample of tissue. Cells from the sample are analyzed under a microscope and a chromosome count is obtained. CVS carries a minimal risk for miscarriage and appears to have a very small risk of causing certain types of limb defects in the fetus as well. In about 3% of cases, CVS produces results that are difficult to interpret, which may lead to a follow-up amniocentesis.

Amniocentesis is the most widely used procedure to obtain fetal cells for genetic testing. The procedure can be performed any time after about 15 weeks of pregnancy. Under ultrasound guidance, a physician passes a thin needle through the lower abdomen into the amniotic sac and removes a small amount of amniotic fluid. Fetal skin cells that normally float in the fluid are then extracted for genetic analysis. Diagnosis of chromosomal disorders by this method is highly accurate. Amniocentesis causes a miscarriage in about 1 in 300 women who have the procedure, but poses no other serious risk to the fetus.

The benefit of CVS and amniocentesis is their accuracy at detecting trisomy 18, while the drawback is their risk to the pregnancy. The procedures are typically not offered unless the risk for a chromosomal disorder in the fetus is greater than the risk of the procedure, such as in pregnant women who are 35 or older, a couple with a previous child with trisomy 18, and any woman who carries, or whose partner carries, a balanced chromosome translocation. Detection of fetal anomalies by ultrasound or an abnormal MSAFP-Plus screen would lead to the option of amniocentesis.

The benefit of ultrasound and MSAFP-Plus is their lack of risk to the pregnancy, while the drawback is that

KEY TERMS

Aneuploidy—An abnormal number of chromosomes in a cell. Trisomy 18 and trisomy 13 are examples of aneuploid conditions.

Chromosome translocation—The exchange of genetic material between chromosomes, which can lead to extra or missing genetic material.

Geneticist—A specialist (MD or PhD) who has training and certification in diagnosing, managing, and counseling individuals/families with genetic disorders. Genetic counselors hold a master's degree in medical genetics and provide many of the same services as geneticists.

Meiosis—The process in which a cell in the testes or ovaries undergoes chromosome separation and cell division to produce sperm or eggs.

Mitosis—The process by which a somatic cell divides into two genetically identical cells in which the total number of chromosomes is maintained.

Mosaicism—A genetic condition resulting from a mutation, crossing over, or nondisjunction of chromosomes during cell division, causing a variation in the number of chromosomes in the cells.

Neonatologist—A physician (pediatrician) who has special training in the care of newborns (neonates).

Nondisjunction—Nonseparation of a chromosome pair, during either meiosis or mitosis.

Perinatologist—A physician (obstetrician) who has special training in managing difficult pregnancies. Some prenatal tests, such as chorionic villus sampling and level II ultrasound, are performed primarily by perinatologists.

Trisomy—The condition of having three identical chromosomes, instead of the normal two, in a cell.

neither procedure is diagnostic. Women who wish to first modify their risk for a fetal chromosomal disorder (and spina bifida) may choose screening. In any case, prenatal testing, whether screening or diagnostic, is never mandatory. Careful consideration must always be given to what action might be taken after an abnormal result and how reassuring a normal result might be.

Postnatal

A newborn with typical signs of Edwards syndrome can sometimes be diagnosed from a physical examination alone, especially by a physician who is familiar with the condition such as a geneticist or neonatologist. However, chromosome testing is the only method to confirm the

diagnosis and should always be performed if Edwards syndrome is suspected. Chromosome analysis helps to determine whether the underlying cause is full, mosaic, or partial trisomy 18 and may exclude other syndromes with similar signs and symptoms. Fetuses and newborns with Edwards syndrome sometimes die before chromosome analysis can be performed. In those cases, the diagnosis unfortunately cannot be confirmed, and an accurate cause and recurrence risk cannot be given.

Chromosome testing will detect full trisomy 18 with near-100% accuracy. Likewise, a translocation of chromosome 18 that produces signs of Edwards syndrome should be detected in virtually every case. Mosaic trisomy 18 presents more of a problem for chromosome analysis. The likelihood of confirming mosaic trisomy 18 depends on the percentage of trisomic cells in the particular tissue examined. Mosaicism, if present, can be confirmed by chromosome testing, and usually is. However, normal chromosome tests do not rule out the possibility of trisomic cells elsewhere in the body.

Treatment and management

Medical management of an infant with Edwards syndrome depends on the number and severity of anomalies present. In order to make the best-informed and most appropriate decisions for their child, parents must establish a close working relationship with the treating physicians.

Regardless of the medical procedures that might be performed, most babies with Edwards syndrome will not survive. Nearly all will be transferred to the neonatal intensive care unit (NICU) after birth. In some cases, parents elect not to have any life-prolonging heroic measures taken should their child experience cardiac or respiratory failure. They may also elect not to have certain types of surgery performed if other complicating medical problems make it unwise.

A more medically stable, less severely affected infant with Edwards syndrome will likely require various medical procedures and treatments. Surgical repair of certain physical anomalies, ventilator (breathing) support, medications, and/or placement of a feeding tube into the stomach are common. A baby may go home and remain there after some length of hospital stay, or may need to be readmitted one or more times. For those children that show some possibility of longer-term survival (more than six months), a plan for their medical care, both in the hospital and at home, must be established. Parents should also be informed of the various educational and support services available to them, including the Support Organization For Trisomy 18, 13, and Related Disorders (S.O.F.T.). Genetic counseling, to discuss the cause, prognosis, and

recurrence risks for their child's type of trisomy 18, can be of great help to parents.

There is no way to prevent the occurrence of trisomy 18. The technology now exists to test multiple embryos conceived by in vitro fertilization for certain chromosome anomalies, but this is very expensive and is only performed at several centers in the world.

Prognosis

The prognosis for a baby born with trisomy 18 is poor. On average, about 40% of newborns with trisomy 18 survive the first week, 20% are alive at one month, 6% at six months, and about 5% live past their first birthday. Survival rates are somewhat higher for children with mosaic or partial trisomy 18. As is the case before birth, males with trisomy 18 have a higher mortality rate than females, with about one-third as many males as females surviving infancy.

The outlook for trisomy 18 is not likely to change much in the coming years. Surgery to repair various birth defects has improved dramatically over the years. However, most babies with trisomy 18 do not die from repairable anomalies. For those parents whose babies are expected to survive some length of time, connecting them with support groups and providing them with accurate information as soon as possible is important.

Resources

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"What Is Trisomy 18?" WebMD. July 19, 2019. <https://www.webmd.com/baby/what-is-trisomy-18#1> (accessed June 7, 2021).

ORGANIZATIONS

- Chromosome 18 Registry & Research Society, 7155 Oakridge Dr., San Antonio, TX 78229, (210) 657-4968, office@chromosome18.org, <http://www.chromosome18.org>
- National Society of Genetic Counselors, 330 N. Wabash Ave., Suite 2000, Chicago, IL 60611, (312) 321-6834, nsgc@nsgc.org, <http://www.nsgc.org>
- Support Organization for Trisomy 18, 13, and Related Disorders (SOFT), 2982 S. Union St., Rochester, NY 14624, (800) 716-7638, <http://trisomy.org>

Scott J. Polzin, MS

Ehlers-Danlos syndrome

Definition

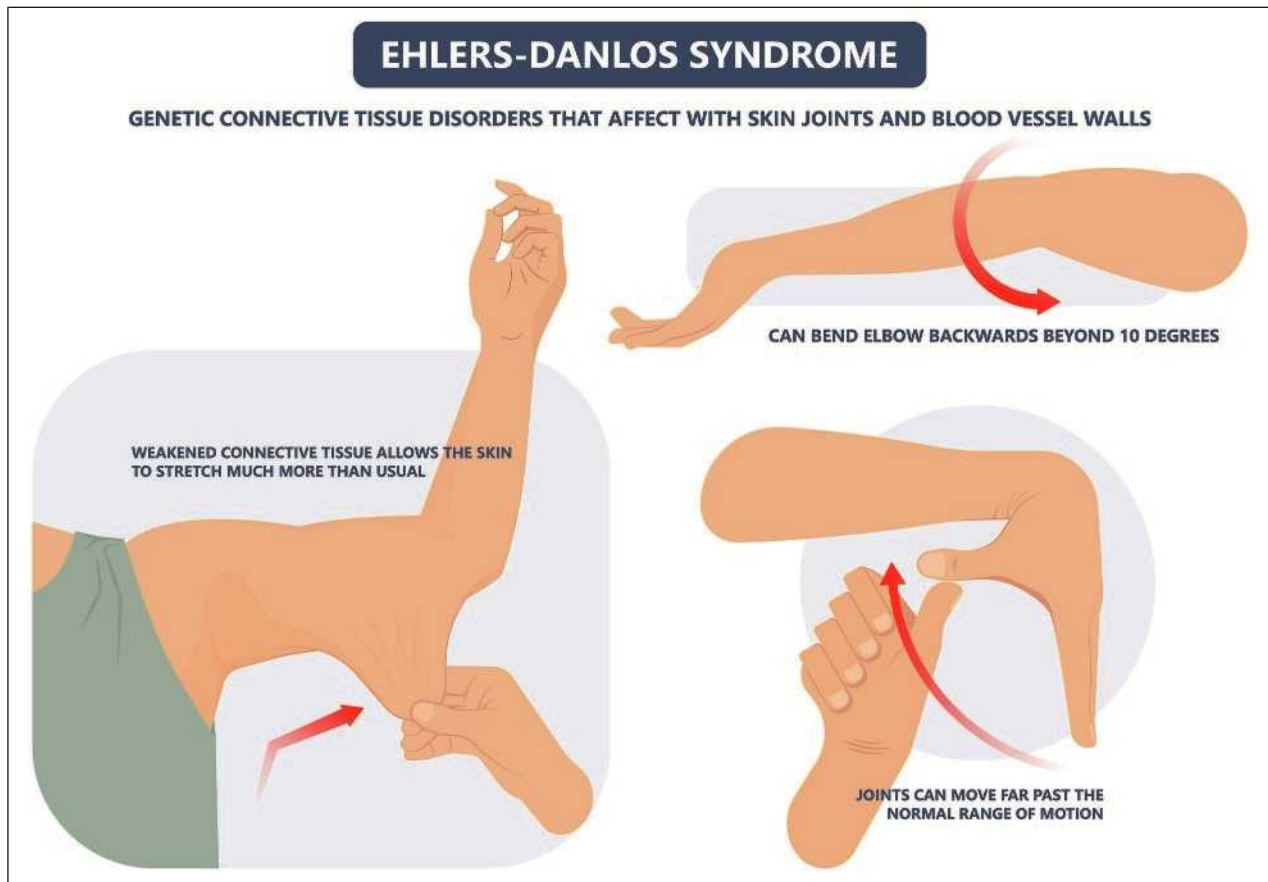
The Ehlers-Danlos syndromes (EDS) are a group of inherited disorders that affect collagen structure and function. Genetic abnormalities in the manufacturing of collagen within the body cause connective tissues to be abnormally weak.

Description

EDS was originally described by the Dutch physician Van Meekeren in 1682. Dr. Edvard Ehlers and Dr. Henri-Alexandre Danlos further characterized the disease in 1901 and 1908 respectively. EDS affects connective tissues of the body, such as skin, joints, and blood vessel walls. It is characterized by sagging skin, overly flexible joints, and weak tissue. These skin and joint abnormalities are caused by genetic mutations that lead to the production of a weakened form of a protein called collagen.

Collagen is a strong, fibrous protein that lends strength and elasticity to connective tissues such as the skin, tendons, organ walls, cartilage, and blood vessels. Each of these connective tissues requires collagen tailored to meet its specific purpose. The many variations in collagen are reflected in the number of genes dedicated to its production. There are at least 28 individual genes in humans that encode for more than 19 different types of collagen. Mutations in these genes can affect basic construction as well as the fine-tuned processing of the collagen.

There are 13 types or classifications of EDS. These classifications are based on the genetic transmission of each type. The characteristics of each type are described in detail at <https://rarediseases.org/rare-diseases/ehlers>



Ehlers-Danlos syndrome symptoms. (Shutterstock/rumruay)

-danlos-syndrome. The types of Ehlers-Danlos syndrome are as follows:

- **Classical type:** Characterized by significantly lax joints, loose skin that bruises and tears easily, joint dislocations, and scoliosis (curvature of the spine).
- **Classical-like type:** Symptoms are similar to classical type, but the mutations and inheritance pattern differs from classical type.
- **Cardiac-valvular type:** A rare type with few classical symptoms but major damage to the aorta (the large blood vessel exiting the heart) that requires surgical correction.
- **Vascular type:** Characterized by loose skin, veins that are more visible than usual, ruptured arteries and bowels, club foot and hip deformities. This type may be fatal.
- **Hypermobility type:** Characterized by joint hypermobility and frequent joint dislocations. Degenerative joint diseases are common.
- **Arthrochalasia type:** Characterized by short stature, severely loose joints, joint dislocations, and in some cases, affected skin.
- **Dermatosparaxis type:** Characterized by extremely fragile skin that is very soft with excessive sagging and folding.

- **Kyphoscoliosis type:** Characterized by fragile globe of the eyes, significant skin and joint laxity, and severe scoliosis.
- **Brittle cornea syndrome:** A variant that affects the cornea of the eye.
- **Spondylodysplastic type:** A variant that affects primarily the spine and hands and can result in short stature and stunted growth.
- **Musculocontractural type:** Characterized by muscle weakness, developmental delays, and progressive multi-symptom complications.
- **Myopathic type:** Characterized by muscle weakness and muscles that do not function properly. Hearing loss and scoliosis may also be present. This variant shares many characteristics with the kyphoscoliosis type.
- **Periodontal type:** Affects the tissues around the teeth and gums and can result in premature tooth loss.

Genetic profile

There are numerous types of EDS, all caused by changes in one of several genes. Identified mutations occur in the *ADAMTS2*, *CHST14*, *COL1A1*, *COL1A2*,



A patient whose skin is very elastic due to the breakdown in collagen levels, a side effect of Ehlers-Danlos syndrome.
(Biophoto Associates/Science Source)

COL3A1, *COL5A1*, *COL5A2*, *COL3A1*, *NF469*, *PLOD1*, *SLC39A13*, and *ZNF469* genes, which are all involved in the collagen-production pathway. Mutations that cause the different forms of EDS disrupt the structure, production, or processing of collagen, which results in the weakening of connective tissues. Although a great deal of information is known regarding the changes in genes that cause EDS and their various inheritance patterns, gene mutations for all types of EDS have not been completely identified.

The manner in which EDS is inherited depends on the specific gene involved. There are two patterns of inheritance for EDS: autosomal dominant and autosomal recessive. Chromosomes are made up of hundreds of small units (genes), which contain the genetic material necessary for an individual to develop and function. Humans have 46 chromosomes, which are matched into 23 pairs. Because chromosomes are inherited in pairs, each individual receives two copies of each chromosome and likewise two copies of each gene, except for the gene that determines biological sex, in which the two genes can be the same (XX) or different (XY).

Changes or mutations in genes can cause genetic diseases in several different ways, many of which are represented within the spectrum of EDS. In autosomal dominant EDS, only one copy of a specific gene must be changed for a person to have EDS, and there is a 50% chance that any child of this person will have the disorder. Classical, vascular, hypermobility, arthrochalasia, myopathic, and periodontal types are inherited in the autosomal dominant pattern.

In an autosomal recessive inheritance pattern, both copies of a specific gene must be changed for a person to have EDS. If only one copy of an autosomal recessive EDS gene is changed, the person is referred to as a

carrier, meaning that he or she does not have any of the signs or symptoms of the disease itself but carries the possibility of passing on the changed gene to a future child. In the autosomal recessive pattern, a child of a carrier has a 25% chance of having the disorder and a 50% chance of being a carrier. Classical-like, cardiac valvular, dermatosparaxis, kyphoscoliotic, brittle cornea syndrome, spondylodysplastic, and musculocontractural types are inherited in an autosomal recessive pattern.

Demographics

According to the Ehlers-Danlos National Foundation, one in 3,500–5,000 people is affected by some form of EDS.

Signs and symptoms

Classical type

The major symptoms involved in EDS classical type affect the skin and joints. The skin has a smooth, velvety texture and bruises easily. Affected individuals typically have extensive scarring, particularly at the knees, elbows, forehead, and chin. The joints are hyperextensible, so there is a tendency toward dislocation of the hip, shoulder, elbow, knee, or clavicle. Due to decreased muscle tone, affected infants may experience a delay in reaching motor milestones. Children may have a tendency to develop hernias or other organ shifts within the abdomen. Sprains and partial or complete joint dislocations are also common. Symptoms can range from mild to severe. EDS classical type is inherited in an autosomal dominant manner.

There are three major clinical diagnostic criteria for EDS classical type: skin hyperextensibility, unusually wide scars, and joint hypermobility. At this time, there is no definitive test for the diagnosis of classical EDS. Both DNA and biochemical studies have been used to help identify affected individuals. In some cases, a skin biopsy has been found to be useful in confirming a diagnosis. Unfortunately, these tests are not sensitive enough to identify all individuals with classical EDS. If there are multiple affected individuals in a family, it may be possible to perform prenatal diagnosis using a DNA information technique known as a linkage study.

Hypermobility type

Excessively loose joints are the hallmark of this EDS type, formerly known as EDS type III. Both large joints, such as the elbows and knees, and small joints, such as toes and fingers, are affected. Partial and total joint dislocations are common and particularly involve the jaw, knee, and shoulder. Many individuals experience chronic limb and joint pain, although x-rays of these joints appear

normal. The skin may also bruise easily. Osteoarthritis is a common occurrence in adults. EDS hypermobility type is inherited in an autosomal dominant manner.

There are two major clinical diagnostic criteria for EDS hypermobility type: skin involvement (either hyperextensible skin or smooth and velvety skin) and generalized joint hypermobility. At this time, there is no test for this form of EDS.

Vascular type

Formerly called EDS type IV, EDS vascular type is the most severe form. The connective tissue in the intestines, arteries, uterus, and other hollow organs may be unusually weak, leading to organ or blood vessel rupture. Such ruptures are most likely to occur between ages 20 and 40, although they can occur any time and may be life-threatening.

There is a classic facial appearance associated with EDS vascular type. Affected individuals tend to have large eyes; a thin, pinched nose; thin lips; and a slim body. The skin is thin and translucent with veins dramatically visible, particularly across the chest.

The large joints have normal stability, but small joints in the hands and feet are loose and hyperextensible. The skin bruises easily. Other complications may include collapsed lungs, premature aging of the skin on the hands and feet, and ruptured arteries and veins. After surgery, there may be poor wound healing, a complication that tends to be frequent and severe. Pregnancy also carries the risk of complications. During and after pregnancy, there is an increased risk of the uterus rupturing and of arterial bleeding. Due to the severe complications associated with vascular type EDS, death usually occurs before age 50. A study of 419 individuals with EDS vascular type completed in 2000 found that the median survival rate was 48 years, with a range of 6–73 years.

There are four major clinical diagnostic criteria for EDS vascular type: thin translucent skin, arterial/intestinal/uterine fragility or rupture, extensive bruising, and characteristic facial appearance. EDS vascular type is caused by a change in the gene *COL3A1*, which codes for one of the collagen chains used to build collagen type III. Laboratory testing is available for this form of EDS. A skin biopsy may be used to demonstrate the structurally abnormal collagen. This type of biochemical test identifies more than 95% of individuals with EDS vascular type. Laboratory testing is recommended for individuals with two or more of the major criteria.

DNA analysis may also be used to identify the change within the *COL3A1* gene. This information may

be helpful for genetic counseling purposes. Prenatal testing is available for pregnancies in which an affected parent has been identified, and the DNA mutation is known or their biochemical abnormality has been demonstrated.

Kyphoscoliosis type

The major symptom of kyphoscoliosis type, formerly called EDS type VI, is general joint looseness. At birth, muscle tone is poor, and motor skill development is subsequently delayed. Infants with this type of EDS have an abnormal curvature of the spine (scoliosis), which becomes progressively worse with age, with affected individuals usually unable to walk by age 20. The eyes and skin are fragile and easily damaged, and blood vessel involvement is a possibility. The bones may also be affected as demonstrated by a decrease in bone mass. Kyphoscoliosis type is inherited in an autosomal recessive manner.

There are four major clinical diagnostic criteria for EDS kyphoscoliosis type: generally loose joints, low muscle tone at birth, scoliosis at birth (which worsens with age), and fragility of the eyes, which may give the white area of the eye a blue tint or cause the eye to rupture. This form of EDS is caused by a change in the *PLOD* gene on chromosome 1, which encodes the enzyme lysyl hydroxylase. A laboratory test is available in which urinary hydroxylysyl pyridinoline is measured. This urine test is extremely sensitive and specific for EDS kyphoscoliosis type. Laboratory testing is recommended for infants with three or more of the major diagnostic criteria.

Prenatal testing is available if a pregnancy is known to be at risk, and an identified affected family member has had positive laboratory testing. An amniocentesis may be performed, in which fetal cells are removed from the amniotic fluid, and enzyme activity is measured.

Arthrochalasia type

Dislocation of the hip joint typically accompanies arthrochalasia type EDS, formerly called EDS type VIIB. Other joints are also unusually loose, leading to recurrent partial and total dislocations. The skin has a high degree of stretchability and bruises easily. Individuals with this type of EDS may also experience mildly diminished bone mass, scoliosis, and poor muscle tone. Arthrochalasia type is inherited in an autosomal dominant manner.

There are two major clinical diagnostic criteria for EDS arthrochalasia type: severe generalized joint hypermobility and bilateral hip dislocation present at birth. This form of EDS is caused by a change in either of two components of collagen type I, called pro α 1(I) type A and

KEY TERMS

Arthrochalasia—Excessive looseness of the joints.

Blood vessels—General term for arteries, veins, and capillaries that transport blood throughout the body.

Cartilage—A tough, elastic tissue that is a building block for bone.

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Connective tissue—A group of tissues responsible for support throughout the body; includes cartilage, bone, fat, tissue underlying skin, and tissues that support organs, blood vessels, and nerves throughout the body.

Dermatosparaxis—Skin fragility caused by abnormal collagen.

Hernia—A rupture in the wall of a body cavity, through which an organ may protrude.

Homeopathy—A holistic and natural approach to health care.

Hyperextensibility—The ability to extend a joint beyond the normal range.

Hypermobility—Unusual flexibility of the joints, allowing them to be bent or moved beyond their normal range of motion.

Joint dislocation—The displacement of a bone from its socket or normal position.

Kyphoscoliosis—Abnormal front-to-back and side-to-side curvature of the spine.

Ligament—A type of connective tissue that connects bones or cartilage and provides support and strength to joints.

Osteoarthritis—A group of diseases and mechanical abnormalities involving degradation of joints.

Scoliosis—Abnormal curvature of the spine, usually defined as greater than 10 degrees to the right or left as the doctor faces the patient.

Tendon—A strong connective tissue that connects muscle to bone.

Uterus—A muscular, hollow organ of the female reproductive tract. The uterus contains and nourishes the embryo and fetus from the time the fertilized egg is implanted until birth.

Vascular—Pertaining to blood vessels.

proa2(I) type B. A skin biopsy may be performed to demonstrate an abnormality in either component. Direct DNA testing is also available.

Dermatosparaxis type

Individuals with this type of EDS, once called type VIIC, have extremely fragile skin that bruises easily but does not scar excessively. The skin is soft and may sag, leading to an aged appearance even in young adults. Individuals may also experience hernias. Dermatosparaxis type is inherited in an autosomal recessive manner.

There are two major clinical diagnostic criteria for EDS dermatosparaxis type. These include severe skin fragility and sagging or aged-appearing skin. This form of EDS is caused by a change in the enzyme called procollagen I N-terminal peptidase. A skin biopsy may be performed for a definitive diagnosis of dermatosparaxis type.

Other types

Other types of EDS are less common and have not been as clearly defined as the aforementioned types. Forms of EDS within this category may present with soft, mildly stretchable skin, shortened bones, chronic diarrhea, joint hypermobility and dislocation, bladder rupture, or poor wound healing. Inheritance patterns within this group include X-linked recessive, autosomal dominant, and autosomal recessive.

Diagnosis

Clinical symptoms such as extreme joint looseness and unusual skin qualities, along with family history, can lead to a diagnosis of EDS. Specific tests, such as skin biopsies, are available for diagnosis of certain types of EDS, including vascular, arthrochalasia, and dermatosparaxis types. A skin biopsy involves removing a small sample of skin and examining its microscopic structure. A urine test is available for the kyphoscoliosis type.

Management of all types of EDS may include genetic counseling to help affected individuals and their families understand the disorder and its impact on other family members and future children.

If a couple has had a child diagnosed with EDS, the chance that they will have another child with the same disorder depends on what form of EDS the child has been diagnosed with and whether either parent is affected by the same disease.

Individuals diagnosed with an autosomal dominant form of EDS have a 50% chance of passing the same disorder on to a child in each pregnancy. Individuals diagnosed with an autosomal recessive form of EDS have a 25% chance of having a child with the disorder.

Prenatal diagnosis is available for specific forms of EDS, including kyphoscoliosis type and vascular type. However, prenatal testing is only a possibility in these types if the underlying defect has been found in another family member.

QUESTIONS TO ASK YOUR DOCTOR

- What is collagen and what functions does it have in the body?
- What is the pattern of inheritance of the various types of Ehlers-Danlos syndrome?
- What medications and other procedures are available for the treatment of my son's Ehlers-Danlos syndrome?
- What kind of future can my son expect to have as a result of inheriting this disorder?

Treatment and management

Medical therapy relies on managing symptoms and trying to prevent further complications. There is no cure for EDS.

Braces may be prescribed to stabilize joints, although surgery is sometimes necessary to repair joint damage caused by repeated dislocations. Physical therapy teaches individuals how to strengthen muscles around joints and may help to prevent or limit damage. Elective surgery is discouraged due to the high possibility of complications.

Alternative treatment

There are anecdotal reports that large daily doses (1–4 g) of vitamin C may help decrease bruising and aid in wound healing. Constitutional homeopathic treatment may be helpful in maintaining optimal health in persons with a diagnosis of EDS. Individuals with EDS should discuss these types of therapies with their doctor before beginning them on their own. Therapy that does not require medical consultation involves protecting the skin with sunscreen and avoiding activities that place stress on the joints.

Prognosis

The outlook for individuals with EDS depends on the type of EDS they have. Symptoms vary in severity, even within one subtype, and the frequency of complications changes on an individual basis. Some individuals have negligible symptoms, while others are severely restricted in their daily life. Extreme joint instability and scoliosis may limit a person's mobility. Most individuals will have a normal lifespan. However, those with blood vessel involvement, particularly those with EDS vascular type, have an increased risk of fatal complications.

EDS is a lifelong condition. Affected individuals may face social obstacles related to their disease on a daily basis. Some people with EDS have reported living with fears of significant and painful skin ruptures, of becoming pregnant (especially those with EDS vascular type), of their condition worsening, of becoming unemployed due to physical and emotional burdens, and of social stigmatization in general.

Clinical trials for EDS, including experimental drug treatments and procedures, are underway. Participation in a U.S. clinical trial is voluntary and at no cost to the participant. All clinical trials receiving U.S. government funding, and some supported by private industry, are posted at <https://www.clinicaltrials.gov>. Foreign trials are listed at <https://www.orpha.net>

Constant bruises, skin wounds, and trips to the hospital take their toll on both affected children and their parents. Prior to diagnosis, parents of children with EDS have found themselves under suspicion of child abuse.

Some people with EDS are not diagnosed until well into adulthood and, in the case of EDS vascular type, occasionally not until after death due to complications of the disorder. Not only may the diagnosis itself be devastating to the family, but in many cases other family members find out for the first time that they are at risk for being affected.

Although individuals with EDS face significant challenges, it is important to remember that each person is unique with his or her own distinguished qualities and potential. Persons with EDS can go on to have families and careers and become accomplished citizens, surmounting the challenges of their disease.

Resources

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- “Ehlers-Danlos Syndrome.” MedlinePlus March 12, 2021. <https://medlineplus.gov/ehlersdanlossyndrome.html> (accessed May 10, 2021).

ORGANIZATIONS

Center for Ehlers-Danlos Syndrome Alliance, 4805 Hospital Drive, Cass City, MI 48726, (989) 872-3372, (989) 912-2203, <https://www.cedsa.org>

Ehlers-Danlos Society, 1732 1st Avenue #20373, New York, NY 10128, (410) 670-7577, <https://www.ehlers-danlos.com>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <https://rarediseases.org>

Java O. Solis, MS
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Revised by Tish Davidson, AM

Elattoproteus syndrome see **Proteus syndrome**

Ellis-van Creveld syndrome

Definition

Ellis-van Creveld syndrome is an individually recognized genetic condition characterized by short stature and malformations of the heart, limbs, nails, and teeth. The name given to this condition originates from Richard W. B. Ellis of Scotland and Simon van Creveld of the Netherlands. Each had a patient with this syndrome in his care when the two met by chance in an English train car on the way to a pediatric conference in the late 1930s.

Description

Ellis-van Creveld (EvC) syndrome primarily affects the skeletal system but is also associated with congenital heart defects. EvC syndrome is one of the six short rib polydactyly syndromes, or SRPS. There is considerable overlap between the features of these six syndromes. Clinical, radiological, and pathological studies are being conducted to determine if there are indeed six distinct SRPS, or if each is a different mutation at the gene that also causes Ellis-van Creveld syndrome.

Ellis-van Creveld syndrome is alternatively known as chondroectodermal dysplasia or mesoectodermal dysplasia. The name “chondroectodermal dysplasia” is meant to indicate a dysplasia, or abnormal growth or development, of the skeleton (chondro-) and the skin (ectodermal). The name “mesoectodermal dysplasia” is meant to indicate an abnormal growth or development of the skin (ectodermal) and primarily the middle portion of the bone (meso-). However, neither term defines the syndrome completely, and Ellis-van Creveld syndrome remains the most used name for both medical and common purposes.

Ellis-van Creveld syndrome is characterized by short arms and legs; short ribs; short fingers; polydactyly, or extra fingers or toes; and dysplastic, or abnormal, teeth and nails. Limb shortening is more noticeable in the legs than in the arms. Many older children affected by EvC syndrome develop knock knee, or genu valgum, which may have to be corrected by orthopedic surgery. The underdeveloped ribs generally cause a condition known as pectus carinatum, in which the chest is narrow and elongated. A sixth finger on both hands occurs in all patients with EvC syndrome, while extra toes are observed in approximately 20% of the EvC syndrome population. Polydactyly in affected individuals is always symmetric. That is, if the left hand possesses a sixth finger, the right hand will also possess a sixth finger.

Dysplastic, or abnormal, teeth and nails are observed in all individuals with EvC syndrome. The most common dental anomalies are teeth present at birth; wide spaces between permanent teeth; the late eruption of or the complete lack of some permanent teeth; and permanent teeth that more closely resemble baby teeth than permanent teeth. The most common nail abnormalities are absent or malformed fingernails or toenails. Thin, brittle hair is also observed in a majority of patients with EvC syndrome.

Congenital heart defects occur in approximately 50%–60% of affected individuals. The most common cardiac abnormality observed is a common atrium rather than the normal two-chambered atrium. This “hole in the heart” can often be surgically repaired, resulting in normal heart function.

Genetic profile

Ellis-van Creveld syndrome is an autosomal, or non-sex-linked, recessive condition. The gene responsible for EvC syndrome has been identified and its locus determined on the distal short arm of chromosome 4p. In 2000, it was shown that the *EvC* gene is the same gene that causes Weyers acrofacial dysostosis.

Certain mutations in the *EvC* gene cause EvC syndrome. In order for EvC syndrome to appear, the affected

KEY TERMS

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Dysplasia—The abnormal growth or development of a tissue or organ.

Heterozygous—Having two different versions of the same gene.

Homozygous—Having two identical copies of a gene.

Postaxial polydactyly—A condition in which an extra finger or toe is present outside the normal fifth digit.

Primary atrial septation—An improper division of the atria of the heart, or a “hole in the heart,” which results in the formation of a common atrium rather than the normal two-chambered atrium.

Short rib polydactyly syndromes—A collection of genetic disorders characterized by abnormally short ribs and extra fingers or toes. Research is ongoing to determine whether these disorders are the result of mutations in a common gene.

Weyers acrofacial dysostosis—A condition resulting from a mutation of the same gene that shows mutation in Ellis-van Creveld syndrome. As is usually the case when comparing expressions of the same gene mutation, the single-dose Weyers acrofacial dysostosis presents milder symptoms than the double-dose Ellis-van Creveld syndrome.

child must inherit a mutation of this gene from each parent. The child must receive two abnormal genes.

When the child receives only a single copy of an abnormal gene that would cause EvC syndrome, that child is affected with Weyers acrofacial dysostosis. Weyers acrofacial dysostosis is an autosomal dominant condition characterized by tooth and nail abnormalities, extra fingers and toes, and milder limb anomalies than those observed in Ellis-van Creveld syndrome. As is often the case in homozygous disorders, EvC syndrome presents much more pronounced physically observable and potentially life-threatening signs than the corresponding heterozygous condition, Weyers acrofacial dysostosis.

Demographics

Ellis-van Creveld syndrome has an incidence of approximately 1 in 60,000 to 200,000 live births. Ellis-

van Creveld syndrome has a much higher occurrence among the Old Order Amish, an isolated and inbred religious community in Lancaster County, Pennsylvania.

As a homozygous condition, both parents of an affected child must carry the abnormal *EvC* gene. The parents of a child with EvC syndrome have a one in four chance of having additional children affected with EvC syndrome. The transmission of such homozygous genetic disorders is facilitated by the close association among potentially related individuals in a relatively small and isolated population such as that of the Amish. Also, a relatively high frequency of EvC syndrome has been observed in the Aboriginal people of Western Australia. This high frequency has been attributed to a founder effect from Dutch castaways and genetic drift caused by the isolation and interbreeding of these peoples.

Signs and symptoms

Ellis-van Creveld syndrome is characterized by short limbs and short body length identifiable at birth. The average adult height range for those affected by EvC syndrome is 43–60 in. (109–152 cm). The head and neck are generally unaffected other than possible abnormalities of the upper lip, and dental anomalies including delayed eruption of the permanent teeth, which are generally underdeveloped and more similar to a child's teeth than to those of an adult. EvC syndrome is further characterized by congenital heart defects, usually a single upper chamber (atrium) rather than the normal two upper chambers. Affected individuals have short, poorly developed ribs, which leads to a narrow chest; this is termed “pectus carinatum.”

Males affected by EvC syndrome may present abnormalities of the penis in which the urethral opening occurs on the underside of the penis rather than at the tip of the glans (hypospadias); they may also have one or both testicles undescended (cryptorchidism). Further skeletal anomalies associated with EvC syndrome include low hips; a spur-like projection at the acetabula, the socket in the hipbone that accepts the head of the thighbone; a fusion of the capitate and hamate bones; two carpal bones, the fusion of which makes the formation of a fist difficult or impossible; knock-knee; clubfeet that turn down and in; and postaxial polydactyly, or extra fingers/toes that arise outside the normal fifth digit. Fingernails and toenails are generally malformed. Neurologically, mental retardation has been observed in patients with EvC syndrome, but it is not the norm. A brain abnormality of one of the normal cavities of the brain (Dandy-Walker syndrome) is also occasionally associated with EvC syndrome.

QUESTIONS TO ASK YOUR DOCTOR

- What does the term “chondroectodermal dysplasia” mean?
- What kinds of treatments are available for dealing with the physical problems associated with my child’s medical disorder?
- What is my child’s prognosis, and what factors might affect that prognosis with age?
- Can you suggest support groups or other organizations for parents of children with Ellis-van Creveld syndrome?

Diagnosis

Ultrasound imaging of developing fetuses can reveal the limb shortening and underdeveloped ribs that are characteristic of the short rib polydactyly syndromes (SRPS), which includes Ellis-van Creveld syndrome. An ultrasound scan is now available after the 16th week of gestation that may identify extra digits in the developing fetus.

Ellis-van Creveld syndrome is generally differentially diagnosed from the other SRPS by the additional presence of atrial abnormalities. However, it is often difficult to distinguish EvC syndrome from two other forms of skeletal dysplasia. These are asphyxiating thoracic dysplasia (ATD), also known as Jeune syndrome; and short rib polydactyly syndrome (SRPS) type III, or Verma-Naumoff type SRPS. Individuals with Jeune syndrome often die of respiratory distress shortly after birth, whereas individuals diagnosed with EvC syndrome are more likely to die from congenital heart failure. Individuals with Jeune syndrome often have extra fingers or toes; but, unlike those with EvC syndrome, this polydactyly is often not symmetric. Individuals with Jeune syndrome do not show the nail and hair abnormalities observed in EvC syndrome. Older children can often be differentially diagnosed with Jeune syndrome rather than EvC syndrome if they develop kidney problems, which may also later lead to kidney failure as adults. Kidney dysfunction is not associated with EvC syndrome.

Verma-Naumoff type SRPS is virtually indistinguishable from EvC syndrome prior to birth. However, individuals with Verma-Naumoff type SRPS also exhibit heart, kidney, and intestinal malformations that are not present in the Ellis-van Creveld population. Verma-Naumoff type SRPS has an essentially 100% mortality rate within hours of birth, as those affected die

from respiratory distress. All three of these conditions arise from autosomal recessive inheritance. The genetic evidence is beginning to further the hypothesis that these three conditions are the result of mutations of the same gene on chromosome 4p that has been identified as the cause of EvC syndrome.

Treatment and management

Genetic counseling of individuals affected with either EvC syndrome or the allelic disorder, Weyers acrofacial dysostosis, may prevent the conception of EvC syndrome-affected children. Congenital heart defects associated with EvC syndrome may be surgically corrected. The potential outcome of such a procedure is normal heart function. Extra fingers or toes (polydactyly) can be surgically removed shortly after birth. This is more a cosmetic treatment than a necessary one in the case of fully developed extra digits. If a person affected with EvC syndrome develops genu valgum (knock knee), he or she may require orthopedic surgery to straighten the legs at the knee. Dental treatment also has an important role in management of EvC syndrome.

Many people of extremely short stature adapt their surroundings to their size. Others choose to undergo one of the bone lengthening procedures that have increasingly become available. These bone lengthening procedures are generally performed only on the limbs. They often do not offer complete relief to the EvC syndrome patient who may also have a smaller than normal thoracic cavity caused by undersized ribs.

Prognosis

Ellis-van Creveld syndrome is generally nonlethal, with approximately two-thirds of those affected surviving to adulthood. Mortality is higher when the congenital heart defects associated with EvC syndrome are also present. Approximately half of those affected with EvC syndrome with heart abnormalities die in childhood due to cardiorespiratory problems associated with these congenital heart defects or associated with pressure on the chest, primarily the lungs, caused by an underdeveloped rib cage. Of these, approximately one-half die within the first six months of life.

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ORGANIZATIONS

Genetic Alliance, 26400 Woodfield Road #189, Damascus MD 20872, (202) 966-5557, info@geneticalliance.org, <http://www.geneticalliance.org>

Paul A. Johnson

Emery-Dreifuss muscular dystrophy

Definition

Emery-Dreifuss muscular dystrophy (EDMD) is a rare childhood-onset degenerative muscle disease seen primarily in males. Emery-Dreifuss muscular dystrophy is characterized by a classic triad of symptoms. These include early-onset contractures, very slow progressive muscle weakness and degeneration involving the upper arms and lower legs, and cardiac (heart) muscle disease.

Description

EDMD is named for the doctors who first described it in the 1960s, Alan Emery and Fritz Dreifuss. EDMD affects the arms, legs, spine, face, neck, and heart. This disease is characterized by contractures of the elbows and the Achilles tendons at an early age, slowly progressive muscle wasting and weakness, and potentially life-threatening heart muscle disease. Intelligence is normal; however, physical problems may be severe.

Symptoms and disease severity may vary between individuals. Three modes of inheritance exist: X-linked, autosomal dominant, and autosomal recessive.

The symptoms of the autosomal dominant and X-linked forms of the disease are identical; however, the autosomal dominant form appears to have a later onset of symptoms.

Genetic profile

EDMD is caused by mutations in the *EMD* and *LMNA* genes. Both of these genes provide instructions for making proteins that are important in creating the nuclear envelope within cells. The nuclear envelope is the membrane that surrounds the nucleus in cells and is responsible for controlling what enters and exits the nucleus.

EDMD is inherited in different ways depending on which genetic mutation is responsible for the condition. Most commonly EDMD is inherited in an X-linked recessive manner and is caused by mutations in the *EMD* gene.

Less commonly, EDMD is inherited in an autosomal dominant pattern, meaning that only one copy of the mutated gene is necessary for the condition to be present. In these cases, EDMD is caused by mutations in the *LMNA* gene. Over 75% of these cases are caused by new mutations in the *LMNA* gene, and the individual has no other family members with the disease. The remaining EDMD cases caused by *LMNA* mutations involve families in which an abnormal *LMNA* is present.

EDMD is usually inherited in an X-linked recessive manner and is caused by mutations in the *EDM* gene. It is the third most common type of X-linked muscular dystrophy. Symptoms begin in the first decade of life. A tendency to walk on the toes is often one of the first signs of EDMD. Muscle weakness first affects the lower extremities usually at age four or five. X-linked diseases map to the human X chromosome, a sex chromosome. Females have two X chromosomes, whereas males have one X chromosome and one Y chromosome. Because males only have one X chromosome, they only require one X-linked disease gene to display disease. Since females have two X chromosomes, the effect of one X-linked recessive disease gene is masked by the disease gene's normal counterpart on her other X chromosome.

In classic X-linked inheritance males are affected, presenting full clinical symptoms of the disease. Females are usually not affected. Affected fathers can never pass X-linked diseases to their sons. However, affected fathers always pass X-linked disease genes to their daughters. Females who inherit the faulty gene but do not show the disease are known as carriers. Female carriers of

X-linked DMD have a 50% chance to pass the disease-causing gene to each of their children.

It is unusual for female carriers of an X-linked disease to show symptoms of the disease. However, in X-linked EDMD, carrier females can exhibit certain symptoms of the disease. Females have two X chromosomes in each of their body cells. Very early on in fetal development, one X chromosome in each cell of a female is inactivated. The pattern of inactivation is random, so carrier females may express the disease-causing gene in some of their cells. An estimated 10%–20% of female carriers of X-linked EDMD display varying symptoms of the disease. Female carriers can display the dangerous heart symptoms of EDMD. Less commonly, carrier females may show late-onset muscle weakness.

In 1994 it was recognized that the X-linked recessive form of Emery-Dreifuss muscular dystrophy is caused by changes, or mutations, in a gene now known as *EMD*. This gene is located on the long arm of the human X chromosome at a location designated as Xq28. This gene codes for emerin, an amino acid protein. Emerin is an important protein normally found on the inner nuclear membrane of skeletal, cardiac, and smooth muscle cells as well as in other tissues. Emerin is missing from the nuclear membranes of males affected with X-linked EDMD. Emerin is not altered in other neuromuscular disorders.

In some families, EDMD may be inherited in an autosomal dominant pattern and is caused by mutations in the *LMNA* gene. Autosomal dominant EDMD is known as Emery-Dreifuss muscular dystrophy 2 (EDMD2), Hauptmann-Thannhauser muscular dystrophy, and scapuloilioperoneal atrophy with cardiopathy. Autosomal dominant disorders affect both sexes equally. In autosomal dominant conditions a person, male or female, requires only one faulty gene to produce disease. There are no unaffected carriers of EDMD2. In families with EDMD2, both males and females can be affected and father-to-son inheritance of the disease can occur. Every child of a person affected with EDMD2 has a 50% chance of inheriting the disease.

In families with EDMD2, affected members exhibit a later onset of the same symptoms as someone affected with X-linked EDMD. Symptoms begin between the ages of 17 and 42. EDMD2 and X-linked EDMD are caused by changes in different genes on different chromosomes.

Muscle biopsy of patients with EDMD2 show normal emerin levels. In families with EDMD2, the disease is caused by changes, or mutations, in a gene known as *LMNA*. *LMNA* contains the coding for proteins lamin A and lamin C and is located in a specific area on the long

arm of chromosome 1 known as 1q21.2. Like emerin, these lamins are associated with the nuclear membrane. People with autosomal dominant EDMD2 have normal levels of emerin and low levels of these lamin proteins. Emerin and these lamins form an important protein complex in a cell's nuclear membrane. The exact role of this complex is unclear. Scientists theorize that this important complex of proteins stabilizes the nuclear membrane and plays a role in regeneration of muscle fibers.

EDMD of autosomal recessive inheritance has been named Emery-Dreifuss muscular dystrophy 3 (EDMD3). For someone to be affected with an autosomal recessive disease they must inherit two copies of an abnormal or mutated *LMNA* gene, one from each parent. A parent who has only one gene associated with autosomal recessive EDMD is not affected by the disease and is known as a carrier of the disease. Two carriers of autosomal recessive EDMD have a 25% chance of having a child affected with the disorder in each pregnancy. Like EDMD2, EDMD3 is caused by mutations in the *LMNA* gene located on the long arm of chromosome 1 at an area designated as 1q21.2.

Demographics

X-linked EDMD is estimated to occur in 1 in 100,000 births. EDMD2 and EDMD3 are far less common. Only males exhibit full symptoms of X-linked EDMD. EDMD2 and EDMD3 may occur in males and females. X-linked EDMD and EDMD2 have been documented in many countries. There does not appear to be a single founder of these diseases, as many families have distinctly different backgrounds and different disease-causing mutations.

Signs and symptoms

EDMD is recognized by a classic triad of symptoms: contractures at a young age, progressive muscle weakness and degeneration involving the upper arms and lower legs, and cardiac (heart) muscle disease.

Contractures

Contractures, or frozen joints, are a hallmark of all forms of EDMD. A contracture is the abnormal shortening of a body part, usually a muscle or a tendon. This shortening creates joint deformity. Contractures usually begin in childhood or adolescence before any muscle weakness is evident. In most cases, contractures are recognized before patients reach ten years of age.

Contractures may display as flexion or extension deformities. In a flexion contracture a muscle or tendon remains abnormally flexed, permanently bending a body part at a joint. In an extension contracture, a muscle or

KEY TERMS

Amniocentesis—A prenatal test in which a small amount of amniotic fluid is removed from the uterus for testing.

Arrhythmia—Abnormally fast, slow, or irregular heartbeat.

Chorionic villus sampling (CVS)—Prenatal test in which a very small sample of the placenta is taken to test for genetic conditions in the infant.

Contracture—Permanent shortening of a muscle or joint.

Creatine kinase (CK)—An enzyme found in the brain, heart, and skeletal muscles; if elevated amounts are discovered, it can indicate the presence of one of several serious medical conditions.

Pacemaker—A medical device placed in the chest that helps regulate heart rate.

Peroneal—Pertaining to the outer aspect of the leg.

Sex chromosomes—Pair of chromosomes that determine whether an individual is male or female.

Tibialis—Either of two muscles of the calf of the leg.

tendon remains abnormally extended, not allowing a body part to bend at a joint. Affected persons cannot control these contractures and cannot release them at will. Contractures are treated with stretching, physical therapy, bracing, and surgery.

People affected with EDMD often have flexion contractures of the elbows and ankles. Elbow contractures force the elbow to remain bent at an angle. Contractures of the Achilles tendons, or heel cords, force the feet to remain in a pointed toe position. Children with EDMD often walk on their toes due to heel cord contractures. Neck and trunk contractures may also occur, restricting movement of the neck or the entire spine.

Scoliosis is commonly found in patients with EDMD. Muscle weakness and degeneration are slowly progressive, affecting a distinct pattern of muscles. This pattern includes the muscles of the upper arms and the muscles of the lower legs. The biceps (inner upper arm), triceps (outer upper arm), tibialis anterior (inner lower leg), and peroneal (outer lower leg) muscles are commonly involved. Later, the muscles of the shoulder girdle and pelvic girdle, the shoulder and hip area muscles that stabilize and support the attachment of the arms and legs, may also be affected. Additionally, the highly specialized muscle of the heart is at risk for weakness and degeneration.

Heart disorders

Heart disease associated with EDMD may be life-threatening. It is, however, potentially treatable. Not all patients with EDMD develop heart involvement. Any heart involvement often becomes apparent in the second to third decade of life. In rare cases, heart problems may be the first symptom of EDMD. Early recognition of heart involvement is of utmost importance as surgical placement of a pacemaker may be lifesaving.

EDMD is associated with cardiac conduction defects (electrical impulse problems), heart muscle degeneration, and unusual tissues (abnormal fatty and fibrous tissues) growing into the heart. Conduction defects can manifest as heart rhythm disturbances known as arrhythmias or, more seriously, heart block. Heart block is a dangerous situation where the heart is unable to respond correctly to its own electrical system. Arrhythmias and heart block can lead to fainting or even sudden death. One uncommon type of heart conduction problem, total permanent auricular paralysis (TPAP), is relatively specific to EDMD. Scientists have found that 33% of 109 published cases of TPAP were due to EDMD.

The level of skeletal involvement in a patient with EDMD is not indicative of the level of heart involvement. Heart problems can be unpredictable, occasionally leading to sudden death without any prior symptom. In a review of 73 cases of X-linked EDMD, scientists found that 30 patients died suddenly between ages 25 and 39. Frequent careful checkups with a cardiologist (heart specialist) are necessary. Preventive surgical implantation of a pacemaker is often considered.

Female carriers of X-linked EDMD may display some symptoms of disease. They can have the dangerous heart problems or, less commonly, muscle weakness. One case of sudden death of a female carrier of X-linked EDMD has been reported. It is recommended that female carriers of X-linked EDMD have regular examinations by a cardiologist.

Diagnosis

Diagnosis of EDMD is based on the classic triad of distinctive clinical symptoms seen in this disease. A diagnosis based on careful neuromuscular examination may be confirmed with muscle biopsy or DNA testing.

Other special laboratory tests and neuromuscular tests may help physicians to confirm or rule out EDMD. Creatine kinase (CK), a muscle enzyme, is often measured when symptoms of muscular dystrophy are present. CK levels are only mildly elevated in EDMD. Muscle biopsy can show microscopic changes in muscle fibers. Muscle biopsy also allows for a very practical test for X-linked EDMD where muscle tissue is stained with a chemical that binds specifically to emerin. If emerin is

QUESTIONS TO ASK YOUR DOCTOR

- What are the characteristic features associated with Emery-Dreifuss muscular dystrophy?
- Can this disorder be diagnosed by prenatal tests?
- If not, how soon after birth can it be diagnosed?
- What is the basis for making a diagnosis of Emery-Dreifuss muscular dystrophy, and how can the disorder be differentiated from similar conditions?
- What is the prognosis for my child, and what steps can I take to improve that prognosis?

present, X-linked EDMD can be ruled out. If emerin is reduced or absent, X-linked EDMD is diagnosed.

Genetic testing and prenatal diagnosis for X-linked Emery-Dreifuss muscular dystrophy is available on a clinical basis. To perform DNA testing for X-linked EDMD a blood sample is required. This method of testing can diagnose female carriers of X-linked EDMD. Prenatal testing requires fetal cells obtained via amniocentesis or chorionic villus sampling. Once the specific alteration in the gene is identified in an affected family member, female relatives at risk to be carriers can be tested and prenatal diagnosis can be offered. Prenatal testing is performed on DNA extracted from fetal cells obtained by amniocentesis or chorionic villus sampling.

Treatment and management

The muscle and skeletal symptoms of EDMD are treated as they appear. People with EDMD should see a neurologist at least once a year. Stretching and working with a physical therapist is useful in preventing or delaying contractures. Occupational therapy can help patients adapt their activities and environment to their own particular needs. Ankle and foot braces are used to prevent leg deformity. Surgery may be necessary to release contractures. Exercise can help maintain muscle use and overall good health. Affected individuals may eventually require a wheelchair or other adaptive equipment.

Individuals with EDMD require frequent, at least yearly, heart checkups with a cardiologist. Heart symptoms can appear suddenly with disastrous consequences, so patients often have a pacemaker implanted before they have had any serious heart problem. Anti-arrhythmia drugs, diuretics, ACE inhibitors, and blood thinners may help with some of the cardiovascular symptoms associated with EDMD.

Heart transplant has been successful. Relatives of patients with EDMD, especially female carriers of

X-linked EDMD, should also be offered yearly screening for heart involvement via electrocardiography and echocardiography.

Scientists are currently researching gene therapy as a possible treatment for EDMD. *EMD*, the gene known to be involved in the X-linked form of EDMD, is a relatively small, less complicated gene. A small gene with a widespread product such as *EMD* shows great promise for gene therapy.

Prognosis

Without serious heart involvement, most people with EDMD are expected to survive at least into middle age. Slow progression of muscle involvement allows most patients to walk and work until middle age or late adult life. Intellect is not affected.

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ORGANIZATIONS

Muscular Dystrophy Association, National Office, 161 N. Clark, Suite 3550, Chicago, IL 60601, (800) 572-1717, <http://www.mda.org>

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Emery-Dreifuss syndrome see **Emery-Dreifuss muscular dystrophy**

Encephalocele

Definition

An encephalocele is a defect characterized by the herniation of brain tissue and membranes through an opening in the cranium. The term comes from two Greek words that mean “contents of the skull” and “hernia.” Other terms for encephalocele include *cephalocele*, *craniocoele*, and *cranium bifidum*.

Description

Encephaloceles are classified as neural tube defects (NTDs), which are a group of disorders occurring due to the failure of closure of the neural tube at about week four of fetal development.

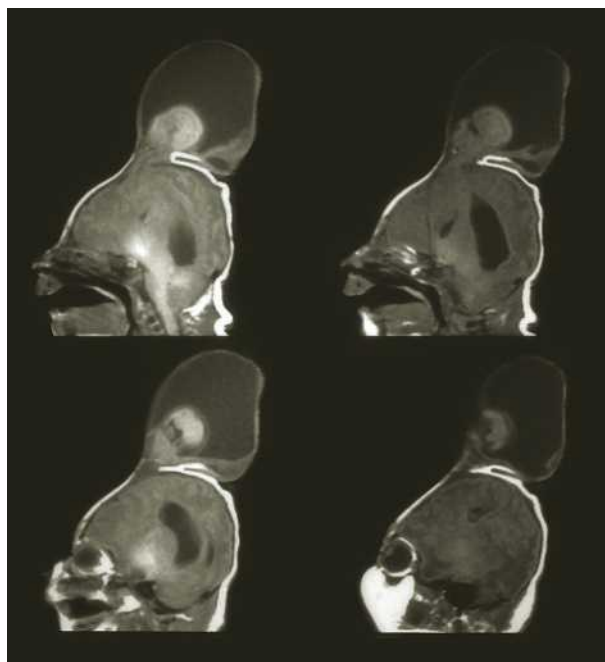
Other neural tube defects include anencephaly and spina bifida. Anencephaly results from failure of closure of the cranial end of the neural tube. This is a lethal condition. Spina bifida results from failure of neural tube closure in the spine. Spina bifida is a variable condition that is usually not lethal, but it causes problems with bladder and bowel control and ambulation (walking). It is usually associated with hydrocephalus (water on the brain), which can be treated with a shunt to drain the fluid into the body cavity. Encephalocele is the rarest neural tube defect.

Encephaloceles are classified according to their location. Occipital (arising at the back of the head where the head meets the neck) encephaloceles occur in 75% of cases, with 90% of these occurring at the midline of the skull; parietal encephaloceles in 10%; and anterior encephaloceles (arising from the base of the nose) in 15%. Anterioposterior encephaloceles have a poorer prognosis.

Genetic profile

The genetics of neural tube defects, including encephalocele, were not well understood as of 2021.

Most encephaloceles are sporadic, following a multifactorial pattern (genetic and environmental factors involved) of inheritance. It is known that there is a genetic basis to encephaloceles and other neural tube defects, and it is believed that neural tube defects may be caused by different genetic factors in different subsets of families. Other malformations and/or chromosomal abnormalities are found in at least 60% of patients with encephaloceles. Proof that genetic factors contribute to encephaloceles is that they are known to run in families, and they have been seen in association with some chromosome abnormalities. The number of genes and their locations are still not known.



A composite set of MRI images from a neonate reveals an encephalocele at the vertex of the head. (Living Art Enterprises, LLC/Science Source)

Occipital encephaloceles are associated with several single-gene syndromes, including Meckel syndrome, dyssegmental dwarfism, Knobloch syndrome, Walker-Warburg syndrome, cryptophthalmos, and von Voss-Cherstvoy syndrome. Anterior encephalocele may occur with frontonasal dysplasia. Encephalocele can also be seen in the amniotic band syndrome, a condition that occurs when part of the fetus's body (most often fingers or a limb) becomes entangled in fibrous bands inside the amniotic sac before birth. The bands cause constriction of the entrapped body parts, leading to reduced blood circulation and congenital abnormalities.

Demographics

The frequency of encephalocele has been reported to be between 1 in 2,000 and 1 in 10,000 live births. Anterior encephalocele is more common in Africa, Thailand, and India. Females outnumber males for occipital encephalocele but not for other types.

The incidence of all neural tube defects is different in different parts of the world. It is highest in northern Europe, specifically the British Isles and especially South Wales. In the United States, it is higher on the East Coast than on the West Coast, and it is highest of all in Appalachia. It is also higher among Hispanics than among either non-Hispanic Caucasians or African Americans.

KEY TERMS

Anencephaly—The absence of a major portion of the brain, upper skull, and scalp during fetal development.

Boomerang dysplasia—A lethal genetic syndrome in which fetal bones and cartilage fail to develop normally; the arm and leg bones are bent into the shape of a boomerang. Infants with this disorder die shortly after birth.

Cryptophthalmos—A congenital malformation of the eye in which the eyelid fails to develop, the eye is either missing or rudimentary, and the orbit of the eye is covered by a fold of skin extending directly from the forehead to the cheek.

Frontonasal dysplasia (FND)—A congenital malformation of the face characterized by a wide, flat nose; abnormally widely spaced eyes; and a cleft that runs down the middle of the face across the nose.

Herniation—The abnormal protrusion of an organ or other structure through a defect or natural opening in a membrane, muscle, bone, or other tissue.

Hydrocephalus—A medical condition that occurs when fluid builds up inside the skull and causes the brain to swell. It is sometimes called “water on the brain.”

Knobloch syndrome—A rare genetic disorder characterized by cataracts in the eye, degeneration and detachment of the retina, and occipital encephalocele.

Meckel syndrome—A fatal genetic disorder characterized by occipital encephalocele as well as other central nervous system defects, large polycystic kidneys, and incompletely developed lungs.

Neural tube defects (NTDs)—A group of disorders in which an opening in the brain or spinal cord persists after the fourth week of fetal development.

Spina bifida—A birth defect in which there is incomplete closure of the spine and the meninges (membranes) over the spinal cord.

von Voss-Cherstvoy syndrome—A very rare genetic disorder characterized by encephalocele, brain abnormalities, upper limb defects, and malformations of the urogenital tract.

Walker-Warburg syndrome—A congenital form of muscular dystrophy that may be accompanied by encephalocele as well as muscular weakness and other abnormalities of the eyes and brain.

The rate of sporadic neural tube defects in the general population is about 1 in 1,000. The chance of a recurrence of a neural tube defect after having an affected child is 2%. After two affected children the risk is 10%. The chance for an affected person to have an affected child is 4%. The chance for a second-degree relative to have an affected child is 0.5%. Third-degree relatives do not have an increased risk. Recurrence risks are given for neural tube defects as a group. A family with a previous child with anencephaly could have a child with spina bifida or encephalocele (the types do not “breed true” in families).

Care must be taken to be sure that the neural tube defect in the family is sporadic and not associated with a genetic syndrome, which would have a higher risk of recurrence.

Signs and symptoms

Symptoms of encephalocele may include hydrocephalus, spastic quadriplegia (paralysis of all four limbs), developmental delay, intellectual disability, growth retardation, uneven gait (ataxia), or seizures.

The size of the cerebral and skull abnormalities associated with encephaloceles is variable. Large

encephaloceles are usually associated with microcephaly (abnormally small head). Microcephaly is usually associated with intellectual disability.

Occipital encephalocele may be asymptomatic. If the ventricles (a set of four interconnected cavities in the brain) are involved, hydrocephalus may occur. Anterior encephalocele may progress in size and may be solid, cystic, or both. There may be microcephaly and/or hydrocephaly, ocular hypertelorism (wide-spaced eyes), and cleft palate. There may be problems with vision, breathing, and feeding in patients with anterior encephaloceles. Many patients have intellectual disability.

Diagnosis

Encephaloceles can be diagnosed by ultrasound examination at around 13 weeks gestation. Ultrasound examination is a screening test, the quality of which is affected by many factors including the machine used, skill of the operator, size and location of the lesion, and position of the fetus.

It is not likely that maternal serum alpha-fetoprotein testing (AFP) or amniocentesis would detect encephalocele. Alpha fetoprotein is a normal serum protein

QUESTIONS TO ASK YOUR DOCTOR

- Please describe the physical characteristics associated with my child's encephalocele.
- Are there steps that we can take before the child's birth to prepare for this disorder?
- What treatments are available to treat the condition after birth?
- What information can a genetic counselor provide my spouse and me about my child's genetic disorder?

produced by the fetal liver. The AFP normally stays within the fetus, with a small amount present in the amniotic fluid from the fetal urine. When there is an "open" neural tube defect, there is a high amount of AFP in the amniotic fluid and the maternal serum. Although encephalocele is a neural tube defect, AFP testing on maternal blood or amniotic fluid detects only open neural tube defects. Encephaloceles are closed neural tube defects, meaning they are covered by a thick covering. This covering does not allow the AFP to leak into the maternal blood or the amniotic fluid in increased amounts that would be detected by the aforementioned tests. Pregnancies in which an encephalocele is diagnosed should be offered an amniocentesis and amniotic fluid biochemistry to better understand the cause of the disorder.

CT scan can be used to determine the contents of the encephalocele once the baby is born. Some centers offer fetal MRI to attempt to classify the encephalocele prior to delivery. This is usually done at 22 weeks gestation. MRI is considered superior to CT scanning for detecting and identifying the soft-tissue contents of an encephalocele.

Treatment and management

Surgery is the mainstay of treatment for infants with encephaloceles. It is usually performed in the time period shortly after birth if the encephalocele does not have a protective layer of skin; otherwise, surgical treatment can be delayed until the fourth month of life. The primary goals of surgery are to replace the protruding tissues within the skull, remove the sac, and correct any defects of the skull and facial features. Hydrocephalus may require the placement of a shunt. Other treatment is primarily supportive.

Nutrition, specifically deficiency of folic acid, has been implicated as causing an increased risk of neural tube defects. All women of childbearing age should take 0.4 mg of folic acid per day to reduce the risk of birth

defects. Women with a previous child with a neural tube defect should take 4.0 mg of folic acid on a daily basis. This amount has been shown to reduce the recurrence risk for neural tube defects by 50%. The Centers for Disease Control and Prevention (CDC) reported in 2015, however, that the recommendation of folic acid supplements is not followed by many pregnant women and that there are still many missed opportunities for prevention of neural tube defects.

Prognosis

Size, location, and contents of the encephalocele determine the outcome for the child. Anterior encephaloceles have a much better prognosis than posterior. Mortality due to occipital encephalocele is reported at about 30% if hydrocephalus is present and 2% if it is not. For all types of encephalocele with hydrocephalus, the mortality rate is 60%. Most patients with parietal encephalocele have associated brain malformations, and intellectual disability occurs in 40%. Massive occipital encephaloceles with microcephaly have a mortality rate of nearly 100%. Patients with encephaloceles that contain a single frontal lobe are more likely to have normal intelligence without hydrocephalus. Posterior encephaloceles have a poorer prognosis if they contain large amounts of the contents of the posterior fossa (an area of the brain at the back of the head), especially the brain stem. Complications such as hemorrhage or air embolism (stroke) can occur.

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“Facts about Encephalocele.” CDC. December 28, 2020. <https://www.cdc.gov/ncbddd/birthdefects/encephalocele.html> (accessed June 7, 2021).

ORGANIZATIONS

Birth Defect Research for Children, 976 Lake Baldwin Lane, Suite 104, Orlando, FL 32814, (407) 895-0802, staff@birthdefects.org, <http://www.birthdefects.org>

March of Dimes Foundation, 1550 Crystal Drive, Suite 1300, Arlington, VA 22202, (888) 663-4637, <http://www.marchofdimes.org>

National Institute of Neurological Disorders and Stroke (NINDS), PO Box 5801, Bethesda, MD 20824, (301) 496-5751 or (800) 352-9424, <http://www.ninds.nih.gov>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

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Epidermolysis bullosa

Definition

Epidermolysis bullosa (EB) is a group of rare inherited skin diseases that are characterized by the development of blisters after minimal pressure to the skin. Blistering often appears in infancy in response to simply being held or handled. In rarer forms of the disorder, EB can be life-threatening. There is no cure for EB. Treatment focuses on preventing and treating wounds and infections.

Description

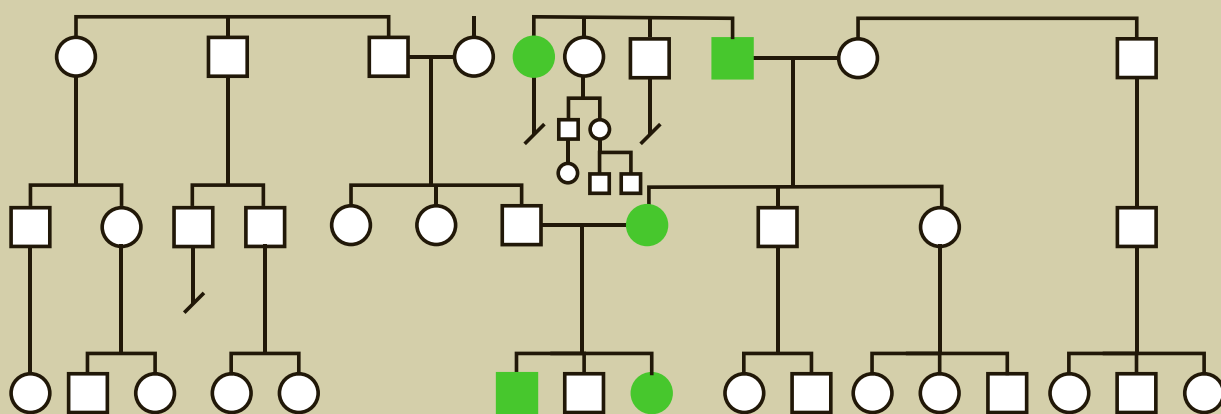
There are three major forms of EB and at least 16 subtypes. The three major forms are EB simplex, junctional EB, and dystrophic EB. EB can range in severity from mild blistering to disfiguring, disabling, or life-threatening disease. Physicians diagnose the form of the disease based on where the blister forms in relation to the epidermis (the skin's outermost layer) and the deeper dermis layer. EB can sometimes affect the mouth, teeth, eyes, nails, esophagus, lungs, and muscles, in addition to the skin.

Genetic profile

The three types of EB are caused by different genetic mutations. Most subtypes of EB simplex are caused by autosomal dominant mutations in the genes responsible for keratin 5 and keratin 14. Keratins are proteins that provide the epidermis with its structural scaffolding. Mutations that result in defective keratin and scaffolding cause the skin to fall apart and blister. Autosomal dominant inheritance means that the disorder occurs in the presence of a single mutated gene, inherited from one parent, even if the gene inherited from the other parent is normal.

Junctional EB is caused by mutations in the genes that encode the proteins collagen17 or laminin-5. These proteins help hold the skin together, and if they are absent or abnormal, the skin can easily separate and blister. Junctional EB is inherited in an autosomal recessive pattern, meaning that two mutated genes, one from each parent, are necessary for the disorder to occur.

Epidermolysis bullosa, simplex



Epidermolysis bullosa, simplex: pedigree analysis chart (Gale)



Hands of a five-year-old girl with epidermolysis bullosa, a skin disease characterized by the development of blisters following minimal pressure to the skin. Here the damage has led to the loss of the thumbnails and middle fingernails.
(Harout Tanielian/Science Source)

Dystrophic EB is caused by mutations in the *COL7A* gene that produces collagen7. These mutations can be either dominant or recessive. Collagen7 is protein in the fibers anchoring the epidermis to the dermis. Abnormal collagen causes fragile, easily separated skin that forms blisters. Dominant dystrophic EB usually causes mild-to-moderate skin blistering with only slight blistering of the mouth, esophagus, and gastrointestinal tract. Recessive dystrophic EB is the most severe and chronic form of EB and can be fatal.

Demographics

EB is often not accurately diagnosed, so its prevalence is unclear. However, it is estimated to affect

between 25,000 and 50,000 people in the United States and to occur in 20 newborns per million.

Signs and symptoms

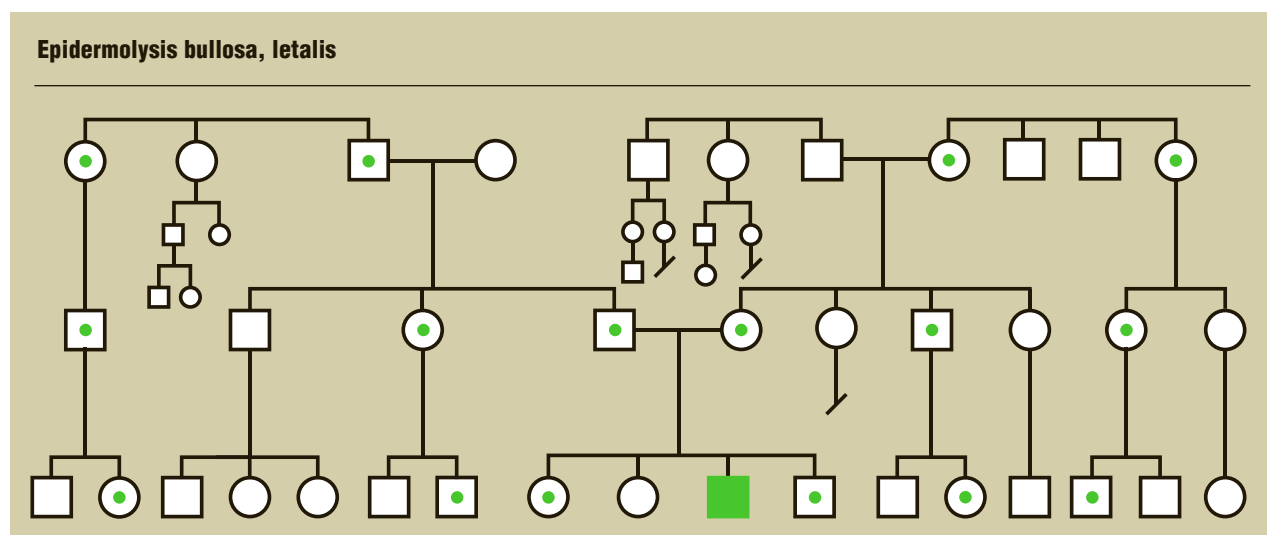
Localized EB simplex, the most common form of EB, is the least serious form of the disease. In most affected individuals, the blisters are mild and do not scar after they heal. Some forms of EB simplex affect just the hands and feet—the areas of the body subject to the most trauma. Generalized EB simplex causes widespread blistering, as well as hair loss and missing teeth.

The many forms of junctional EB all cause widespread blistering. Although this form of EB does not lead to scarring, skin often shrinks on the areas most prone to blistering, such as the elbows and knees. In one form of junctional EB, called gravis junctional EB of Herlitz, the blistering can be so severe that affected infants may not survive due to massive infection and dehydration.

Dystrophic EB varies greatly in severity, but more typically affects the arms and legs. Recessive dystrophic EB develops at or shortly after birth, and there is extensive skin and internal blistering. Recurrent scarring of the fingers and toes can cause a deformity called pseudo-syndactyly, and the hands and arms may become fixed in stiff positions (contractures). Blistering of the mouth, esophagus, and digestive tract can make eating very painful.

Diagnosis

Physicians and researchers distinguish between the three major types of EB based on which layer of the epidermis separates from the deeper dermis layer of the skin below. Patients suspected of having EB will have a fresh



Epidermolysis bullosa, letalis: pedigree analysis chart (Gale)

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance in which only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are needed to display the trait or disease.

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Dermis—The layer of skin beneath the epidermis.

Epidermis—The outermost layer of the skin.

Keratin—A tough, water-insoluble protein found in the nails, hair, and the outermost layer of skin. Human hair is made up largely of keratin.

Laminin—A protein in connective tissue that is important for cell adhesion.

Pseudosyndactyly—A joining together of the fingers or toes from scarring that can occur with severe forms of epidermolysis bullosa.

blister biopsied for examination under an electron microscope or under a conventional microscope using a technique called immunofluorescence, which helps to map the underlying structure.

Genetic diagnosis of the underlying gene mutation may be available, especially if a family gene mutation has been identified. However, parents or siblings may show no sign of the disorder, either because the parents are carriers of the recessive trait and have no symptoms or because it is caused by a new genetic mutation in the individual.

Treatment and management

Mild forms of EB may require little or no treatment. People with the Weber-Cockayne subtype of EB simplex—the most common form of EB—almost never even seek medical care. However, severe forms require intensive daily care by family members, similar to care for burn victims. Because the skin is very fragile, extreme care must be taken with dressing changes to prevent further damage. Tape cannot be applied directly to the skin, and bandages should be soaked off. Infection is a major concern, so a topical antibiotic, such as bacitracin, mupirocin, or sulfadiazine, should be applied routinely. The anticonvulsant phenytoin is sometimes effective against recessive dystrophic EB, because it decreases production of an enzyme that breaks down collagen. Children with severe EB usually require treatment from a team of specialists.

QUESTIONS TO ASK YOUR DOCTOR

- How do the various types of epidermolysis bullosa differ from each other?
- How is this genetic disorder transmitted from one generation to the next?
- I have a child with epidermolysis bullosa; what are the chances that I will have a second child with the same disorder?
- Is genetic screening available for the gene mutations that cause epidermolysis bullosa?

Prognosis

The prognosis for EB depends on the type and subtype. Individuals with EB simplex generally live normal lives. The severity of the junctional and dystrophic forms of EB can vary greatly. Some forms of junctional EB improve with age. Infants affected with some forms of EB often do not survive infancy or suffer from severe scarring and disfigurement.

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ORGANIZATIONS

American Academy of Dermatology, P.O. Box 1968, Des Plaines, IL 60017, (847) 240-1280 or (866) 503-SKIN (7546), (847) 240-1859, <https://www.aad.org>

Dystrophic Epidermolysis Bullosa Research Association (DEBRA) of America, 75 Broad St., Suite 300, New York, NY 10004, (212) 868-1573 or (855) CURE-4-EB, (212) 868-9296, staff@debra.org, <http://www.debra.org>

Epidermolysis Bullosa Medical Research Foundation, 2757 Anchor Ave., Los Angeles, CA 90064, (310) 205-5119, <https://www.ebmrf.org/>

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Epidermolysis bullosa junctionalis-disentis
type see **Epidermolysis bullosa**

Epigenetic inheritance

Epigenetic change is a change in phenotype (observable characteristics) without a change in genotype (the genetic makeup of an organism). Epigenetic changes are heritable, which means they may be passed from one generation to the next, and potentially reversible changes in gene function that occur without a change in the sequence of DNA in an organism. Instead, these changes result from how genes are expressed—the activation and deactivation of those genes.

Epigenetic inheritance, specifically the inheritance of genetic control markers by offspring, has gained the attention of evolutionary scientists. This transgenerational inheritance is initiated during gamete formation. Epigenetic transcriptional control mechanisms rather than the genetic code are responsible for this form of inheritance.

Environmental factors induce the markers for epigenetic control of development and cellular differentiation

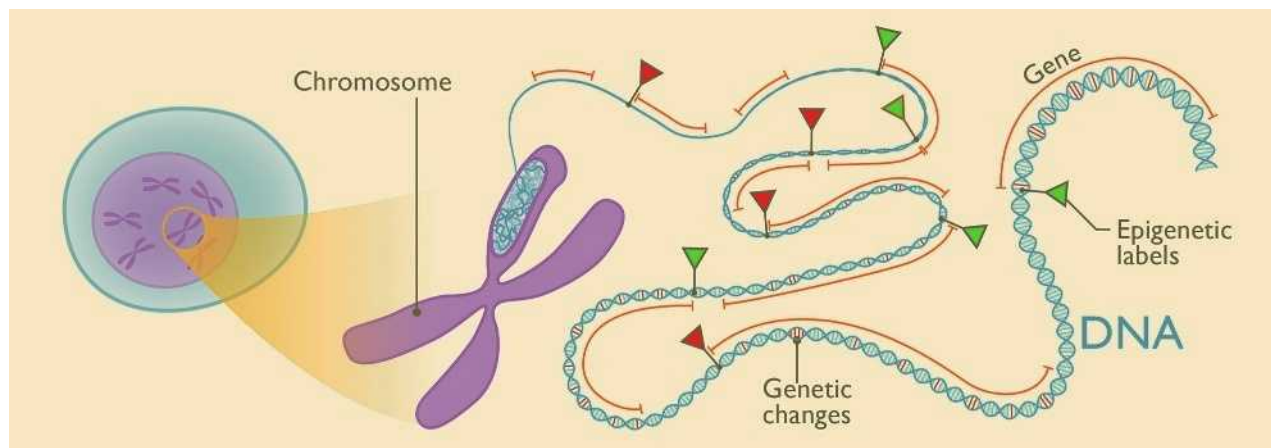
in higher life forms. Most marks are removed in gamete formation, and some marks are heritable. The inheritance of acquired characteristics, or Lamarckism, may explain newly appreciated heritable changes in phenotype due to epigenetics. There has been renewed interest in Lamarckism, proposed by French zoologist Jean-Baptiste Lamarck (1744–1829) and supplanted by Mendelian genetics in view of increased understanding and appreciation of epigenetics. Evolutionary theory must adapt to account for transgenerational epigenetic inheritance.

Epigenetic markers and controls

Epigenetic markers act like punctuation in the way that DNA will be read and acted upon. An exclamation point tells the cell to upregulate or strongly express a gene. A comma tells the cell to slow or pause the process, down-regulating a gene, and a period stops the process entirely, deactivating or silencing the gene. Epigenetic markers are added by writer proteins and may be modified or removed by editor proteins, and some are inherited.

DNA methylation and histone acetylation patterns that regulate gene expression may be inherited, and transcriptional interference through the transmission of small interfering RNAs can alter the phenotype of the zygote. The third type of transgenerational epigenetic inheritance is the formation of metabolic loops. In loops, a gamete's mRNA or protein product controls its own gene expression at the transcription level. The zygote perpetuates the control loop to affect inheritance after fertilization. Each of these mechanisms is found in mammals.

The epigenome comprises the DNA and a large series of proteins and small molecules that bind to the double helix. They serve to alter gene activity. Epigenetics are inherited phenotypical changes to the resulting



Epigenetic markers on a DNA double helix including a chromosome and cell. Epigenetics is the study of heritable phenotype changes that do not involve alterations in the DNA sequence. (Medicalwriters/Science Source)

KEY TERMS

DNA methylation—The addition of methyl groups to DNA, which suppresses gene transcription. Suppressing genes is the basis of epigenetics.

Histone acetylation—The addition of an acetyl group, a three-carbon molecule, at one end of a histone molecule. This DNA acetylation alters gene function without changing any DNA base pairings.

Phenotype—The observable physical properties of an organism; its appearance, behavior, actions, and traits.

chromatin without alterations to the genetic sequence. The phenotypical changes are expressed as changes in cellular or physiological activity or changes in gene expression. Both environmental and developmental forces can cause phenotypic changes that are heritable to daughter cells.

Chemical mechanisms of altering phenotype include DNA methylation, histone acetylation, inhibition of gene expression by RNA, and the binding of repressor proteins to silencer sequences. Any of these can last several cell division cycles, and some may survive gamete formation. For these covalent modifications to the epigenome, a series of enzymes creates and maintains patterns of these markers.

Promoters in different cell types have different nucleosome positions. This variation is a result of histone acetylation patterns and results in differential gene expression and cell differentiation. Nucleosomes block transcription by binding to DNA. Their placement can be influenced by DNA methylation too, and those positions are sometimes inherited.

Molecular sequencing techniques sensitive to DNA methylation and protein chemistry techniques that detect acetylated histones have facilitated rapid advancement of our understanding of transgenerational epigenetic inheritance. For example, we now know that natural populations display many epigenetic variations or a high epimutation rate. Epimutations in phenotype can create heritable variations that can ultimately enable adaptation alongside genetic mutations and profoundly influence evolution.

The fate of epigenetic markers

Epigenetic modification within cells is reset during meiosis. Most methyl groups are removed from DNA, and histone acyl groups are absent. Removal or retention

mechanisms of these markers in either gamete affect inheritance. After fertilization, acetylated histones from sperm are replaced with unmodified histones from the female's cytoplasm, and male DNA is demethylated, thus deprogramming it. Maternal DNA remains methylated and distinguishable from male DNA. Then, during DNA replication, DNA polymerase is coupled to enzymes that reproduce the DNA methylation and histone acetylation patterns from the parent cell.

Contribution to phenotypes

Transgenerational epigenetic inheritance can evolve if the environment is stable across generations. With selective pressure, genetic change may ultimately follow. There is evidence of inheritance that is stable for generations shaping human lives. Now, the relative importance of genetic and epigenetic inheritance is subject to debate.

Epigenetic inheritance in humans

Near the end of the Civil War in 1865, conditions in the Confederate prisoner of war (POW) camps were inhumane. The overcrowding of Union Army prisoners was severe, and prisoner death rates climbed. The traumatic nature of the experience affected survivors for life. When they returned to society, their health, job prospects, and life expectancy suffered. Researchers contend that the prisoners' offspring inherited these impediments.

They studied the health records of nearly 4,600 descendants of former prisoners who had not themselves suffered the hardships of a POW camp. These descendants suffered higher rates of mortality than the wider population. The POWs passed on some element of their own trauma to their offspring.

Many deaths in the prisoners' offspring were due to higher rates of cerebral hemorrhage and cancer. The daughters of former POWs did not suffer these effects, though. Only sons born after their fathers' trauma were affected in a sex-linked pattern, suggesting the epigenetic change happened on the X chromosome during or after the trauma.

Revising evolutionary theory

That the genetic code is not the sole basis of inheritance is evident. Environmentally induced phenotypes can control gene expression and be passed for several generations as epigenetic markers are passed. While epigenetic regulation of gene expression occurs during the differentiation of somatic cells and in response to the environment, inheritance of these markers by the offspring constitutes transgenerational epigenetic inheritance.

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Epigenome

The epigenome consists of DNA and the small molecules and proteins that bind or attach to the double helix and modify or mark it by tightly wrapping specific genes to deactivate them and relaxing others to activate them, enabling their expression. Epigenomics is the study of these markers that switch parts of the genome on and off at specific times and locations, and the factors that influence them, which in many cases may be passed down to from generation to generation.

Epigenetics are inherited phenotypical changes to the resulting chromatin without alterations to the genetic

sequence. The phenotypical changes are usually expressed as changes in cellular or physiological activity or change in gene expression. Both environmental and developmental forces can cause phenotypic changes that are heritable to daughter cells.

Chemical mechanisms of altering phenotype include DNA methylation, histone acetylation, inhibition of gene expression, and the binding of repressor proteins to silencer sequences. Transcriptional repression due to silencer binding can last several cell division cycles.

In multicellular life, cellular differentiation is driven by the state of the epigenome. Stem cells differentiate to become the cell lines of the embryo that then develop into more fully differentiated cells. Through the activation or inhibition of certain genes, the epigenome orchestrates its own cell's phenotypes.

Molecular characteristics of the epigenome

Transgenerational epigenetic inheritance occurs when the cell divides, and the epigenome structure responsible for a phenotypic change is seen in a gamete. The egg or sperm will carry the modification to next generation.

Processes of the epigenome

Epigenetic processes include paramutation, imprinting, bookmarking, gene silencing, X chromosome inactivation, positional effects, DNA methylation, maternal effects, damage due to teratogens (substances that may produce physical or functional defects in the human embryo or fetus after exposure during pregnancy), the regulation of histone modifications and heterochromatin.

DNA damage and changes in the epigenome

DNA is damaged about 60,000 times a day per cell naturally. The damage is usually repaired. Epigenetic changes, however, can endure the cell replication process. Double-strand DNA breaks can lead to DNA methylation and gene repression. Breaks can also lead to changes in modification of histone genes that alter chromatin structure and gene activity.

Enzymes that accumulate at the site of DNA breakage recruit chromatin remodeling proteins that change the structure of nucleosomes and the activity of DNA repair genes. DNA damage can also lead to hypomethylation of the chromatin, alternate protein binding activity, and gene transcription.

Building the epigenome

There are several types of inheritance systems that play a part in cell memory.

KEY TERMS

DNA methylation—The addition of methyl groups to DNA, which suppresses gene transcription. Suppressing genes is the basis of epigenetics.

Histone acetylation—The addition of an acetyl group, a three-carbon molecule, at one end of a histone molecule. This DNA acetylation alters gene function without changing any DNA base pairings.

Paramutation—a heritable change in the expression of one allele that results from an interaction of this allele with another allele for the same trait. The paramutation-affected allele can be passed to subsequent generations.

Phenotype—The observable physical properties of an organism; its appearance, behavior, actions, and traits.

Transcriptional repression—Methods that inhibit transcription such as protein binding to promoters to impede binding of RNA polymerase.

Covalent Modifications

Covalent modifications of either DNA, such as cytosine methylation and the hydroxy methylation (introduction of a hydroxymethyl group into a compound) of histone proteins play central roles in many types of epigenetic inheritance. Chromatin remodeling includes a change in the way DNA wraps around histone proteins. It can affect gene expression and can be inherited.

Histone modifications occur along the whole protein. The unstructured N-termini of histones (called histone tails) are most frequently modified, though. These modifications include numerous covalent bonds. Acetylation of histones changes their charge and reduces their affinity for DNA, leaving room for transcription factors to assemble. So, gene expression is activated.

Other chromatin remodeling proteins may bind in the region of acetylated histone tails and alter transcription rates. Methylation of histone 3, for example, is associated with condensation of the chromosome to heterochromatin.

Multiple modifications can work together to change the structure of nucleosomes and chromatin. 5-methylcytosine is deaminated naturally and sometimes changed to thymine by the mismatch repair system. Replacement of cytosine with thymine reduces the number of methylation target sites on chromosomes. Then, enzymes responsible for methylation work to add a methyl group to newly synthesized strands replicating the parent strand pattern.

Chromosomes can adopt stable alternate states with stable gene expression levels that are heritable based on methylation patterns of histones. Methylation patterns are established and maintained by at least three methyltransferases and two demethylation enzymes.

Epigenetic effects of RNAs

For some RNA transcripts, transcription factor activity of the proteins they encode acts to recruit the transcription complex. RNA signaling includes differential recruitment of chromatin-modifying complexes and DNA methyltransferases to specific loci by RNAs during differentiation and development. For some genes, epigenetic changes are mediated by the production of differently spliced splice transcripts, or by formation of double-stranded RNA (RNAi). Descendant cells inherit these changes. RNA can also spread to other cells by diffusion. RNA from sperm and to a greater extent the egg alters gene expression in several generations of offspring.

Micro RNAs are non-coding transcripts less than 30 nucleotides long. As of 2021, more than 2,000 microRNAs (miRNAs) have been cataloged. One controls transcription of 100 to 200 genes by affecting the degradation of their transcripts. In turn, miRNAs can be epigenetically controlled through DNA methylation and histone binding.

Nucleosome placement

Promoters in different cell types have different nucleosome positions, resulting in differential gene expression and cell differentiation. Nucleosomes block transcription by binding to DNA. Their placement can be influenced by covalent modifications such as DNA methylation, and those positions are sometimes inherited.

Epigenetics during mammalian development

In mammals, most cells irreversibly differentiate, with only stem cells retaining the potential to differentiate into several cell types. Epigenetic changes can result from environmental exposures. For example, maternal dietary supplementation with genistein causes epigenetic changes affecting expression of the genes that affect coloration and cancer development. Research on the impact of other known teratogens and carcinogens (cancer-causing agents), on methylation signatures is underway.

Some epigenetic inheritance can endure the reproductive process and become generational. Although most of these multigenerational epigenetic traits are lost over

several generations, they are another aspect of evolution and adaptation. Epigenetic inheritance can differ from traditional genetic inheritance. However, rates of epigenetic changes, or epimutation, can be much faster than rates of mutation, and those mutations are usually easily reversed.

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Kimberly A. Napoli

Epilepsy

Definition

Epilepsy is a chronic (persistent) disorder of the nervous system. The primary symptoms of this disease are periodic or recurring seizures that are triggered by sudden episodes of abnormal electrical activity in the brain. The term "seizure" refers to any unusual body functions or activities that are under the control of the nervous system.

Description

The word "epilepsy" is derived from the Greek term for seizure. Seizures can involve a combination of sensations, muscle contractions, and other abnormal body

functions. They may appear spontaneously—without any apparent cause—or they can be triggered by a specific type of stimulus such as a flashing light. Specific cases of epilepsy may result from known causes, such as brain injury, or may have no apparent cause (referred to as idiopathic epilepsy). Idiopathic epilepsy may be initiated by a combination of genetic and environmental factors.

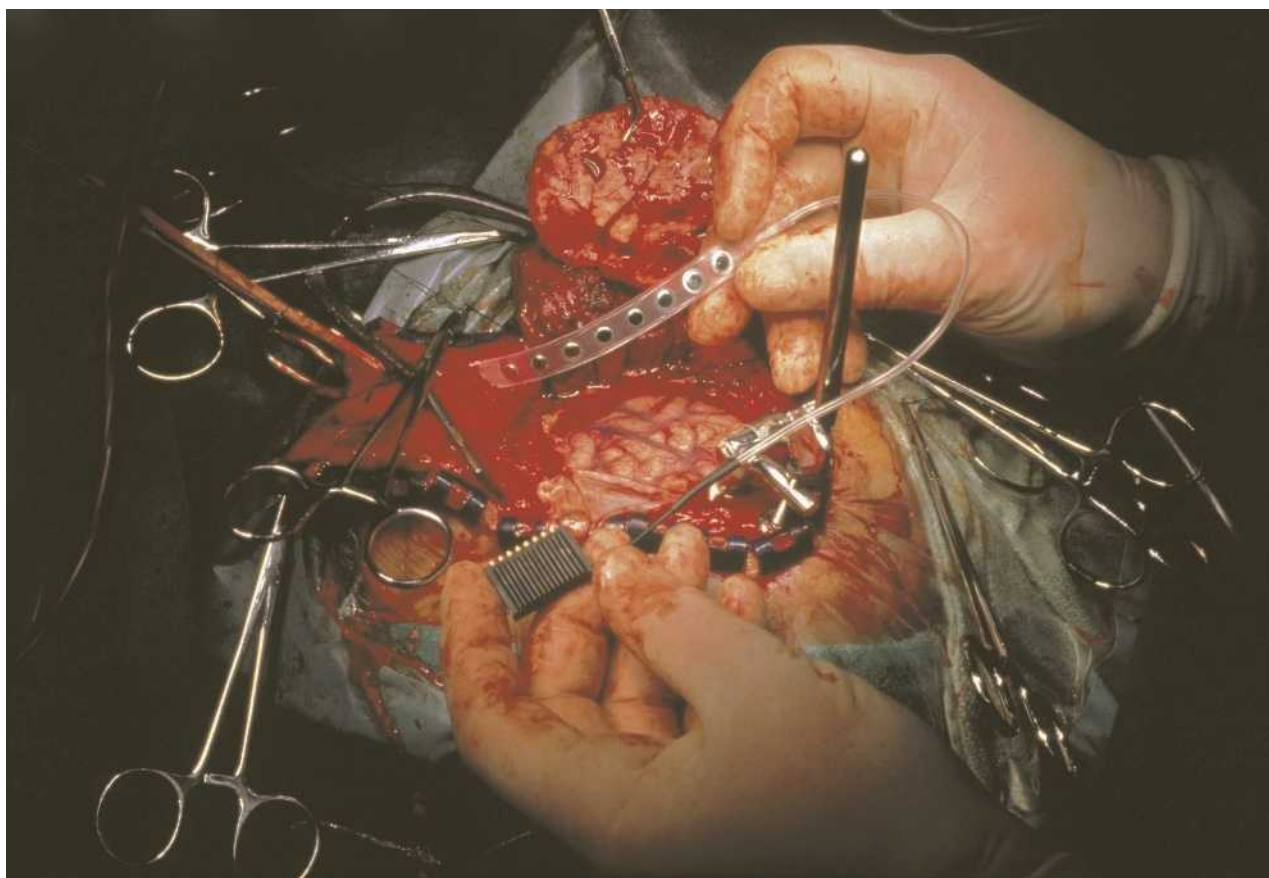
An epileptic seizure involves a transient (temporary) episode of abnormal electrical activity in the brain. During a seizure, many nerve cells within a specific region of the brain may begin to fire at the same time. This activity may then spread out over other parts of the brain. In addition to abnormal physical symptoms, seizures can bring on emotions ranging from fear, anger, and rage to joy or happiness. During a seizure, patients may experience disorientation, spontaneous sensations of sounds, smells, visions, and distorted visual perception—such as misshapen objects and places.

Epilepsy can be caused by some event or condition that results in damage to the brain such as strokes, tumors, abscesses, trauma (physical injury), or such infections as meningitis. Epilepsy can also be triggered by inherited (genetic) factors or some form of injury or trauma at birth. The causes of epilepsy vary somewhat by age group, however. Genetic factors, head trauma, and congenital malformations of the brain are the most common causes in children. Head trauma is the most common cause in young adults. Head trauma, tumors, and stroke are the leading causes in middle-aged adults, and stroke and Alzheimer's disease are the most common causes in older adults.

Symptoms of this disorder can appear at any age. Seizures can damage and destroy brain cells, and scar tissue can develop in the section of brain tissue where seizures originate.

There are many forms of epileptic seizures. The parts of the body that are affected by a seizure and the distinctive characteristics, duration, and severity of the symptoms may be used to distinguish each type of epilepsy. Patients can experience more than one type of seizure. The nature of the symptoms depends on where in the brain the seizure originated and how much of the brain is involved. Seizures can be classified as either generalized or partial. Partial seizures involve abnormal activity in a specific region of the brain.

Generalized (also called tonic-clonic) seizures last about two minutes and are the result of abnormal electrical activity that spreads out over both sides or hemispheres of the brain. They were formerly referred to as grand mal seizures. The patient will usually lose consciousness and fall during the episode. The term "tonic"



Neurosurgery to correct epilepsy. At center is the surface of the cerebrum. Black sutures are attached to the meninges (membranes) that surround the brain. The surgeon holds an electrode to be implanted into the brain to control seizures. (*John Greim/Science Source*)

refers to the first phase of a generalized seizure in which the body muscles become taut or stiff. This phase is followed by the strong, rhythmic muscular contractions (convulsions) of the clonic phase. Sometimes a patient's breathing may be hampered by a brief stoppage of the respiratory muscles, causing the skin to develop a bluish tinge due to lack of oxygen.

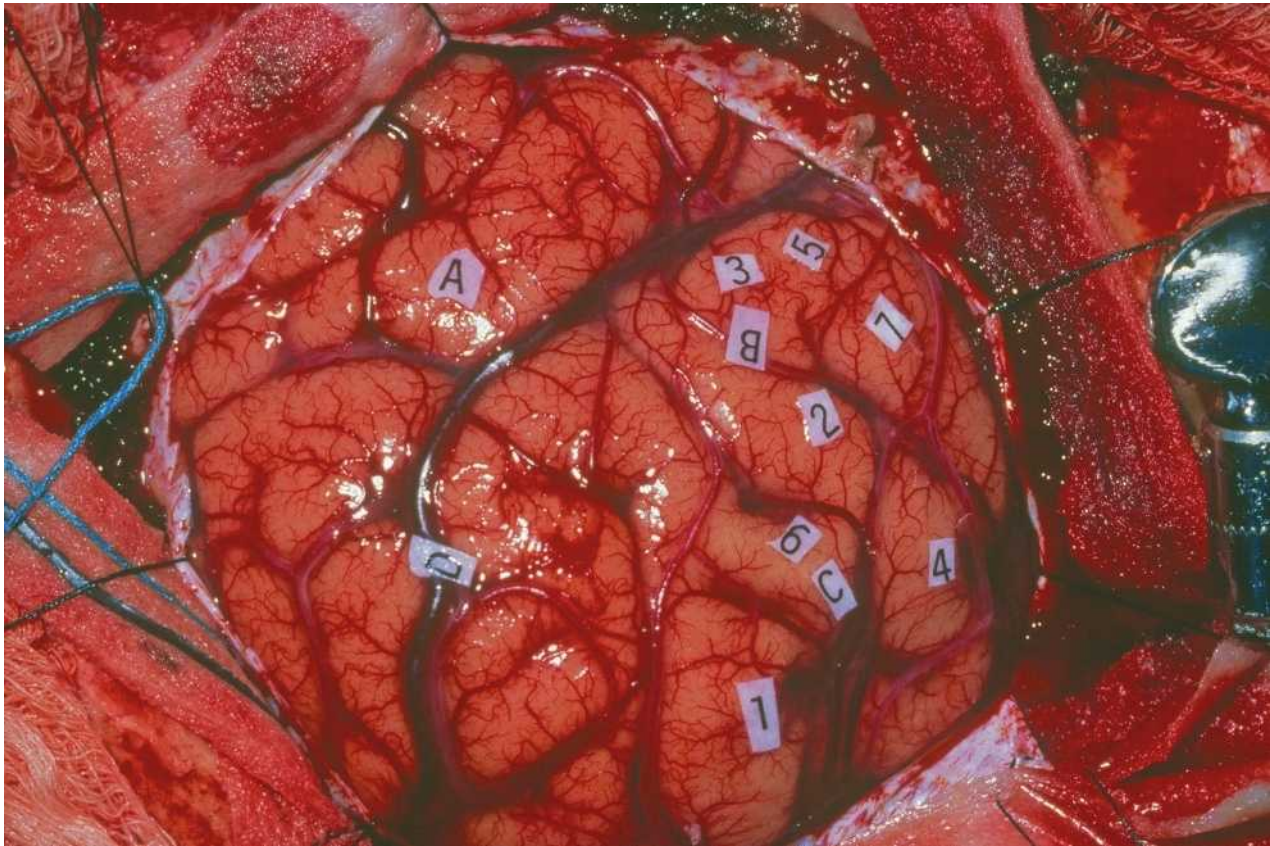
Epileptic seizures can also be classified as complex or simple. Complex seizures generally involve a loss of consciousness, whereas simple seizures do not. Simple partial seizures can start out localized (focal) and then evolve into secondary generalized episodes in which the initial abnormal electrical activity spreads to involve other parts of the brain. Patients may actually remember the physical and psychological events that occur during a simple seizure, such as the types of movement, emotions, and sensations, but they frequently are completely unaware of the event. Partial seizures are more common in adults.

An absence seizure (once called *petit mal*) typically results in brief periods of lack of awareness and some

abnormal muscle movement. The patient usually does not fall during the seizure episode but may become absent-minded and unresponsive. They may also appear to be staring into space. Absence seizures last about five to ten seconds.

How seizures affect a person's memory depends where in the brain seizures occur. Seizures can interfere with learning, storage, and retrieval of new information. For example, a form of epilepsy that produces seizures in the temporal lobe of the brain can cause a serious deterioration (loss) of memory function. Early treatment can help prevent or reduce memory loss.

In some forms of epilepsy, seizures can be triggered by a particular mental—or cognitive—activity. For example, the simple activity of reading aloud can trigger a seizure in patients with reading epilepsy. Symptoms include face muscle spasms. In medical terms, this type of epilepsy is referred to as *idiopathic localization-related epilepsy*. This term means that seizures occur in one part of the brain (in this case, the temporal lobes) and that there is no apparent cause that brought on the disorder.



Epilepsy. Brain recording during surgery, with areas of the brain mapped and labeled for analysis. (Southern Illinois University/Science Source)

Genetic profile

Genetic factors contribute to about 40% of all epilepsy cases. Most of the generalized epilepsy syndromes and some of the partial epilepsy syndromes have an inherited component. Medical researchers suggest that at least 500 genes may somehow be involved in the development of various forms of epilepsy. As of 2021, 126 epilepsy-associated genes or loci are listed in the Online Mendelian Inheritance in Man database. Most of these genes cause or contribute to a wide range of seizure and epilepsy types, severities, intellectual functioning, and other conditions. Some of them can make people with epilepsy more susceptible or sensitive to environmental factors that initiate or start seizures. Only a few types of epilepsy, however, are thought to be monogenic (caused by just one gene). Different mutations may lead to abnormal brain development or progressive degeneration of brain tissue. Some gene mutations make nerve cells hyperexcitable. These abnormal nerve cells can trigger outbursts of abnormal patterns of electrical activity that can initiate an epileptic seizure.

Specific gene locations called gene markers have been linked to various forms of the disease, such as

juvenile myoclonic epilepsy. However, researchers have discovered that some individuals who possess this gene do not develop symptoms of this disease. In some pairs of identical twins with this gene, one twin might appear normal while the other develops typical symptoms of epilepsy. Thus, genetic inheritance seems to be just one of many factors that influence the possibility of developing epilepsy symptoms. Some genetic mutations may also reduce the effectiveness of antiepileptic medication. One of the major goals of epilepsy research is to determine how a patient's genetic makeup can influence their response to drug therapy.

In 2017, the International League Against Epilepsy (ILAE) issued a revised classification of the epilepsies and divided them into categories according to levels of diagnosis: seizure type, epilepsy type (focal, generalized, combined generalized and focal, and unknown) and epilepsy syndrome as well as etiology (the cause or causes), reflecting recent advances in diagnosis and genetics:

- **Seizure type**—Seizures are classified into focal onset, generalized onset, and unknown onset.
- **Epilepsy type**—The categories are generalized epilepsy, focal epilepsy, combined generalized and focal epilepsies,

and unknown, which indicates that the clinician is unable to determine whether the type is generalized or focal, because there is not enough information.

- Epilepsy syndrome refers to a cluster of features involving distinct seizure types, EEG, and imaging features that tend to occur together. A syndrome often has a typical age at onset, intellectual and psychiatric disorders, seizure triggers, and sometimes prognosis.

Genetic syndromes that include seizure disorder

Genetic syndromes in which seizure disorder is part of the clinical picture include Angelman syndrome, caused by a deletion in the long arm of the maternal form of chromosome 15 at 15q11.2-q13; Rett syndrome, caused by mutations in the *MECP2* gene on the long arm of the X chromosome at Xq28; Pitt-Hopkins syndrome, caused by mutations in the *TCF4* gene on the long arm of chromosome 18 at 18q21.1; and tuberous sclerosis complex, caused by mutations in the *TSC1* gene on the long arm of chromosome 9 at 9q34.13 or the *TSC2* gene on the short arm of chromosome 16 at 16p13.3.

Two other genetic syndromes that include seizures are Sturge-Weber syndrome, which is thought to be associated with mutations in the *GNAQ* gene on the long arm of chromosome 9 at 9q21.2; and Prader-Willi syndrome, caused by a deletion in the long arm of the paternal form of chromosome 15 at 15q11.2-q13.

Chromosomal deletion/duplication syndromes

There are three chromosomal duplication/deletion syndromes in which seizures are a prominent characteristic. They include chromosome 22q deletion syndrome, in which genetic material lost from the long arm of chromosome 22 at 22q11.2 results in congenital heart disease, facial anomalies, and immune system deficiencies as well as seizures. This deletion syndrome has been variously known as DiGeorge syndrome, Shprintzen syndrome, and velocardiofacial syndrome.

The second disorder in this category is Wolf-Hirschhorn syndrome, caused by deletions in the short arm of chromosome 4 at 4p16.3. This syndrome is accompanied by growth retardation and some intellectual disability as well as seizures.

The third deletion syndrome is 1p36 deletion syndrome, in which a deletion on the short arm of chromosome 1 results in patients with an abnormally small head (microcephaly) and misshapen facial features as well as seizures.

Metabolic disorders

Zellweger syndrome is a disorder caused by mutations in any of several *PEX* genes, which code for

peroxins, proteins that are needed for the normal assembly of peroxisomes, organelles within cells that break down very long-chain fatty acids and some types of amino acids. The *PEX1* gene is located on the long arm of chromosome 7 at 7q21.2; the *PEX2* gene is located on the long arm of chromosome 8 at 8q21.11; the *PEX5* gene is located on the short arm of chromosome 12 at 12p13.31; the *PEX10* gene is located on the short arm of chromosome 1 at 1p36.32; and the *PEX26* gene is located on the long arm of chromosome 22 at 22q11.21. Children with Zellweger syndrome typically suffer from loss of liver function as well as seizures and usually die within their first year.

Other genetic metabolic disorders associated with seizures include lysosomal storage diseases and disorders of glycosylation.

Mitochondrial disorders

There are two genetic disorders in this group that have seizures as a presenting symptom. One is mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, which is caused by mutations in the genes in mitochondrial DNA—most often the *MT-TL1*, *MT-ND1*, and *MT-DN5* genes. These mutations impair the ability of the mitochondria to convert simple sugars and oxygen to energy and to make proteins.

The second disorder in this group is myoclonic epilepsy with ragged red fibers (MERRF) syndrome, which derives its name from the clumps of diseased mitochondria that accumulate in muscle fibers and appear ragged and red in color when stained with Gömöri trichrome stain. MERRF syndrome results from mutations in the *MT-TK*, *MT-TL1*, *MT-TH*, *MT-TS1*, *MT-TS2*, and *MT-TF* genes.

Single-gene mutations

Single-gene mutations associated with epilepsy include the following types of epilepsy:

- Autosomal dominant nocturnal frontal lobe epilepsy: caused by mutations in the *CHRNA4* gene on the long arm of chromosome 20 at 20q13.33; the *CHRN2* gene on the long arm of chromosome 1 at 1q21.4; and the *CHRNA2* gene on the short arm of chromosome 8 at 8p21.2.
- Benign familial neonatal seizures are caused in newborns by mutations in the *KCNQ2* gene on the long arm of chromosome 20 at 20q13.33 or the *KCNQ3* gene on the long arm of chromosome 8 at 8q24.22.
- Generalized epilepsy with febrile seizures has been traced to mutations in the *SCN1A* gene on the long arm of chromosome 2 at 2q24.3; the *SCN2A* gene, also on the long arm of chromosome 2 at 2q24.3; and the *SCN1B* gene on the long arm of chromosome 19 at 19q13.12.

- Mutations in the *GABRG2* gene on the long arm of chromosome 5 at 5q34 are associated with both generalized epilepsy with febrile seizures and familial febrile seizures.

Demographics

Epilepsy affects about 1% of the population in North America by age 20 and 3% by age 70; one in 26 Americans will develop epilepsy over the course of a lifetime. Approximately three million Americans and 65 million people throughout the world have epilepsy. It is the second-most common neurological disorder and affects both sexes and all races and ethnic groups; however, it is slightly more common in males than in females. The highest incidence is in children younger than age 10 and adults older than age 70.

Epilepsy is more common in Asia and Africa than in Europe and North America because of the higher rates of traumatic injury and infectious diseases (particularly parasitic diseases) in the developing world. Worldwide, the most common cause of epilepsy is infection. Epilepsy may arise in a wide range of conditions including neurocysticercosis, tuberculosis, HIV, cerebral malaria, subacute sclerosing panencephalitis, cerebral toxoplasmosis, Zika virus, and cytomegalovirus. It also may develop after an infectious disease has resolved. For example, following viral encephalitis (inflammation of the brain caused by a virus such as influenza, herpes simplex, measles, mumps, rubella, rabies, chickenpox, or West Nile virus), some patients develop seizure disorders.

Signs and symptoms

Patients who have been diagnosed with epilepsy may have little warning that they are about to experience an epileptic seizure. Some patients experience an unusual feeling, or aura, that can act as a warning that an episode is about to start. Auras generally precede actual seizures. An aura may take the form of an unusual sensation such as a fearful feeling, a mental image, or a peculiar taste, smell, or sound. A period of confusion or stupor known as the post-ictal period may follow a seizure. Getting a good night's sleep is a common problem for young children with epilepsy. Lack of sleep can then lead to behavior problems and drowsiness during the daytime.

Diagnosis

Diagnosis of epilepsy is complicated by several factors, such as the fact that people can have a so-called first seizure caused by low blood sugar, sleep deprivation, eclampsia of pregnancy, kidney or liver dysfunction, or electrolyte disturbances. Many people who have a first seizure never have a second one; doctors therefore prefer

not to give antiseizure medications to a patient in this category unless he or she has other risk factors for epilepsy (including family history). In addition, conditions such as alcohol withdrawal and psychogenic non-epileptic seizures (PNES) may be difficult to distinguish from true seizures without EEG testing. For these reasons, epilepsy is defined as the occurrence of at least two unprovoked seizures occurring more than 24 hours apart.

Early symptoms of epilepsy include excessive staring, easy distraction, and difficulty maintaining attention. To confirm the diagnosis, doctors look for neurological (nervous system) abnormalities such as speech or vision defects or defects in brain structure or other parts of the nervous system. The goal of the diagnostic testing is to identify where the seizures are originating. EEGs (electroencephalographs) are used to monitor electric activity—patterns of nerve impulses in the brain. A type of neuroimaging called magnetic resonance imaging (MRI) is also used extensively to try to pinpoint the location and type of abnormalities (referred to as lesions) in brain structures that cause episodes of epileptic seizures. In some cases, videotaping seizures and monitoring the patient's EEGs may be useful for identifying the specific type of epilepsy.

Idiopathic epilepsy—those cases for which no specific cause can be identified—is presumed to have a genetic basis. As of 2021, molecular genetic testing was available for more than 80 genes linked to various types of epilepsy, and hundreds of other genes are associated with genetic syndromes that have seizures as a symptom. However, there is no single test for all known epilepsy-associated genetic mutations.

Treatment and management

Currently, no cure exists for epilepsy. However, a wide range of treatments are available that provide varying degrees of success in controlling the symptoms of epilepsy.

Medications

Medication is the most effective and widely used treatment for the symptoms of epilepsy. Most medications work by interfering with or stopping the abnormal electrical activity in nerve cells that cause seizures. This form of treatment is generally referred to as anticonvulsant therapy. Medication is considered effective if the patient is free of seizures for at least one year.

Anticonvulsants are powerful drugs that can produce a variety of side effects, including nausea, fatigue, dizziness, and weight change. They can also increase the risk of birth defects, especially involving the early stages of

KEY TERMS

Absence seizure—A type of epileptic seizure characterized by a brief loss of, and return to, consciousness, usually without being followed by a period of confusion or disorientation.

Aura—A disturbance in one or more of the five senses before the beginning of an epileptic seizure.

Congenital—Present at birth.

Convulsion—Involuntary contractions of body muscles that accompany a seizure episode.

De novo mutation—A mutation that arises in a child that is not present in either parent.

Eclampsia—The onset of seizures in a pregnant woman with pre-eclampsia, a condition characterized by protein in the urine, high blood pressure, and sometimes other organ dysfunction.

Idiopathic—Of unknown origin.

Ketogenic diet—A high-fat, low-carbohydrate diet used to treat epilepsy in children who do not respond to anticonvulsant medications.

Lesion—A defective or injured section or region of the brain (or other body organ).

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Mitochondrial genes—A group of 37 genes contained in the DNA of mitochondria (mDNA), the

energy-producing organelles in cells. In humans, mDNA is inherited solely from the mother.

Myoclonic epilepsy—Epilepsy characterized by sudden jerking or twitching in the arms, legs, or upper body.

Post-ictal—Referring to the period following an epileptic seizure and its alterations in consciousness.

Psychogenic non-epileptic seizure (PNES)—An event that resembles an epileptic seizure but lacks the electrical discharge associated with epilepsy. PNES is associated with psychiatric disorders, most often conversion disorder, and is often triggered by a psychological trauma of some kind.

Seizure—Any unusual body function or activity that is under the control of the nervous system.

Status epilepticus—A potentially life-threatening seizure that either lasts longer than five minutes or consists of two seizures within a five-minute period without the patient returning to normal consciousness between the seizures.

Sudden unexplained death in epilepsy (SUDEP)—A fatal complication of epilepsy that accounts for about 15% of deaths in epilepsy patients. It is thought to result from a combination of factors, including cardiac and respiratory as well as neurological factors.

embryonic development of the nervous system when taken during pregnancy.

Doctors prefer to put their patients on just one type of anticonvulsant drug. Some patients, however, experience more effective relief from their epilepsy symptoms by taking a combination of two different but complementary forms of medication. The choice of medication depends on the type of seizure that affects a patient and the patient's medical history—including response to other drug therapies—age, and gender. For example, the drug carbamazepine is one of the most effective medications and has little impact on important cognitive functions such as thinking, memory, and learning.

Newer medications generally produce fewer side effects than their predecessors. Research into gene therapy may ultimately be the most effective form of epilepsy treatment, but it is still in the very early stages.

Unfortunately, medication is ineffective for more than one-third of known cases of epilepsy. More than

30% of patients with epilepsy cannot achieve and/or maintain adequate control of their seizures. In addition, some genetic mutations may reduce the effectiveness of antiepileptic medications.

Surgery

Surgery is recommended for some patients for whom medication cannot effectively control the frequency or severity of their seizures. It is a treatment option only in extreme cases where doctors can identify the specific site in the brain where seizures originate. The most promising candidates for surgery are those with a single lesion on the temporal, frontal, or occipital lobes of the brain.

Prior to surgery, the patient must complete extensive testing to determine the precise patterns of seizures and to locate their point of origin in the brain. Patients spend extended stays in the hospital during which their seizures are recorded on video and with the aid of EEGs. This machine records patterns of electrical activity in the brain

QUESTIONS TO ASK YOUR DOCTOR

- I have been told that epilepsy runs in our family. What are the chances that my children will inherit this disorder?
- What is the cause of my child's epilepsy?
- What other individuals—family, friends, neighbors, school friends, or others—should we tell about our child's epilepsy?
- Should we consider brain surgery as a method for curing our child's epilepsy?

by using sensors (referred to as electrodes) attached to various parts of the body.

The surgical procedure involves the removal of a small part of brain tissue in the region suspected of being the origin of the seizures. The anterior temporal lobe and hippocampus are the most common areas in which tissue is removed. In some studies, more than 83% of patients were free of seizures following surgery, and 97% showed significant improvement in their condition.

Other therapies

Vagus nerve stimulation (VNS) is another form of treatment for some cases of epilepsy that are unresponsive (referred to as refractory epilepsy) to other forms of medical therapy. VNS may also be recommended for patients who cannot tolerate the side effects of medication. This procedure involves implanting a device that stimulates the vagus nerve, located in the left side of the neck. In one study, this treatment reduced seizures by 78%.

Deep brain stimulation (DBS) is another method approved for treatment of epilepsy by the Food and Drug Administration (FDA). DBS involves the implantation of electrodes in the brain, attached by wires to a battery-operated pulse generator implanted beneath the skin of the patient's abdomen or the skin over the area near the collarbone. DBS appears to be helpful in treating patients who do not respond to antiseizure medications.

In 2021, researchers reported successful treatment of drug-resistant epilepsy using a brain-computer interface (BCI), a communication system capable of converting neural activities into signals and providing real-time seizure detection and prediction as well as delivery of warning stimuli or therapies. The BCI not only continuously monitors the patient's brain waves for signals of an impending seizure, it automatically responds with electric

pulses that can prevent the seizure before it occurs. It also can trigger an implanted electrical neurostimulator to prevent, abort, and control seizures.

A special dietary program is another treatment option for patients who are not good candidates for surgery or those who have had little success with anticonvulsant medication. This form of treatment, called the ketogenic diet, can be effective for many types of epilepsy. It is most appropriate for young children, whose parents can follow the rigid requirements of the diet. Older children and adults tend to have greater difficulty in sticking to the dietary rules for an extended period of time. The ketogenic diet is a stringent diet that is very high in fat but low in proteins, carbohydrates, and calories. The excessive fat produces high levels of a substance called ketones (which the body makes when it breaks down fat for energy). Somehow, these ketones help to reduce the incidence of epileptic seizures. The success of this form of treatment varies. For some patients, the high-fat diet is the best form of treatment. For others, the diet is less effective.

Prognosis

As of 2021, there was no cure for epilepsy, but seizures can be effectively controlled in about 70% of patients. Patients with the poorest prognoses are those who have a large number of seizures in the first six months after the initial seizure; those who show little response to the initial course of therapy; those with generalized seizures; those with psychiatric problems; and those with family histories of epilepsy. Unfortunately, epilepsy can shorten a person's lifespan; patients with epilepsy have a risk of death between 1.6 and 4 times higher than that of the general population. The chief causes of death in epilepsy patients are suicide (four to six times more common in epilepsy patients than in the general population); trauma resulting from falls; status epilepticus (a condition in which seizures follow each other without recovery of consciousness in between); and sudden unexpected death in epilepsy, or SUDEP. About 15% of deaths of epilepsy patients are due to SUDEP.

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ORGANIZATIONS

American Epilepsy Society, 135 South LaSalle Street, Suite 2850, Chicago, IL 60603, (312) 883-3800, info@aesnet.org, <http://www.aesnet.org>

Epilepsy and Brain Mapping Services, Huntington Hospital, 100 W. California Boulevard, Pasadena, CA 91105, (626) 397-5000, <https://www.huntingtonhospital.org/our-services/neurology/epilepsy-and-brain-mapping/>

Epilepsy Foundation, 3540 Crain Highway, Suite 675, Bowie, MD 20716, 24/7 seizures helpline (800) 332-1000, (301) 459-3700, <http://www.epilepsy.com>

International League Against Epilepsy (ILAE), 2221 Justin Road, Suite 119-352, Flower Mound, TX 75028, (860) 586-7547, <https://www.ilae.org>

National Institute of Neurological Disorders and Stroke, P.O. Box 5801, Bethesda, MD 20824, (301) 496-5751 or (800) 352-9424, <http://www.ninds.nih.gov>

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Erythropoietic porphyria

Definition

Erythropoietic porphyria (EPP) is an inherited condition that leads to the build-up and heightened excretion of porphyrins or precursors to porphyrins. It is inherited in an autosomal recessive pattern, which means that both parents must transmit the disorder. Of all the porphyria conditions, this is the most disfiguring.

The disorder is also known as congenital erythropoietic porphyria (CEP), congenital porphyria, Gunther's disease, and Gunther porphyria.

Symptoms may be recognized in early infancy; however, they may be found as early as in utero or as late as adulthood.

Description

In erythropoietic porphyria, affected individuals suffer a deficiency in an enzyme needed to break down porphyrins; therefore, the substance accumulates in the blood. As the porphyrins accumulate, they cause major disruptions to the affected parts of the body, leading to enlargement of the liver or spleen and creating multiple types of anemia and other blood disorders.

Genetic profile

EPP can result from mutations in the ferrochelatase (*FECH*) and delta-aminolevulinic acid synthase-2 (*ALAS2*) genes. Disease that results from *ALAS2* gene mutations is less common and is called X-linked protoporphyria (XLP) instead of EPP.

The *FECH* mutation is inherited in an autosomal recessive manner, and it is common for the affected individual to inherit a severe mutation from one parent and a weak mutation from the other. Weak variants of *FECH* are common in Caucasians and rare in African American, Japanese, and Chinese populations. The weak variant is called a "hypomorphic" variant because it causes the production of a less-than-normal amount of ferrochelatase but will not cause EPP on its own.

KEY TERMS

Corneal—Pertaining to the cornea of the eye, which is the clear covering that protects the front of the eyeball.

Hygroma—A condition in which fluid builds up in a sac or cyst.

Photosensitivity—Abnormal sensitivity to light.

Porphyrin—An organic compound containing nitrogen.

Splenectomy—Removal of the spleen.

Thrombocytopenia—Abnormally low platelet levels in the blood.

Wood's light—An ultraviolet light used in medical settings because of its ability to create fluorescence in the presence of substances such as porphyrins.

The more severe mutation of *FECH* is expressed in all individuals with EPP. Carriers of this mutation are not affected as long as they do not also carry the weak variant at the other *FECH* locus. Carriers of the severe mutation will have some children with EPP if their partner is also a carrier for the weak or severe *FECH* gene mutation.

In XLP, mutations of the *ALAS2* gene are found on the X chromosome and cause increased synthesis of the enzyme ALAS2 in the bone marrow. This is considered a gain of function mutation and has been described in different XLP families. In XLP the overproduction of protoporphyrin exceeds necessary levels for the production of heme and hemoglobin. Like hemophilia and other X-linked genetic diseases, XLP is more common in men, because unlike women who have two X chromosomes, men only have one X chromosome and will be affected if they inherit an *ALAS2* mutation. Women with an *ALAS2* mutation will pass that mutation to half of their daughters, who will usually be carriers, and to half of their sons, who will be affected with XLP.

Demographics

Erythropoietic porphyria is very rare. As of 2021, only 150 cases had been reported worldwide.

Signs and symptoms

Causes

The cause of this disorder is genetic. It is necessary for both parents to carry the genetic material for the disease in order for an offspring to have it.

Symptoms

Symptoms are related to where the stores of excess porphyrins are located in the body. They may reside in plasma, red blood cells, urine, and feces. In infants, the condition may lead to red urine, and teeth may also take on a red stain. Blistering of the skin may occur.

EPP can cause photosensitivity; sun exposure to the skin may result in extreme reactions including severe blistering, scarring, pigment changes, skin infections, enlarged spleen (splenomegaly), and anemia. Secondary infections resulting from sun exposure may become so severe as to lead to amputation, particularly of the fingers, as well as portions of the ear, eyelids, and nose.

There is a literature report of a boy in Serbia who was diagnosed at age 16 after he exhibited red urine for a period of six months. A mild form of adult-onset erythropoietic porphyria has been described in medical literature, which included such symptoms as an enlarged spleen and hemolytic anemia, photosensitivity, and thrombocytopenia.

Erythropoietic porphyria also causes symptoms of the eye, including blepharitis, conjunctivitis, and loss of eyelashes and eyebrows. Corneal scarring may occur, sometimes leading to blindness.

Diagnosis

Examination

In newborns, photosensitivity may begin as early as the first few days of life. In diapers of infants with the disorder, urine and feces will contain pink areas when viewed under a Wood's light. The abundance of pink is indicative of urine and feces that have higher-than-normal levels of porphyrins.

The disorder may be diagnosed prior to birth and is one cause of fetal anemia, which requires transfusion. One report in the medical literature discusses cases in which diagnosis occurred during gestational weeks 14 and 19. The main diagnostic feature was the presence of cystic hygroma. By weeks 19 and 22, both fetuses developed nonimmune hydrops fetalis. They also showed intrauterine growth retardation, hyperechogenic bones and kidneys, and dark amniotic fluid due to the raised levels of porphyrins. German scientists identified four gene mutations: *C73R*, *-86A*, *G236V*, and *L237P*.

It is believed that cases that show symptoms later in life are less severe.

Tests

Amniocentesis, which may be performed at 16–18 weeks of pregnancy, may reveal the disorder because

QUESTIONS TO ASK YOUR DOCTOR

- What are the risks of transfusion?
- What are the signs that transfusion is no longer effective?
- How will splenectomy help in my long-term prognosis?

uroporphyrinogen III cosynthetase is found in cultured amniotic cells and in genetic testing.

A Japanese study published in 2002 found that tears contain evidence of excess porphyrins. The scientists concluded that it was important to check for the presence of porphyrins in tears, as build-up of the substance in the eyes could lead to eye damage.

Treatment and management

Traditional

Therapies performed in this procedure include blood transfusion, splenectomy, and substances such as charcoal and cholestyramine, which bind the porphyrins and prevent their absorption. Bone marrow transplant has also been performed on patients with severe cases. Patients with an enlarged spleen may undergo surgical removal of that organ (splenectomy).

Because reactions to sun exposure may lead to serious consequences, avoiding the sun is essential.

Blood transfusions are used in more severe cases. In persons who have depended on repeated transfusions, bone marrow transplant may be considered. Researchers recommend that definitive diagnoses be made as early as possible so that bone marrow transplant may be considered earlier in the course of the disorder.

Treatment has also been accomplished with hydroxyurea; however, long-term use may result in untoward side effects that may involve the eye.

Drugs

Steroids may be given to reduce the size of the spleen if it is enlarged.

Prevention

Erythropoietic porphyria cannot be prevented; however, medical procedures such as transfusion and splenectomy may prevent serious complications. Because the disorder requires gene mutations from both parents, genetic counseling is recommended.

Prognosis

Prognosis depends on the severity of the disorder in a particular person and its response to treatments such as splenectomy and transfusion. Transfusion becomes less effective during puberty. Bone marrow transplant has achieved longer-term success.

Prognosis is usually better for those with the adult-onset form of the disease, which tends to be milder. Prognosis also depends on eye involvement, as complications such as corneal scarring may lead to blindness.

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- American Porphyria Foundation, 4915 St. Elmo Avenue, Suite 200, Bethesda, MD 20814, (866) APF-3635, (301) 347-7166, info@porphyriafoundation.org, <https://porphyriafoundation.org/>

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Erythropoietic protoporphyria

Definition

Erythropoietic protoporphyria, which is an inherited disorder, was identified as a clinical syndrome in 1961. Individuals with this disorder have a significant increase

KEY TERMS

Enzyme—Substance in the body that causes a reaction to occur.

Photosensitivity—Abnormal sensitivity to sunlight.

in protoporphyrin, a substance involved in making a component of red blood cells. The classic symptom is severe photosensitivity.

Description

In erythropoietic protoporphyria, protoporphyrin accumulates in bone marrow, red blood cells, plasma (liquid portion of the blood), skin, and the liver. The accumulation of this material creates severe sensitivity to sunlight as well as damage to the liver.

The normal erythrocyte level of protoporphyrin is 60 microg/dl of red blood cells. Persons with erythropoietic protoporphyria may have levels of protoporphyrin as high as 1,000 microg/dl of red blood cells.

Exposure to sunlight makes active the protoporphyrin molecules, which leads to destruction of nearby tissue. Protoporphyrins that accumulate in the liver can lead to bile stones. When the substance accumulates in the liver, it can lead to damage to that organ.

A study published in 2013 reported the cause of one patient's mutation to be from a substitution of nucleotide thymine for nucleotide cytosine, causing the malformation of the *FECH* gene and ultimately resulting in this blood disorder.

A person with this syndrome is at risk for severe liver damage, possibly requiring a transplant.

Genetic profile

This syndrome is rare, possibly because the set of circumstances required for its presence is complex. While some researchers have found evidence of dominant inheritance (from one parent), others have found that the disorder is autosomal recessive (present in both parents). The most recent understanding is that the mutant gene is inherited from one parent, while the other parent has low activity of the enzyme ferrochelatase.

Demographics

The disorder has not been found in persons of African descent.

Signs and symptoms

Erythropoietic protoporphyria is an inherited disorder. Symptoms arise because of the accumulation of a substance called protoporphyrin. The chief cause of the build-up of this material is a deficiency in ferrochelatase, which is an enzyme. The classic symptom, which often begins during childhood, is severe sensitivity to light, or photosensitivity.

Sensitivity is so severe that it includes long-wavelength ultraviolet light, which reaches the person through window panes. Very soon after exposure to sunlight, persons experience severe skin pain and swelling because the molecules of protoporphyrin are activated by natural light.

Protoporphyrin accumulates in the bone marrow, red blood cells, plasma, skin, and ultimately in the liver. In addition to the cutaneous symptoms, affected individuals may develop bile stones and disorders of the liver such as pain in the abdomen and jaundice, as well as an enlarged spleen. Studies have also shown malabsorption of iron leading to anemia.

Diagnosis

Examination

Erythropoietic protoporphyria is most often diagnosed during childhood, usually by the time the child reaches ten years of age. Cases of adult-onset disease have been reported, but they are less common. The classic symptom is swelling and severe skin pain following exposure to the sun. Physicians may not recognize the disorder because the child does not have any blistering or scarring from the damage.

Tests

Prenatal and postnatal tests are currently available to diagnose an individual suspected of having erythropoietic protoporphyria. A molecular genetic test can be performed for the *FECH* gene, which is the gene that codes for the enzyme ferrochelatase. A mutation of this gene will show within the DNA analysis targeted on the erythropoietic protoporphyria panel. This particular test, either prenatally using chorionic villi, amniotic fluid and cultured cells or postnatally using whole blood, is more than 98% accurate for identifying mutations.

Treatment and management

Traditional

Persons with erythropoietic protoporphyria are instructed to avoid sunlight. In fact, avoiding sunlight is

QUESTIONS TO ASK YOUR DOCTOR

- Will sun-protective clothing offer protection?
- How effective is the application of sunblock?
- What distance away from a window should I stay on a sunny day?
- How often should my liver function be monitored?

the foundation for avoiding a severe reaction. If a person is exposed, treatment is the same as that given for sunburn.

If gallstones develop, persons with this disorder need to have them surgically removed.

Drugs

Beta-carotene, which will cause the skin to become more yellow if taken in sufficient doses, may be taken as a treatment. This substance offers the skin a level of sun protection; however, affected individuals are still instructed to avoid sunlight. It is important that the beta-carotene used is pharmaceutical grade. A popular brand is Lumitene, which is given to children under age 14 years in doses ranging from 30 to 150 mg per day. The adult dose normally ranges from 30 to 300 mg per day. The dose is usually adjusted according to the severity of the person's symptoms as well as his or her tolerance to beta-carotene. Concern has been reported for the use of synthetic beta-carotene supplements in smokers due to a potential association with lung cancer.

A study reported in 2009 found improvement in photosensitivity in five patients treated with afamelanotide, a hormone that enhances formation of melanin, which is a pigment in the skin. These five patients showed improved ability to withstand artificial light; they also experienced an increase in melanin density after four months.

A 2013 study reported improvement of symptoms via low doses of intravenous iron therapy in a 23-year-old Caucasian male heterozygous for the disorder.

Liver disease associated with this disorder is sometimes treated with cholestyramine.

Prevention

Erythropoietic protoporphyria cannot be prevented; however, a 2014 study revealed that antisense oligonucleotide-based therapy can improve the condition of individuals with the disorder by increasing the production

of the wild type FECH mRNA that codes for the protein necessary for the correct levels of protoporphyrin.

Symptoms may also be alleviated by refraining from exposure to sunlight. The potential for serious liver damage should be monitored through yearly blood workups.

It is recommended that persons with the disorder wear medic alert bracelets so that in the event of a medical emergency, emergency personnel will understand that these individuals must not be exposed to bright light such as that found in an operating room. The information will also convey to medical personnel the need to avoid certain medications that may impact the liver.

Clothing should cover as much of the body as possible. Long sleeves and long pants or skirts are recommended. Protective films should be placed on windows, including those in the car. The usual sunscreens are not effective in persons with this disorder. Semi-opaque sunscreens, such as those with zinc oxide, that create a physical barrier may offer some degree of protection; however, persons with the disorder are advised to stay out of sunlight. Artificial light may also cause symptoms.

Prognosis

In most cases, persons with erythropoietic protoporphyria experience reactions to sunlight without other symptoms. However, some individuals develop liver damage, which may be fatal. Gallstones have been reported, even in younger patients. When these appear, they are surgically removed.

Persons who have erythropoietic protoporphyria syndrome are instructed to have yearly blood tests to measure the build-up of porphyrin in the red blood cells. They must also have liver function tests (blood tests) yearly, as well as urine and fecal testing.

In severe cases, affected individuals may require a liver transplant.

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Essential hypertension

Definition

Essential or primary hypertension, the most common form of hypertension, is elevated blood pressure that develops without apparent cause. Genetic factors, however, appear to play a role in increasing the risk of developing the disorder.

Normal blood pressure refers to a range of values rather than a specific set of numbers and varies with factors such as age, race, and gender. A blood pressure reading greater than 140/90 mm Hg (millimeters of mercury pressure) is generally considered to be elevated. In this measurement, 140 refers to the systolic pressure (the maximum pressure in the arteries when the heart contracts). The 90 refers to the diastolic pressure (the lowest pressure in the arteries when the heart is relaxed between contractions).

Description

More than 95% of all elevated blood pressure can be classified as essential hypertension. When a disease, other physical problems, medications, or even temporary physical exertion or stress causes high blood pressure, the condition is called secondary hypertension.

Blood pressure refers to the force exerted by blood against the interior walls of the body's blood vessels. There are three categories of blood pressure corresponding to the three types of blood vessels: arterial, capillary,

and venous. In individuals with hypertension, arterial pressure (recorded as two numbers: systolic and diastolic pressure) is the most important measurement to obtain. The reason is that because of their relative proximity to blood flowing forcefully from the heart, arteries must withstand the highest pressures of all the body's blood vessels.

The body requires a relatively constant blood pressure level to ensure adequate passage of nutrients and oxygen to organs and tissues. To maintain a constant level of pressure, the body must balance and respond to a number of factors such as:

- volume of blood in the circulatory system
- amount of blood ejected by the heart (stroke volume)
- heart rate
- thickness of the blood (viscosity)
- elasticity of the arteries

When the systolic or diastolic pressure is elevated for an extended period of time, such as months or years, the heart has to work harder and may become damaged, along with the blood vessels. If it remains untreated, high blood pressure can lead to a variety of serious health problems, including heart disease, stroke, and kidney failure.

Genetic profile

Studies suggest that some people with essential hypertension may inherit abnormalities of the sympathetic nervous system—the part of the nervous system that controls heart rate, blood pressure, and the diameter of blood vessels. It is estimated that the risk of developing essential hypertension is increased two- to fourfold if one or both parents are diagnosed with the disorder.

Researchers have identified the chromosomes (11 and 18) that house the genes responsible for blood pressure regulation, although narrowing down the range of specific genes involved in hypertension is more difficult.

Genes under intense study are those that regulate a group of hormones known as the angiotensin-renin-aldosterone system. This system influences all aspects of blood pressure control, including blood vessel contraction, sodium and water balance, and cell development in the heart.

When blood pressure drops, the kidneys release an enzyme called renin, which initiates a chain reaction to bring blood pressure back up. Renin acts on angiotensinogen (a plasma protein) to produce the hormone angiotensin I (an inactive form), which is then converted to angiotensin II (an active form of the hormone) by the angiotensin-converting enzyme (ACE). Angiotensin II then stimulates the adrenal glands to release the hormone

KEY TERMS

Angiotensinogen—A plasma globulin (protein) formed in the liver and directly involved in the regulation of blood pressure.

Diastolic blood pressure—Blood pressure measured when the heart is resting between beats.

Renin—An enzyme produced by the kidneys.

Sphygmomanometer—An inflatable cuff used to measure blood pressure.

Systolic blood pressure—Blood pressure measured when the heart contracts (beats).

Vasodilator—Any drug that relaxes blood vessel walls.

aldosterone, which decreases kidney sodium excretion, thereby causing blood vessels to constrict and resulting in fluid retention and an increase in blood pressure.

Researchers believe that this angiotensin-renin-aldosterone system evolved millions of years ago to protect humans. By retaining salt and water and narrowing blood vessels, the body was ensured an adequate blood flow and the ability to repair injured tissue. Over time, however, this system outlived its original protective function and led to serious health complications.

Demographics

It is estimated that one in three Americans have high blood pressure; it is also estimated that one in five people who have high blood pressure are unaware of the problem. Also, hypertension is much more common among Caucasians than among Hispanics. Low levels of nitric oxide, which has been observed in individuals—particularly African Americans—with elevated blood pressure may be an important factor in the development of essential hypertension.

The prevalence of essential hypertension increases with age until at least the age of 80. Statistics indicate that more than half of all Americans over the age of 65 have hypertension. In those under the age of 55, essential hypertension is more common in males than in females. Over age 75, the rate is higher for women (78%) than for men (67%).

Signs and symptoms

People with essential hypertension may go years without showing symptoms. For this reason, high blood pressure is often called the “silent killer.” The first

symptom may be a heart attack or stroke. However, many people with hypertension may experience one or more of the following symptoms:

- headache
- dizziness
- blurred vision
- irregular or rapid heartbeat
- nosebleeds
- fatigue

Diagnosis

Although genetic studies hold hope for detecting, evaluating, and treating hypertension in the future, there are no reliable genetic screening tests for the disorder. Thus, essential hypertension is a condition that cannot be diagnosed until it has developed; it is often diagnosed during a routine physical or medical examination.

Blood pressure is measured by an instrument called a sphygmomanometer. A cloth-covered rubber cuff is wrapped around the upper arm and inflated. When the cuff is inflated, an artery in the arm is squeezed to momentarily stop the flow of blood. Then the air is let out of the cuff while a stethoscope placed over the artery is used to detect the sound of the blood spurting back through the artery. This first sound is the systolic pressure. The last sound heard as the rest of the air is released is the diastolic pressure. Both sounds are recorded on the mercury gauge of the sphygmomanometer.

Because a number of factors such as pain, stress, or anxiety can cause a temporary increase in blood pressure, hypertension is not diagnosed on the basis of one elevated reading. Also, blood pressure results may be different depending on which arm is used. Thus, if a blood pressure reading is 140/90 or higher for the first time, the physician will have the individual return for another blood pressure check. Diagnosis of essential hypertension is usually made based on two or more readings after the first visit.

A typical physical examination to evaluate hypertension includes:

- medical and family history (especially important to determine a genetic contribution)
- physical examination
- examination of the blood vessels in the eye
- chest x-ray
- electrocardiograph (EKG)
- blood and urine tests

QUESTIONS TO ASK YOUR DOCTOR

- What blood pressure range is suggestive of hypertension in my child?
- How can we tell if his hypertension is a result of genetic or environmental factors?
- Are there treatments for hypertension caused by genetic factors and, if so, what are they?
- What steps can we take to help keep my child's blood pressure under control?

Treatment and management

There is no complete cure for essential hypertension because unlike secondary hypertension, there is no single cause of the problem; it is a complex disorder only determined in part by genes. Environmental (lifestyle) factors interact with genetic factors to produce hypertension.

Essential hypertension can be treated and managed effectively even if an individual has a genetic predisposition to the disorder. If essential hypertension is mildly or even moderately high, it may be possible to bring it down to a normal level without medication. Weight loss, changes in diet, and exercise may be the only treatment necessary. General nonpharmacologic recommendations include:

- reducing the amount of salt (sodium) and fat in the diet
- exercising regularly
- maintaining a healthy weight
- limiting alcohol and caffeine consumption
- quitting smoking
- reducing stress through stress management techniques, relaxation exercises, or counseling

If lifestyle changes are not effective in lowering blood pressure to a normal level, medication may be prescribed. There are many types of drugs available to treat essential hypertension. The main categories of drugs include:

- diuretics (help kidneys eliminate excess salt and water from the body's tissues and blood, thereby reducing swelling and lowering blood pressure)
- beta-blockers, alpha-blockers, and alpha/beta blockers (act on nervous system to slow heart rate and reduce the force of the heart's contractions)
- angiotensin-converting enzyme (ACE) inhibitors (block the production of substances that constrict blood vessels and reduce salt and water buildup in the tissues)

- calcium channel blockers (block the entry of calcium into muscle cells in artery walls, making arteries more relaxed)
- vasodilators (relax artery walls and lower blood pressure rapidly)
- peripheral-acting adrenergic antagonists (act off nervous system to relax arteries and reduce the force of the heart's contractions)
- centrally acting agonists (act on nervous system to relax arteries)

When a blood pressure medication is prescribed, it is important to:

- take the medication regularly, exactly as prescribed
- report any side effects immediately
- have regular follow-up visits with a physician

It may take weeks or even months to find the most effective pharmacologic treatment. Once an effective drug or combination of drugs is found, individuals with high blood pressure may require treatment for the rest of their lives.

Prognosis

The higher the blood pressure, the worse the prognosis generally is. However, most serious complications of essential hypertension can be delayed or even avoided by receiving regular blood pressure checks, and by treating the disorder as soon as it is diagnosed.

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American Heart Association, 7272 Greenville Ave., Dallas, TX 75231, (800) 242-8721, review.personal.info@heart.org, <http://www.heart.org/HEARTORG>

American Society of Hypertension (ASH), 45 Main St., Suite 712, Brooklyn, NY 11201, (212) 696-9099, ash@ash-us.org, <http://www.ash-us.org>

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Essential tremor

Definition

“Tremor” is derived from the Latin term meaning “to shake.” It is an involuntary rhythmic back-and-forth shaking of a part of the body, resulting from alternating or irregular contractions of muscles. Essential tremor (ET) is the most common movement disorder. It is a syndrome characterized by a slowly progressive tremor of certain body parts, most commonly the arms, hands, and head, when the respective body part is maintained in a constant position.

Description

James Parkinson in 1817 was the first to describe and differentiate ET from the tremor seen in Parkinson’s disease. ET is also called benign essential tremor or familial tremor. ET is called benign since it does not increase an individual’s risk of mortality, and it is called essential since the cause was initially unknown. Several gene mutations that cause ET have now been identified.

ET is caused by abnormal communication between certain areas of the brain, including the cerebellum, thalamus, and brain stem. In most cases, the tremor is mild and nonprogressive; however, a few people with ET have a slowly progressive form with the tremor eventually involving the voice box, tongue, legs, and trunk. ET can be quite disabling if the tremor is severe and widespread, and it can substantially affect a person’s quality of life.

Genetic profile

ET can occur either as a random form called sporadic or more commonly, as an autosomal dominant inheritance form with variable penetrance. In autosomal dominant inheritance, an individual only needs one mutated gene to develop the condition, and if the condition has variable penetrance, only some descendants may develop it.

Some cases of ET appear to be sporadic, but this could be due to the fact that in certain families all

individuals who inherit the gene do not show symptoms. In familial ET, 50% of patients develop symptoms by 40 years of age, while sporadic ET has a later age of onset.

Most studies indicate that 50%–70% of ET is familial. First-degree relatives are five times more likely to develop ET than a person without an affected relative. Children of affected individuals have a 50% risk of inheriting the gene, and expression of this is nearly complete by 70 years of age. It is unclear as of 2021 whether the symptoms of familial ET begin earlier with each successive generation, a process called anticipation.

Several susceptibility genes have been identified in ET. One is a familial essential tremor gene called *ETM1* or *FET1*, found on the long arm of chromosome 3. Another is *ETM2* on the short arm of chromosome 2. A third mutation in chromosome 4p may also cause postural tremor. A mutation of chromosome 6p23 has also been linked to a few cases of ET, as has a mutation in *LINGO1* (leucine-rich repeat and Ig-containing domain 1) variant rs9652490.

Demographics

ET is one of the most common neurologic movement disorders of adults. It affects about 10 million people in the United States alone, and it is more prevalent than Parkinson’s disease or Alzheimer’s disease. The incidence of ET has two distinct ages of onset: one occurs in individuals in their early 20s, and the second involves adults in their 60s. ET can occur in children, although onset is rare before age ten. There is no major ethnic or gender difference, although males tend to have more severe tremor in the arms or legs and females have more severe head tremor.

Signs and symptoms

Tremor is usually the only symptom seen in ET, although there is some data to suggest that additional symptoms may include changes in cognition, personality, mood, and hearing.

There are three types of tremor that can be observed in ET: postural tremor, kinetic tremor, and internal tremor. The most common tremor of ET is a postural tremor, seen when the patient is voluntarily maintaining a fixed antigravity position of a limb or holding outstretched hands. This resembles a physiologic tremor that is present in everyone but is more severe in an affected individual. Postural tremor usually begins in both hands simultaneously, but 10%–15% of patients notice tremor onset in the dominant hand. Tremor usually moves from the hands to the arms over time. Initially the tremor may be noticeable only during periods of fatigue or anxiety,

but it becomes more constant over time. The severity of tremor varies considerably even from day to day. Tremor worsens with emotion, cold, hunger, and fatigue and tends to increase with age. It can range from being mild and a minor annoyance in one individual to severe and disabling in another family member.

Some patients have worsening of tremor while performing goal-directed tasks, such as writing, buttoning a shirt, or drinking from a cup. This is called intention or kinetic tremor. This type of tremor is worse than a positional tremor and is the major cause of disability.

The third type of tremor is internal tremor, which is a feeling of general shakiness or a sensation of vibration inside the body.

In about 30% of patients, the tremor involves the head region. Head tremor (titubation) is the second most common body part to be affected and can occur either in isolation or with hand tremors. Head tremor is in mostly a horizontal sideways pattern, as if indicating no. Voice and tongue tremor causes dysarthria (difficulty in articulating words) and quavering or shaky speech, and it is usually seen with advancing age above 65. Tremor generally disappears during sleep and is minimal during periods of rest.

Memory, intellect, strength, and muscle tone remain intact. Some associated symptoms like ataxia (unsteady and uncoordinated gait) and dystonia (repetitive movements and abnormal postures) can also be seen.

Diagnosis

Although ET is a common condition seen in general medical practice, diagnosis may be difficult and treatment challenging. It is best diagnosed and treated by a neurologist or a physician trained in movement disorders. No biomarkers, blood tests, or imaging tools are available to assist in diagnosis. Thyroid disease, excess caffeine consumption, and medication side effects should be excluded, as these can mimic ET. Magnetic resonance imaging scans are used only to exclude other causes of tremor, such as multiple sclerosis.

Diagnosis is mainly clinical and depends on recognizing the postural tremor, absence of rest tremor that is seen in Parkinson's disease, presence of tremor for more than three years, a decrease in tremor with alcohol consumption, and a family history of similar tremor. Clinical tremor questionnaires and rating scales can be helpful in the diagnosis and in assessing response to treatment. During the neurological assessment, the physician may use simple tests like spiral or line drawing, handwriting, tasks such as taking a water-filled cup to the mouth, articulating vowels, and so on, to determine the extent and

severity of ET. An accelerometer is a simple device attached to the fingers that measures tremor frequency.

Exclusion criteria for ET include the following symptoms:

- prominent dystonia
- known causes of enhanced physiologic tremor
- psychogenic origin of primary orthostatic tremor
- isolated voice tremor
- isolated position or task-specific tremor
- isolated tongue or chin tremor
- isolated leg tremor

Treatment and management

Treatment is based on how disabling the symptoms are to the patient, since early treatment has not been shown to stop or delay the disease progression. There is a 50% chance that the tremor will respond to currently available medications without undue side effects. Sometimes trials with multiple medications may have to be done before the tremor responds. Depending on coexisting medical conditions and neurological diseases, treatment must be individualized.

Lifestyle changes, including elimination of caffeinated foods like sodas, coffee, and chocolates, and other stimulants like cigarettes, are the first step in treatment. Biofeedback, acupuncture, yoga, tai-chi, and guided imagery are techniques that can be used in patients in whom the tremor worsens with stress and anxiety. In 50% of patients, alcohol may reduce tremor for up to two hours, but this is not to be considered therapy. Excessive alcohol consumption can worsen tremor as a rebound phenomenon.

Adaptive devices like wrist weights and plate guards can help to minimize tremor and interference with daily activities. Specially designed utensils (such as rocker knives and utensils with large handles) and electrical appliances (such as can openers and toothbrushes) can make daily activities easier. Certain simple precautions can enable many people to continue their normal daily activities. For example, objects should be grasped firmly but comfortably and held close to the body. Cylinders of foam can be placed around handles to make them easier to hold. Other helpful measures include using straws, button hooks, Velcro fasteners, zipper pulls, and shoe horns. Counseling may be needed to help patients deal with social isolation resulting from severe tremor.

The most commonly used medication to treat ET is propranolol, which is a beta-blocker. It prevents the action of adrenaline and reduces tremor amplitude. It is available in a short- and long-acting form. The effect of

KEY TERMS

Acupuncture—An alternative health procedure based on ancient Chinese methods, involving insertion of thin needles at specific pressure points in the body.

Alzheimer's disease—A neurodegenerative disease marked by the loss of cognitive ability, generally over a period of 10–15 years, associated with the development of abnormal tissues and protein deposits in the brain.

Anticipation—The apparent tendency of certain diseases to appear at earlier ages and with increasing severity in successive generations.

Ataxia—A condition of bodily incoordination and unsteadiness that is most often caused by disease activity in the cerebellum.

Autosomal dominant—A type of genetic inheritance in which a trait (or a disease) is produced even when only one copy of an abnormal gene is present.

Biofeedback—A technique in which patients are trained to gain some voluntary control over certain physiological conditions, such as blood pressure and muscle tension, and to promote relaxation.

Cerebellum—The lower back part of the brain responsible for functions such as maintaining balance and coordinating and controlling voluntary muscle movement.

Computed tomography (CT)—A special radiographic technique to visualize internal organs using a computer to combine multiple x-ray images into a two-dimensional cross-sectional image.

Dysarthria—Refers to a group of speech disorders caused by disturbances in the strength or coordination of the muscles of the speech mechanism as a result of damage to the brain or nerves.

Dystonia—A movement disorder involving prolonged muscle contractions that cause twisting and repetitive movements or abnormal posture.

Functional magnetic resonance imaging (fMRI)—A form of imaging of the brain that registers blood flow to functioning areas of the brain.

Gamma amino butyric acid (GABA)—An amino acid that functions as the major inhibitory neurotransmitter in the nervous system.

Gamma knife—Equipment that precisely delivers a concentrated dose of radiation to a predetermined target using gamma rays.

Globus pallidus—A small paired structure present in the deep portion of the brain in front of the brain stem that is considered a part of the basal ganglia and helps in movement control.

Inferior olivary nucleus—A small collection of cells seen in the lower part of the brain stem, which has connections to the cerebellum and is involved in control of movements.

Magnetic resonance imaging (MRI)—An imaging technique that uses the properties of magnetism to create nondestructive, three-dimensional, internal images of the soft tissues of the body, including the brain, spinal cord, and muscle.

Multiple sclerosis—A progressive autoimmune disease in which the body attacks its own central nervous system, gradually destroying the white fatty substance that surrounds nerve fibers, thereby damaging sites in the brain and spinal cord.

Orthostatic—Posture that is maintained while standing.

Parkinson's disease—A progressive disease occurring most often after the age of 50, associated with the destruction of brain cells that produce dopamine and characterized by tremor, slowing of movement, and gait difficulty.

Penetrance—The extent to which a disease expresses itself in individuals that have the mutation; for example, if all individuals with the abnormal gene exhibit the disease, the disease is said to have complete penetrance.

Positron emission tomography (PET)—A form of nuclear medicine scanning that measures brain activity using low doses of a radioactive substance.

Red nucleus—A small structure present in the brain stem that is involved in the control of movement.

Sporadic—Disease that is apparently not hereditary.

Tai-chi—A Chinese system of physical exercises that uses slow, smooth body movements to help with posture control and relaxation.

Thalamus—A pair of large egg-shaped structures near the brain stem that act as the main sensory relay station and help with control of movement.

Titubation—Tremor of the head.

Yoga—An exercise that combines relaxation and breathing techniques to combat stress and help circulation and movement of the joints; yoga has its origin in ancient Indian medicine.

QUESTIONS TO ASK YOUR DOCTOR

- What is the long-term effect of essential tremor?
- What special care does a person with essential tremor require?
- What other healthcare professionals should I consult?
- Are there organizations or support groups where I can talk to other people who have essential tremor?
- Do you have information I can take home?

the short-acting form lasts for three to four hours and is suitable for taking prior to a specific task, such as giving a speech or attending a social gathering. It is rare for the tremor to completely disappear with treatment, but about 60% of patients respond to it. The medication works best for hand tremor. Side effects include lowering of blood pressure and heart rate, aggravation of asthma, depression, fatigue, and impotence. Primidone is a barbiturate and is the second most commonly used medication. It was originally developed as an antiseizure medication and is taken once a day at night in order to minimize the side effects of drowsiness and fatigue. It can be used for long periods of time with minimal side effects. Other medication treatments include gabapentin and benzodiazepines like diazepam and clonazepam. A combination of propranolol and primidone can be used in resistant cases. Newer therapeutic approaches include botulinum toxin injection into the muscles, such as neck muscles, to treat head tremor. Transient weakness may be experienced, but the therapeutic effect lasts for three to six months.

Invasive surgical intervention is usually reserved for patients with severe disabling unilateral tremor, bilateral tremor, head and voice tremor, functional disability that interferes with the activities of daily living, or tremor that is unresponsive to the highest tolerated doses of medications.

The thalamus is a paired structure deep inside the brain. It is intimately involved in movement regulation. In thalamotomy, a small pea-sized hole is made in the thalamus on the side opposite to the tremor to disrupt faulty circuits. Because the thalamus is close to vital brain stem structures, the surgery has to be done only by an experienced neurosurgeon. Postoperatively, some temporary side effects like confusion, weakness, and speech difficulty may occur. Bilateral thalamotomy is not advised, as it may cause loss of speech and other

permanent neurologic problems. Thalamotomy is especially helpful in patients with severe unilateral hand, arm, and leg tremor and is effective in up to 80% of patients. In a similar method using gamma knife, a small burn is made in the thalamus without a hole or operation being necessary.

Thalamic stimulation, or deep brain stimulation (DBS), is an alternative to thalamotomy. DBS involves implanting an electrode (a fine wire) deep in the center of the thalamus. The electrode is connected to a stimulation device (implantation pulse generator) similar to a pacemaker that is placed under the skin below the collarbone. By sending painless, high-frequency electrical currents through the electrode, it interrupts communication between tremor cells and helps the thalamus rebalance the tremor control messages. Patients may turn the pulse generator on and off by passing a hand-held magnet over the device. The batteries that power the pulse generator need to be surgically replaced every three to five years. Tremor reduction occurs within seconds of activation and can be quite dramatic. Significant or complete tremor reduction occurs in approximately 80% of people with this procedure, and efficacy has continued for six to seven years. The main advantages of this procedure are that implantation on both sides of the brain is possible, the device can be adjusted for optimal effect, and the device may be removed if desired. Other potential targets for DBS in ET include globus pallidus and subthalamic nucleus.

Prognosis

ET does not increase a person's risk of mortality, but it can result in varying levels of functional difficulty and disability depending on how severe the tremor is. With advancing age, the amplitude of the tremor worsens, and it is this feature that results in major disability. The patient with ET is disabled either due to physical limitations or from the resulting social embarrassment, which can lead to social withdrawal and depression. Everyday tasks that need fine motor skills and manipulation become difficult, such as writing, using utensils, drinking from a glass, or applying makeup. Patients may opt for early retirement or change jobs due to the severity of tremor.

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International Essential Tremor Foundation, PO Box 14005, Lenexa, KS 66285-4005, (888) 387-3667, (913) 341-1296, info@essentialtremor.org, <http://www.essentialtremor.org>

National Institutes of Health/National Institute of Neurological Disorders and Stroke Brain Resources and Information Network, PO Box 5801, Bethesda, MD 20824, (800) 352-9424 or (301) 496-5751, <http://www.ninds.nih.gov>

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Ex vivo lentiviral gene therapies

Definition

Ex vivo lentiviral gene therapy is a method of inserting, modifying, or removing bits of genetic material in an organism by using a virus from the lentiviral family. Ex vivo means that the genetic material is added to cells outside of the body and then introduced back into the body. Lentiviruses infect an organism by inserting DNA into the host cell's DNA. Ex vivo lentiviral gene therapy is often used to treat a disease by correcting problems in the genome.

Description**History**

The idea of gene therapy was first introduced in the late 1970s, but it was not until 1990 that the first successful human gene therapy trial occurred. A four-year-old girl named Ashanthi DeSilva was treated for adenosine deaminase deficiency (ADA). ADA is a severe and rare genetic disease that makes the immune

system unable to fight off infections from bacteria and viruses. This condition is often lethal, and patients need to largely stay at home because of their increased risk of infection.

Ashanthi had a variant in each copy of the gene that produces the protein adenosine deaminase. As a result, her body could not produce adenosine deaminase, which is required for a normally functioning immune system. During the procedure, some of Ashanthi's cells were removed. A virus called an adenovirus was used to insert a normal copy of the gene that produces adenosine deaminase into these cells. The cells containing the normal gene were then transfused back into her body.

The gene therapy was very successful and had no significant side effects. Ashanthi has since married and works to help other people with genetic conditions. This therapy was groundbreaking and led to the birth of a new field.

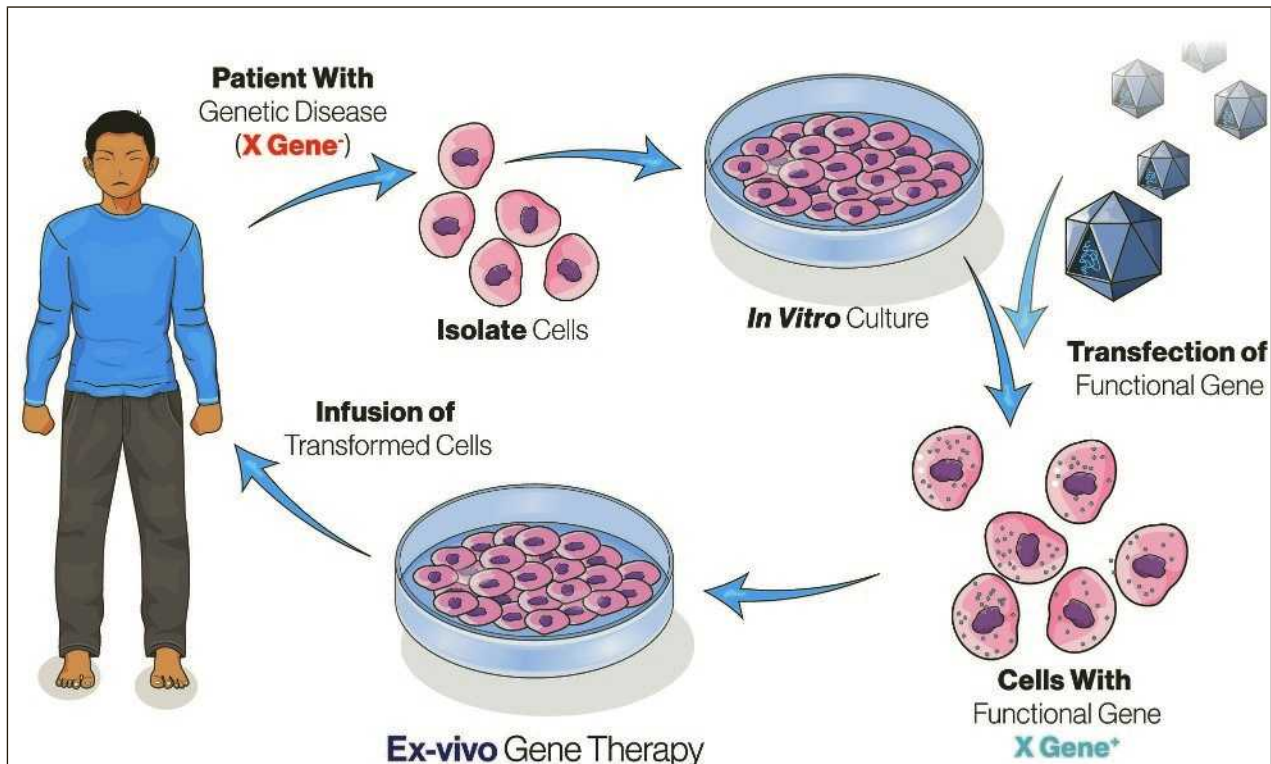
Unfortunately, there were problems with later clinical trials. Five of twenty participants with a similar immune deficiency disease who underwent gene therapy developed cancer. The virus that delivered the normal gene to the participants' cells turned on a cancer-causing gene. In 1999, during another trial using an adenovirus, a participant who was being treated for another disease died from an immune reaction. These trials resulted in a pause of gene therapy clinical trials for about ten years.

Gene therapy gradually rebounded, and in 2003, China became the first nation to approve it for clinical use as treatment for head and neck cancer. In 2017, the FDA approved two gene therapies in the United States. Since then, gene therapy has experienced a boom, and the FDA expects to approve 10 to 20 gene therapies every year by 2025.

In 2021, a gene therapy trial using a lentiviral by Bluebird Bio was halted because two patients developed cancer. It is not yet known whether the therapy itself caused the cancer.

Lentiviral and other viral vectors

One key requirement for gene therapy is a vehicle that can deliver the genetic material to the target cells. These vehicles, also called vectors, can be viruses or non-viral. The first vector used was an adenovirus. This virus was first isolated from human tissue in 1953. Usually, this virus does not cause serious symptoms in healthy people, but it can cause serious symptoms in people who have weak immune systems. The advantage of the adenovirus is that it does not integrate into the host's DNA, which can sometimes cause problems.



Ex vivo gene therapy. (Shutterstock/Art of Science)

In 1996, lentivirus vectors based on the HIV virus were developed for use in gene therapy. Lentiviruses are retroviruses. Retroviruses make a DNA copy of their RNA and insert it into the cells of their hosts. Lentivirus vectors are used in both gene therapy and cellular therapy. Cellular therapy involves transferring whole cells into a host. Lentiviruses vectors used in gene therapy are designed so that the virus does not replicate and cause an infection.

Use of lentiviral vectors

Gene therapy was initially designed to treat diseases that are caused by a variant in a single gene, like cystic fibrosis. It is now being investigated as treatment for cancers, autoimmune diseases like arthritis, and infectious diseases.

Gene therapy can be somatic or germline. Somatic gene therapy involves adding, removing, or changing the genetic material in tissue or cells, which results in the production of a naturally occurring protein that is lacking or not functioning correctly in an individual patient. Germline gene therapy adds, removes, or changes the genetic material in reproductive cells, or embryos, to correct genetic defects that could be passed on to future generations. Germline gene therapy is currently prohibited in the United States.

Gene therapy using lentivirus vectors has been used in clinical trials to treat immune diseases, inherited genetic diseases, and cancer. For example, lentiviral vectors have been used to change cells so that they are more receptive to cancer chemotherapies. The first cellular therapy using a lentivirus vector was approved in 2017 for the treatment of leukemia.

Lentiviral vectors have also been used to transport tools for editing genes, such as in CRISPR/Cas, which is a tool derived from the immune system of bacteria that can be used in gene therapy. CRISPR/Cas can be used to change an organism's DNA by making a cut in the DNA at a specific location and tricking the body's DNA repair mechanism to make the desired change.

These vectors have also been used in research to change the amount or stop the production of protein produced by a gene. This can be used to help study the function of different genes. In the future, it may also be used to treat disease.

Lentiviral vectors which do not integrate into the host genome (NILVs) are being researched. Research has been done on the use of NILVs in vaccines against infectious diseases and cancer. They have been successful in trials performed on animals. Further research needs to be done to see whether they will work safely on humans.

KEY TERMS

Cell—A building block that provides structure to the body and performs all of its functions. Cells contain genetic information and can copy themselves. The four main types of cells are: skin, nerve, muscle and connective tissue.

DNA (deoxyribonucleic acid)—The genetic material that contains the instructions for creating proteins.

Ex vivo—Referring to a procedure that takes place outside a living organism.

Gene—A sequence of bases in a DNA sequence that contains the instructions for a protein.

Genome—The complete set of genetic instructions of an organism.

Host—The body that the virus vector is infecting.

In vivo—Referring to a procedure that takes place within a living organism.

Pathogenic variant (mutation)—Any change in the sequence of a genome that causes disease.

Protein—Responsible for the structure and all of the functions of the body and cells.

RNA (ribonucleic acid)—The genetic material that is involved in creating proteins.

Tissue—Made up of cells that have a common function. The four types of tissue are: connective, epithelial (skin), muscle, and nervous tissue.

Variant—Change in the sequence of a genome.

Vector—A viral or non-viral vehicle that delivers the genetic material.

Advantages of lentiviral vectors

There are many advantages for using lentivirus vectors in gene therapy, including:

- They can provide long-term treatment.
- They can insert large genes into the DNA of the host.
- It is relatively easy to grow large amounts of the virus.
- They are effective in infecting the host.
- They can even be used for cells that are not dividing like nerve cells.
- Lentiviral vectors can fix more than one gene at a time.
- They can be used for gene therapy that directly injects the viral vector into a living organism.

QUESTIONS TO ASK YOUR DOCTOR

- Would gene therapy help my condition?
- Are there any gene therapies available that my child would qualify for?
- What risks can I expect with this type of gene therapy?

Disadvantages of lentiviral vectors

Although there are advantages to using lentiviral vectors, there are also many safety issues associated with the use of viral vectors. One of the biggest potential problems is that the lentivirus might insert DNA into other unintended region of the host's DNA which can cause problems. For example, it could insert DNA into a cancer-causing gene, resulting in a mutation and an increased risk of cancer. In some cases, it could result in mutations that can get passed down to future generations. Lentiviral vectors are a little less likely than other retrovirus vectors to cause unintended mutations.

Some other potential problems with lentiviral vectors are:

- Lentivirus vectors that can cause an infection of the host might mistakenly be used.
- The lentivirus vector could become activated by another virus infecting the cell and become infectious.
- They can create molecules that can be toxic to the cell.
- Infected patients could pass on a new and infectious virus to people around them.

Researchers need to consider these risks when developing clinical trials using lentivirus vectors. They need to ensure that they are not using vectors that can cause an infection in the host. They also need to ensure that the vector that they are using has a low risk of causing unintended mutations.

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National Human Genome Research Institute. Communications and Public Liaison Branch, National Human Genome Research Institute, National Institutes of Health, Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, (301) 402-2218, <http://www.genome.gov>

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Exome sequencing

Definition

Exome sequencing (ES) is a technique developed since 2007 for identifying or determining the exact order of all the portions of the genes in an organism's genome that code for proteins. These gene portions are called exons, and the total of all the exons in a genome is called the exome. The human exome accounts for 180,000 exons, or 1%–2% of all the DNA in an individual human's genome—about 30 million base pairs. The word *exon* was formed from "EXpress" and "regiON," because the exon is the region of the gene expressed in the protein produced by the gene. Exome sequencing is also called whole-exome sequencing, abbreviated WES.

In most DNA sequences, the exons are separated by noncoding portions of the gene called introns. The word *intron* is derived from "INTragenic" and "regiON," because the introns are located inside the gene (intra-genic) between the exons. Prior to the process of amino acid transcription, the introns are spliced out of

messenger RNA, leaving only the exons to transcribe the final gene product.

Description

ES (or WES, for whole-exome sequencing) is a relatively new technique for identifying the protein-coding portions of an individual's genome. It is one of several innovations in DNA sequencing that were developed shortly after 2005, when so-called next-generation sequencing—variously called high-throughput sequencing, massively parallel sequencing, and shotgun sequencing—technology was introduced. Next-generation sequencing was the first major breakthrough in sequencing DNA since the development of the Sanger method in 1977 by Frederick Sanger in the United Kingdom. The Sanger method was time-consuming, expensive, and limited to sections of DNA that were only about 1,000 base pairs (bp) in length. As a result, using the Sanger sequencing method—which was state of the art in 1990—means that the Human Genome Project required 13 years to complete its sequencing of a human genome, and the task had to be divided among several different research centers.

Next-generation sequencing is both faster and less expensive than the original Sanger method, as it can sequence many strands of DNA at the same time and also sequence longer sections of DNA than the Sanger method allowed. The phrase "shotgun sequencing" refers to the fact that next-generation sequencing methods break up, or shear, an organism's entire genome into many small fragments, similar to the effect of a shotgun blast. The fragments are sequenced individually, then read by a computer that identifies overlapping segments in the fragments and uses these overlaps to place them in the correct order to reconstruct the full genome.

Exome sequencing begins with shotgun shearing of a genome, followed by one of several so-called target-enrichment strategies to identify the exons in the genome and separate them from the noncoding regions. This step is called targeted capture. Several different biotech companies offer kits containing the reagents needed to capture the exons as well as the equipment to interpret the results. After the exons have been captured, the exome is sequenced. It can then be analyzed to identify disease-causing mutations that underlie rare Mendelian diseases.

Purpose

Exome sequencing has been used since 2008 to identify genetic variants that cause rare single-gene diseases. In 2009 the method proved successful in identifying a mutation in a known gene, the *MYH3* gene, as the cause of Freeman-Sheldon syndrome (FSS). In 2010, exome sequencing was used to identify a previously unknown gene on the long arm of chromosome 16, *DHODH*, as

KEY TERMS

Allele—One of several alternative versions of a gene or genetic locus.

Base pair (bp)—Any of the complementary nucleotide bases (adenine-thymine and cytosine-guanine in DNA; adenine-uracil and cytosine-guanine in RNA) held together by weak hydrogen bonds. Base pairs form links between the two strands of DNA.

Bioinformatics—An interdisciplinary scientific field that combines statistics, engineering, mathematics, and computer science to capture and understand biological data.

De novo mutation—A genetic variant that occurs in a child but is not present in either parent.

Exome—The part of a genome formed by all its exons.

Exon—The DNA sequence of a gene that codes for a protein.

Genome—The complete genetic material of an organism.

Genome-wide association study (GWAS)—A method for identifying genes involved in human disease by searching a number of human genomes for small variations that occur more commonly in people with a given disease than in those who do not have the disease.

Genomics—A subspecialty of genetics that focuses on the study of the genome.

Intron—Any of the portions of a gene that does not code for amino acids.

Mendelian disease—Any genetic disease that is caused by a single gene and follows the basic Mendelian patterns of inheritance.

Next-generation sequencing—A general term for massively parallel sequencing of large portions of DNA base pairs, performed by first fragmenting the DNA, reading the individual fragments in parallel, and then reassembling the reads to obtain the sequence of the entire genome.

Nucleotide—A building block of a nucleic acid (DNA or RNA), consisting of a sugar molecule, a phosphate

group, and one of the nitrogen-containing bases (adenine, cytosine, guanine, and thymine in DNA; adenine, cytosine, guanine, and uracil in RNA).

Phenotype—The physical appearance and biochemical characteristics of an organism resulting from the interactions between its genotype (genetic makeup) and the environment.

Proband—In genetics, a particular subject (person or animal) being reported on or studied. In most cases, the proband is the first affected member of a family with a genetic disorder who brings the condition to the attention of doctors and researchers.

Sanger sequencing—The earliest method for sequencing DNA, devised by Frederick Sanger in the United Kingdom in 1977 and used as the primary method of sequencing until 2002. It is still used to validate the results of so-called next-generation sequencing. The Sanger method involves first separating the two strands of DNA and then adding chemically altered forms of the adenine, cytosine, guanine, and thymine bases. The altered bases stop the process of DNA replication as they are added to the strand of DNA, resulting in a series of short pieces of DNA. These short pieces are placed in order from shortest to longest in order to read the entire original sequence of DNA.

Structural variations—Variations in the structure of an organism's chromosome that are larger than single-nucleotide polymorphisms but smaller than a chromosome abnormality. Structural variations can include deletions, duplications, and insertions as well as copy number variations. Many structural variations are linked to genetic diseases but many more are not.

Throughput—In general, the rate at which data can be processed, or the work that a computer can do in a specific period of time. High-throughput sequencing refers to any of a set of technologies that can produce large numbers of DNA sequences concurrently.

the cause of Miller syndrome, an extremely rare genetic disorder characterized by multiple facial malformations. In addition to identifying genes associated with known single-gene disorders, exome sequencing has also been found helpful in identifying *de novo* mutations, particularly in multiple malformation syndromes and mental retardation.

Exome sequencing has several advantages over older methods of identifying disease-causing alleles for rare disorders. Genome-wide association studies (GWAS), which are used to identify genetic variations across a large number of different human genomes, are useful in identifying genetic markers of common diseases like asthma, type 2 diabetes, or heart disease, but are not

QUESTIONS TO ASK YOUR DOCTOR

- Given my personal and family history, would you recommend exome sequencing for me?
- What is your opinion of direct-to-consumer exome sequencing?
- Do you think exome sequencing will continue to be used in research and clinical practice, or do you think it will become obsolete as whole-genome sequencing continues to drop in price?

useful in identifying the mutations that cause rare disorders. The scanning of a large number of different genomes that is used in GWAS is not helpful in studying rare disorders because these disorders have few affected families with probands who can be studied. In addition, many of these rare disorders affect the ability of probands (the initial individuals identified as having the disorder) to reproduce, which increases the difficulty of studying inheritance patterns in these disorders.

Second, whole-exome sequencing is an efficient method for looking for disease-causing mutations because it targets the protein-coding region of the genome. The exome is thought to account for 85% of disease-causing mutations, as most genetic disorders result from defective proteins. By contrast, the noncoding portions of genes have relatively minor effects on human phenotypes (the externally observable characteristics of an individual that result from the interactions between the organism's genetic makeup and its environment). The exome thus represents the portion of the genome that contains genetic variants with large effects on health. Exome sequencing of a small number of individuals affected by a rare genetic disorder but unrelated to one another thus facilitates the identification of the gene that causes the disorder.

A third consideration that favors exome sequencing is its lower cost. While next-generation sequencing makes it possible to sequence an entire individual human genome (called whole-genome sequencing or WGS) in a reasonable amount of time (days to weeks, as compared to the 13 years that the Human Genome Project required to sequence the first complete human genome), WGS is about five or six times as expensive as whole-exome sequencing or WES. Although the cost of WGS continues to decline as the power of computers increases, sequencing a complete human genome cost about \$6,000 as of April 2015, according to the National Human Genome Research Institute. According to the Broad Institute in Cambridge, Massachusetts, whole-exome sequencing

can be performed for about \$1,000. The lower cost of WES as well as its focus on the protein-coding regions of the genome makes it a practical approach to identifying disease-causing mutations associated with monogenic disorders.

Limitations

Whole-exome sequencing has several limitations as well as advantages. First, the phrase “whole-exome” is a bit of a misnomer because even the most accurate targeted capture methods as of 2015 missed between 3% and 5% of the exons in an exome. If a suspected disease-causing mutation is thought to be in the missing section of the exome, it must be identified by another method, most often polymerase chain reaction, although whole-genome sequencing can also be used. Second, not all protein-coding sections of the human genome have yet been identified, thus current exome sequencing can target only known exons. Third, exome sequencing will not detect harmful mutations in noncoding sections of the genome that are known to be associated with certain genetic disorders. These noncoding sections include structural variations in chromosomes and microRNA molecules.

Fourth, whole-exome sequencing identifies a large number of single-nucleotide variations (SNVs) of unknown significance as well as potentially disease-causing mutations. The number of such variations ranges from about 24,000 in African American samples to 20,000 in Caucasian Americans. Although there are several strategies for filtering out the nonproblematic variations, there are usually several hundred SNVs remaining that require sorting and analysis by genetics professionals. A related problem is the discovery of what are called off-target mutations (sometimes called secondary or incidental findings) during whole-exome sequencing. An off-target mutation is one that is not relevant to the condition for which the test was ordered but indicates the likelihood of future disease in the person being tested. An example would be the discovery of a mutation in one of the genes linked to breast cancer—an adult-onset disorder—in a small child being tested for mutations related to vision disorders.

The present limitations of WES have led to a debate in the field of genomics as of 2015 regarding the future utility of exome sequencing. Some researchers predicted that WES would have a limited “shelf life” and would be replaced entirely by WGS as the cost of whole-genome sequencing continues to drop. Others maintained that the shorter time frame required to perform WES (1/15 the time required to sequence an entire human genome) and the smaller amount of data requiring storage

(1/15 the volume required for WGS) would guarantee an ongoing place for whole-exome sequencing.

Applications

As of 2015, WES was used in both genetic research and clinical diagnosis.

Research

Since the earliest discoveries of disease-causing mutations in 2009, exome sequencing has been used in research to study subjects other than disease-causing mutations in humans. These other fields include the need to identify disease-causing mutations in non-human primates, including rhesus monkeys and chimpanzees; to obtain new insights into the process of human evolution; and to study population genetics (the study of changes in allele frequency and distribution within a specific population). The interpretation of these findings requires collaboration from specialists in many disciplines, including experts in the field of bioinformatics as well as geneticists, biologists, anthropologists, and epidemiologists.

Clinical medicine

Exome sequencing has been used for clinical diagnostic purposes since 2009. In 2009 a group of clinicians at Yale discovered that a 10-year-old boy initially thought to have Bartter syndrome, a rare kidney disorder characterized by low levels of potassium in the blood, actually had congenital chloride diarrhea (CCD), a condition caused by a previously unknown mutation in the *SLC26A3* gene. Since 2009, new causative genes for at least 150 inheritable disorders have been identified using either whole-exome or whole-genome sequencing.

The rapid pace of these new discoveries has led to a set of new ethical as well as practical concerns for high-quality patient care as well as the most effective use of advanced technologies. In 2012 the American College of Medical Genetics and Genomics (ACMG) drew up a policy statement regarding the clinical applications of whole-exome and whole-genome sequencing. Their first recommendation concerned the indications for WES and WGS in clinical diagnostic assessment. The ACMG recommended WES or WGS in the following situations:

- The patient's phenotype or family history suggests a genetic cause, but the patient's phenotype does not resemble that of a genetic disorder for which a clinical single-gene test currently exists.
- The patient has a genetic disorder with a high degree of genetic heterogeneity, making WES or WGS a more practical approach because both methods can analyze a number of different genes simultaneously.

- The patient is likely to have a genetic disorder, but the tests presently available for that disorder have failed to obtain a diagnosis.

The ACMG also recommended pretest genetic counseling regarding the expected outcomes; the likelihood of and reporting of off-target or secondary findings; and discussion of which results will or will not be disclosed to the patient. In addition, the ACMG recommended obtaining informed consent from the patient for the use of findings of unknown significance that might be a subject for future research. Ongoing questions related to both WES and WGS include issues of permanent versus temporary data storage; patient confidentiality; obtaining informed consent from children and adolescent patients; and disclosure to insurance companies.

Direct-to-consumer exome sequencing

Various companies based in the United States and China began offering direct-to-consumer (DTC) exome sequencing tests as early as 2011. Although private individuals have been able to purchase WGS for several years from such companies as Illumina, the whole-genome tests cost several thousand dollars and were marketed primarily to researchers. In 2011, a company called 23andMe offered a whole-exome sequencing test for \$999 but was forced to drop the health-related results formerly sent to customers when the Food and Drug Administration ordered the company to discontinue its personal genome service. Another company, Gene by Gene, which is based in Houston, offers WES for about \$895, while Beijing Genomic Institute (BGI) in China offers WES for about \$500.

Genetics professionals are concerned about the trend toward DTC exome sequencing, as it has already led to anxious consumers consulting genetic counselors on their own. As whole-exome sequencing yields large amounts of complex data that are time-consuming to interpret, DTC marketing of WES is presently more likely to confuse and worry consumers than to help them.

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American College of Medical Genetics and Genomics (ACMG), 7220 Wisconsin Ave., Suite 300, Bethesda, MD 20814, (301) 718-9603, (301) 718-9604, acmg@acmg.net, <http://www.acmg.net>

National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Dr., MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, (301) 402-2218, <http://www.genome.gov><http://www.genome.gov/10005049>

NIH Intramural Sequencing Center (NISC), 5625 Fishers Lane, RM 5N-01, MSC9400, Bethesda, MD 20892-9400, (301) 451-0282, nisc@nhgri.nih.gov, <http://www.nisc.nih.gov>

Office of Public Health Genomics, Centers for Disease Control and Prevention, 1600 Clifton Rd., NE, MS E61, Atlanta, GA 30333, (404) 498-0001, genetics@cdc.gov, <http://www.cdc.gov/genomics/default.htm>

Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS), 6701 Democracy Blvd., Suite 1001, MSC 4874, Bethesda, MD 20892, (301) 402-4336, (301) 480-9655, ordr@nih.gov, <https://rarediseases.info.nih.gov>

Rebecca J. Frey, PhD

Expanded carrier screening (ECS)

Definition

Expanded carrier screening (ECS) refers to tests designed to determine whether someone is a carrier for one or more genetic conditions and at risk for having a child with a genetic condition or disorder. ECS tests for many genetic conditions at the same time. It is typically used to screen couples without a personal or family history of a genetic condition. It can be done before or during pregnancy.

Description

The goal of carrier screening is to identify people at increased risk for having a child with a genetic condition or disorder. About 2% to 4% of couples are at risk for having a child with a condition or disorder that can be detected through ECS. If the parents are found to be carriers, then testing needs to be done on the fetus to see whether the fetus has inherited the condition.

Historically, carrier screening was only offered to parents who were thought to be at a higher risk for having

a child with a genetic condition; that is, parents with a personal or family history of a genetic disease or those with an ancestry that put them at higher risk. For example, people of Mediterranean background might be offered β -thalassemia carrier screening, and those with Ashkenazic Jewish heritage might be offered Tay-Sachs screening. Carrier screening also tested only at-risk parents for one or a few genetic conditions, which is called targeted carrier testing.

Targeted carrier testing misses many couples who are carriers since most do not have a family or personal history of a genetic condition. Also, most do not fall into an at-risk category based on ancestry, or it is difficult to determine their ancestry.

Testing the general population for multiple genetic conditions at one time became feasible with the discovery of new technologies and decreased costs. The decrease in costs and desire of healthcare providers to offer more equitable carrier screening to the general population prompted the development of the first ECS tests in 2009.

ECS is not recommended for families that have a family history of a particular genetic disease. In these cases, targeted carrier testing for the specific disorder is preferable. Targeted carrier testing can test for a greater range of variations for a particular disorder than ECS can.

Types of conditions ECS identifies

Most ECS panels test between 100 and 300 genetic conditions. About 30% to 40% of people who are tested are found to be carriers. Around 1% to 3% of couples who do ECS are found to be at risk for having an affected child. ECS tests typically determine whether someone is a carrier for one or more autosomal recessive and X-linked genetic conditions.

A person who has an autosomal recessive condition has a pathogenic (disease causing) variant (mutation) in both copies of a gene that causes this condition. This gene is found on one of the 22 non-sex chromosomes. The person's parents are each carriers of one variant. A carrier for an autosomal recessive genetic disease has a pathogenic variant in one copy of a gene and one functioning copy of that same gene. Carriers often do not have symptoms because they have one functioning copy of the gene. Two carriers of an autosomal recessive condition have a one in four or 25% chance of passing it on to their children.

An X-linked condition results from a pathogenic variant on a gene on the X chromosome. Females have two X chromosomes, and males have an X and Y chromosome. These are called the sex chromosomes. Females get one X chromosome from their mother and one from their father. Males get one X chromosome from their

KEY TERMS

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a nonsex chromosome is required for a disease or inherited trait to develop in an individual.

Autosomal recessive—A pattern of inheritance in which both copies of a defective gene on a nonsex chromosome are required for a genetic disorder to manifest in a person.

Carrier—Person who has a pathogenic variant (mutation) in one copy of a gene. Carriers often do not have symptoms. Two carriers of an autosomal recessive condition have a one-in-four (25%) chance of passing it on to their children.

Cell—Building block that provides structure to the body and performs all the functions of the body. Cells contain genetic information and can copy themselves. The four main types of cells are: skin, nerve, muscle, and connective tissue.

Chromosome—The package of DNA found in each cell of the human body apart from the red blood cells. Humans have 22 pairs of autosomes (1 to 22) and one pair of sex chromosomes (XY). Females have two X chromosomes, and males have an X and Y chromosome. Normally, individuals inherit one chromosome of each pair from their mother and one from their father.

DNA (deoxyribonucleic acid)—The genetic material that contains the instructions for creating proteins.

DNA base—One unit in a DNA sequence. The four DNA bases are adenine (A), guanine (G), thymine (T),

and cytosine (C). The sequence of these bases is the genetic code that contains the instructions for creating proteins.

DNA sequence—The sequence of DNA bases that contains the instructions for creating proteins. A three-base sequence in the DNA contains the instructions for making a particular amino acid.

False negative—A test result that indicates that a disease or condition is not present when it actually is.

False positive—An error in which a test result incorrectly indicates the presence of a disease that is not actually present.

Gene—A sequence of bases in a DNA sequence that contains the instructions for one protein.

Panel—A specific ECS test.

Pathogenic variant—Any change in the sequence of a genome that causes disease.

Residual risk—The chance that an individual may still be a carrier for a certain condition even though the person screened negative.

Targeted carrier testing—Testing to see whether a person is a carrier of only one or a few conditions that the person is at risk for based on personal or family history or ancestry.

Variant—Change in the sequence of DNA.

X-linked—A condition caused by a pathogenic variant on the X chromosome.

mother and one Y chromosome from their father. Males are affected when they inherit the gene variant from their mother. In most cases, a female who inherits a pathogenic variant in one copy of the gene that causes the X-linked condition does not have symptoms. She is called a carrier. There are exceptions; some carrier females can have symptoms. Carrier females have a one-in-two or 50% chance that their sons will be affected and one-in-two or 50% chance that their daughters will be carriers. Daughters of affected males will all be carriers, and sons of affected males will not be affected.

Some ECS panels test for autosomal dominant disorders. Someone with an autosomal dominant condition has a pathogenic variant (mutation) in one copy of a particular gene. Individuals with an autosomal dominant condition have a one-in-two (50%) chance of passing it on to their children. ECS testing for autosomal dominant

conditions can unexpectedly diagnose a genetic disease in the parent undergoing testing.

How ECS testing is performed

Either both individuals in a couple are tested at once, or they are tested sequentially. If testing is done during pregnancy, then testing of both parents at once is recommended. This is so that testing of the fetus, if required, can be done earlier. ECS panels that test for autosomal dominant conditions should be done on both parents at the same time because their child may be at risk for inheriting the condition if either parent has a pathogenic variant.

Testing can be done through a blood draw, collection of saliva, or by scraping cells from the cheek. If both parents are carriers for a variant in the same gene, then the child can be tested to see whether the child has inherited the condition. Testing of the fetus can be done through

QUESTIONS TO ASK YOUR DOCTOR

- Do you offer ECS testing?
- Which ECS test would you recommend?
- What conditions are tested for by the ECS you offer?
- How accurate is the ECS test?
- Does the ECS test you offer test for autosomal dominant conditions?

amniocentesis, in which fetal cells are taken from the amniotic fluid surrounding the fetus or by chorionic villus sampling (CVS) in which a sample of placental tissue is taken.

Although ECS can be performed during pregnancy, it is better to do it before gestation. Early testing increases the parent's options. For example, carrier parents may choose not to have children; to adopt; or to use a donor egg or sperm. They may also choose in vitro fertilization (IVF) with pre-implantation diagnosis, which allows the doctor to implant only embryos without the identified genetic condition.

ECS accuracy

ECS tests vary in accuracy. The accuracy can be lower for nonclinical tests, such as direct-to-consumer genetic tests performed at home. The accuracy of testing for some conditions versus others will vary even within the same ECS test. False positive and false negative rates indicate the accuracy of a test. The false positive is a result that incorrectly states that the person is a carrier. False positives typically happen if a mistake happens during the test. For most ECS tests, false positives for common conditions and variants are rare. If a very rare variant is detected, then it is more likely to be a false positive. A false positive can sometimes happen if a variant is mistakenly attributed to a particular condition.

In the case of false negatives, the individual is incorrectly identified as not a carrier. The false negative rate is higher than the false positive rate for many conditions in many ECS tests. False negatives can happen if the lab makes a mistake and misses the variant. More often, false negatives happen because the ECS panel does not test for the variant in the person being tested. This outcome occurs because the variant is not yet known to cause the disease, or because this particular panel does not test for this variant. The false negative rate depends on the number of variants that are tested for a particular condition. The false negative rate can differ among different labs

that may test for different variants. Even when a person screens negative for a condition, there is a residual risk. Residual risk for a particular condition is the chance that the person is actually a carrier even though the person screened negative. For more common conditions the residual risk may be known, but it is not known for many of the rarer conditions included in an ECS test.

Reasons to use ECS

Couples use ECS for various reasons:

- They may choose not to have children if they are carriers.
- They may choose to adopt or use donor eggs or sperm if they are carriers.
- They may choose to use in-vitro fertilization and only implant normal embryos if they are carriers.
- They may want reassurance that they are not carriers.
- If they learn they are carriers, they may choose to do prenatal testing for reassurance or to help prepare for a child with a genetic condition.
- If they learn they are carriers, they may seek prenatal testing and choose to terminate an affected pregnancy.

Potential issues

There are a number of issues that parents need to consider when deciding whether to use ECS. For example, not all carriers are identified through ECS, and not all conditions can be identified. Also, results may be incorrect.

In addition, some conditions and variants detected through ECS have variable symptoms. Some people with the condition may have no symptoms at all. In such cases, it can be difficult to predict the severity of the condition for an affected fetus.

Some ECS panels test for autosomal dominant conditions. In these cases, parents who undergo testing may unexpectedly be diagnosed with a genetic condition. Some people may not want this information.

Most ECS panels test for conditions that start in childhood and are lethal or moderate to severe. Some test for adult-onset conditions that parents might not want to know about.

There can also be emotional risks to testing. It can be upsetting for individuals to find out they are carriers even if their fetus is not at risk. If one parent is tested at a time, then the wait for the results for the other person can be unsettling. During gestation, parents can be troubled to learn that their child has a genetic condition.

Choosing a test

ECS tests vary greatly. The accuracy between these tests also can vary significantly. Before choosing a test, individuals should find out more about the false positive and false negative rates for different conditions that are included in the ECS panel. It is important to choose a panel from a reputable lab that is recommended by a healthcare provider. Testing for more conditions is not always better because some of the conditions tested for may be rare and not much may be known about them. Individuals may also want to choose an ECS test that includes pre- and post-test genetic counseling, or they may ask their healthcare provider if they can have genetic counseling before deciding if they want to be tested.

Individuals may also want to choose a test based on the type of conditions it seeks to identify. Different ECS panels vary significantly. For example, a 2017 survey of ECS testing found that the number of conditions tested for varied from 40 to 1,792. The types of conditions tested for also vary among tests, and this survey found that only three conditions were tested for by all ECS tests.

Individuals who are concerned about a particular condition should confirm that the condition is included in the panel they use. Furthermore, they could check to see whether the chosen ECS panel tests for irrelevant conditions. Individuals should also determine what information they want to discover. For example, they may not want to know about conditions that can have mild or no symptoms. Similarly, they may not want to find out about conditions with symptoms that first appear in adulthood.

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Fabry disease

Definition

Fabry disease is a genetic condition that typically affects males. It is caused by deficiency of an enzyme, a chemical that speeds up another chemical reaction. Fabry disease can affect many parts of the body including the kidneys, eyes, brain, and heart. Pain in the hands and feet and a characteristic rash are classic features of this disease.

Description

The symptoms of Fabry disease were first described by Dr. Johann Fabry and Dr. William Anderson in 1898. The enzyme deficiency that leads to the disease was identified in the 1960s. Fabry disease is caused by a change (mutation) in the *GLA* gene. This gene is responsible for the production of the enzyme alpha-galactosidase A. Alpha-galactosidase A normally breaks down globotriaosylceramide, which is a natural substance in the body that is made of sugar and fat. A mutation in the *GLA* gene leads to a decrease in alpha-galactosidase A activity, which, in turn, leads to an excess of globotriaosylceramide. The excess globotriaosylceramide builds up in blood vessels (veins, arteries, and capillaries) and obstructs normal blood flow. It also builds up in parts of the skin, kidneys, heart, and brain. It is this buildup that inhibits normal function and leads to the symptoms associated with the disease.

The symptoms of Fabry disease are variable. Some individuals with Fabry disease have severe complications, while others have very mild symptoms. The first sign of the disease may be a painful burning sensation in the hands and feet (acroparesthesia). A red rash, most commonly between the belly button and the knees (angiokeratoma), is also common. The outer portion of the eye (cornea) may also become clouded in individuals with Fabry disease. The progressive buildup of

globotriaosylceramide can also lead to kidney problems and heart disease in adulthood.

Genetic profile

The gene that produces alpha-galactosidase A is located on the X chromosome. It is called the *GLA* gene. Since the *GLA* gene is located on the X chromosome, Fabry disease is considered to be X-linked. This means that it generally affects males.

A person's sex is determined by his or her chromosomes. Males have one X chromosome and one Y chromosome. Females, on the other hand, have two X chromosomes. Males who possess a mutation or change in their *GLA* gene will develop Fabry disease. Females who possess a mutation in one of their *GLA* genes typically do not develop many of the symptoms associated with Fabry disease. This is because a female's other X chromosome does not have the mutation, and the normal chromosome can take over the function of the abnormal chromosome and keep her from getting the disease. However, these women are considered to be carriers. If a woman is a carrier, she has a 50% risk with any pregnancy to pass on her X chromosome with the mutation. Therefore, with every male pregnancy she has a 50% risk of having an affected son, and with every female pregnancy she has a 50% risk of having a daughter who is a carrier.

Demographics

Fabry disease affects approximately 1 in 40,000 live births; about 5,000 people in the United States have been diagnosed with the disease as of 2021. It occurs evenly among all ethnic groups. Almost always, only male children are affected. Although female carriers of the disease occasionally develop symptoms of the disease, it is rare for a female carrier to be severely affected.

Signs and symptoms

The signs and symptoms of Fabry disease vary. Some individuals with Fabry disease have many severe

KEY TERMS

Acroparesthesia—Painful burning sensation in hands and feet.

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Angiokeratoma—A skin rash made up of red bumps. The rash most commonly occurs between the navel and the knees.

Blood vessels—A general term for arteries, veins, and capillaries that transport blood throughout the body.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted through either the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Cornea—The transparent structure of the eye over the lens that is continuous with the sclera in forming the outermost protective layer of the eye.

Dialysis—A process in which special equipment purifies the blood of a patient whose kidneys have failed.

Enzyme replacement therapy—Giving an enzyme to a person who needs it for normal body function. The enzyme is given through a needle inserted into the body.

Left ventricular enlargement—Abnormal enlargement of the left lower chamber of the heart.

Mitral valve prolapse—A heart defect in which one of the valves of the heart (which normally controls blood flow) becomes floppy. Mitral valve prolapse may be detected as a heart murmur, but there are usually no symptoms.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Proteinuria—Excess protein in the urine.

symptoms, while other individuals' symptoms may be few and mild. The symptoms typically increase or intensify over time. This progression is caused by the slow buildup of globotriaosylceramide as the person ages.

A painful burning sensation in the hands and feet (acroparesthesia) is one of the first symptoms of Fabry disease. This pain can be severe and may grow worse with exercise, stress, illness, extreme heat, or extreme cold. Another symptom of Fabry disease typically present during childhood is a red rash (angiokeratoma). This rash typically develops between the navel and the knees. Children with Fabry disease may also have a clouding of the outermost portion of the eye (cornea). This symptom is usually diagnosed by an eye doctor (ophthalmologist). The cloudiness may increase with time. A decreased ability to sweat is another common symptom of Fabry disease.

Due to the progressive nature of Fabry disease, most affected individuals develop additional symptoms by age 40. The buildup of globotriaosylceramide in the heart can lead to heart problems. These heart problems can include changes in the size of the heart (left ventricular enlargement), differences in the heartbeat, and leaky heart valves. Mitral valve prolapse is a particular type of leaky heart valve that is common in Fabry disease, even in childhood. The excess globotriaosylceramide can also disrupt normal blood flow in the brain. In some cases this can cause dizziness, seizures, and stroke. The kidneys are other organs affected by Fabry disease. Kidney problems can lead to an abnormal amount of protein in the urine (proteinuria). Severe kidney problems can lead to kidney failure.

Although the symptoms of Fabry disease usually occur in males, female carriers may occasionally exhibit symptoms of the disease. Some carriers experience pain in their hands and feet. Carrier females may also have proteinuria and clouding of their cornea. It is rare for a female to experience all of the symptoms associated with Fabry disease.

Diagnosis

Initially, the diagnosis of Fabry disease is based on the presence of the symptoms. It should also be suspected if there is a family history of the disorder. The diagnosis of Fabry disease is definitively made by measuring the activity of the alpha-galactosidase enzyme. When the activity is very low, it is diagnostic of Fabry disease. This enzyme analysis can be performed through a blood test. Measuring the activity of the enzyme can also detect a female carrier. Women who are carriers of Fabry disease have enzyme activity that is lower than normal.

QUESTIONS TO ASK YOUR DOCTOR

- My physician has recommended that I have a prenatal test for Fabry disease. What will that test show, and why should I have it?
- What are the most common symptoms of Fabry disease?
- My doctor has recommended enzyme replacement therapy for my child with Fabry disease. What does this treatment involve?
- Will enzyme replacement therapy cure my child of Fabry disease? If not, what improvements can we expect to see?

Prenatal diagnosis is possible by measuring the alpha-galactosidase A activity in fetal tissue drawn by amniocentesis or chorionic villus sampling (CVS). Fetuses should be tested if the mother is a carrier. A woman is at risk of being a carrier if she has a son with Fabry disease or if someone in her family has Fabry disease.

Treatment and management

There is currently no cure for Fabry disease. However, enzyme replacement therapy (ERT) is an option. Clinical trials done over a ten-year period and published in 2015 concluded that weekly infusions of ERT (as opposed to the bimonthly infusions that had previously been studied) better slow the decline of renal function. This can increase the lifespan of a patient diagnosed with the disease by up to 13 years. ERT is currently the only FDA-approved treatment for Fabry disease.

Individuals with Fabry disease are recommended to have routine evaluations of their heart and kidneys. Some individuals with kidney disease require a special diet that is low in sodium and protein. Dialysis and kidney transplantation may be necessary for patients with severe kidney disease. Certain medications may reduce the risk of stroke. Finally, individuals with Fabry disease are advised to avoid the situations that cause the pain in their hands and feet to grow worse. In some situations, medication may be required to reduce the pain.

Prognosis

The prognosis for individuals with Fabry disease is good, especially with the arrival of enzyme replacement therapy. Currently, affected individuals survive into adulthood with the symptoms increasing over time.

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- International Center for Fabry Disease, Department of Genetics and Genomic Sciences, Icahn School of Medicine, 1 Gustave L. Levy Place, New York, NY 10029-5674, (212) 241-6500, fabry.disease@mssm.edu, <https://icahn.mssm.edu/research/fabry/what-is>
- National Institute of Neurological Disorders and Stroke. Division of Extramural Research, P.O. Box 5801, Bethesda, MD 20824, 352-9424, <http://www.ninds.nih.gov>
- National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 263-9938, <http://www.rarediseases.org>

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Facioapalatoosseous syndrome see **Otopalatodigital syndrome**

Facioscapulohumeral muscular dystrophy

Definition

The term *muscular dystrophy* refers to a group of conditions characterized by progressive muscle weakness and atrophy (wasting or deterioration). Many different types of muscular dystrophy have been described, each

of which has unique features and usually a unique underlying genetic cause. Facioscapulohumeral muscular dystrophy (FSHD) takes its name from the parts of the body most affected by the disorder: *facio* refers to the face, *scapulo* to the shoulder blades, and *humeral* to the bone of the upper arm. There were two recognized forms of FSHD as of 2021: type 1 (FSHD1), which accounted for about 95% of diagnosed cases of FSHD, and type 2 (FSHD2), which accounted for the remaining 5%.

Facioscapulohumeral dystrophy is also known as Landouzy-Dejerine muscular dystrophy, after the two French physicians, Louis Landouzy (1845–1917) and Joseph Jules Dejerine (1849–1917), who first described the disorder in 1886.

Description

Facioscapulohumeral (FSH) muscular dystrophy is a disorder that first affects the muscles of the face and shoulders. Usually, the first signs of weakness appear before the age of 20 years. The symptoms of FSH muscular dystrophy vary in severity but are not fatal. One in five people who are affected require a wheelchair after the age of 40 years. The symptoms of FSH muscular dystrophy are quite variable, even within the same family. Some individuals who have the altered DNA sequence involved in type 1 FSHD never develop noticeable symptoms. Most people with the condition first notice weakness in various parts of the upper body in their teenage years. Muscles of the shoulders and face are usually the first to be affected. These may remain the only parts of the body that are affected, or the weakness may progress to include the pelvic muscles, the lower limbs, and the hands. Intelligence and life expectancy are not affected.

Genetic profile

The genetics of FSH muscular dystrophy are complex. As of 2021, two distinct forms of the disorder have been identified, FSHD type 1 (FSHD1), which accounts for about 95% of diagnosed cases of FSHD; and FSHD type 2 (FSHD2), which accounts for the remaining 5%. While FSHD type 1 is inherited in an autosomal dominant pattern, FSHD type 2 has a digenic inheritance pattern, which means that mutations in two different genes are necessary for the affected person to show signs of the disorder.

FSHD type 1

The autosomal dominant inheritance pattern in FSHD type 1 means that an affected person has a 50% chance with each pregnancy to pass the altered gene on to their child. Every person has two copies of every DNA sequence, one inherited maternally and the other inherited

paternally. The altered DNA sequence that causes FSH muscular dystrophy type 1 is the D4Z4 repeat in the subtelomeric region of the long arm of chromosome 4 at 4q35. The term *subtelomeric* means that the region is close to the end of the chromosome. A normal chromosome 4 will contain between 11 and 150 repeats of D4Z4. Within the D4Z4 repeat region is a gene called *DUX4*, which is ordinarily inactive, as the large number of D4Z4 repeats in a normal chromosome contains a high number of methyl groups that keep the *DUX4* gene repressed, or “turned off.”

In an abnormal chromosome 4, however, the D4Z4 region is shortened so that it has only 1–11 repeats. This small number of repeats lowers the number of methyl groups attached to this section of the chromosome, leading to a condition called hypomethylation. Hypomethylation allows the *DUX4* gene to become active (able to code for proteins). Although it is not known as of 2021 exactly how an activated *DUX4* gene causes the muscle weakness characteristic of FSHD type 1, it is thought that the gene codes for an abnormal protein that leads to damage to muscle cells or their premature death.

The *DUX4* gene lies next to a regulatory section of DNA on chromosome 4 that is called a pLAM sequence. A functional pLAM sequence is required for the *DUX4* gene to code for its protein. If this sequence is not functional, the *DUX4* gene cannot produce its protein. Copies of chromosome 4 with a functional pLAM sequence are called permissive, while copies without a functional sequence are called nonpermissive. Because each cell in a person’s body has two copies of chromosome 4, an individual may have two permissive copies of the chromosome, two nonpermissive copies, or one of each. FSHD can develop only in a person with at least one permissive copy of chromosome 4.

When an autosomal dominant condition is present in multiple generations of a family, usually someone from each generation is affected. If a person is the first in his or her family to have an autosomal dominant condition, doctors often assume that the gene mutated for the first time in the egg or sperm that came together to make that person. This type of mutation is called a new, or *de novo*, mutation. About 30% of cases of FSHD type 1 are thought to result from *de novo* mutations in chromosome 4.

FSHD type 2

Although FSHD type 2 is characterized by the same clinical symptoms as FSHD type 1, it is inherited in a different pattern known as digenic inheritance. In digenic inheritance, a person must have mutations in two separate genes in order to develop the symptoms of the disorder. In

FSHD type 2, the person has a normal number of D4Z4 repeats on chromosome 4 at 4q35, but has a mutation in the *SMCHD1* gene on the short arm of chromosome 18 at 18p11.32. This gene codes for a protein that ordinarily adds methyl groups to the D4Z4 region of chromosome 4, which keeps the *DUX4* gene inactive. Mutations in the *SMCHD1* gene reduce the amount of protein available to prevent the activation of the *DUX4* gene. If a person with a mutation in the *SMCHD1* gene has also inherited a permissive copy of chromosome 4, he or she will develop FSHD type 2. In most cases, the patient has inherited the defective copy of the *SMCHD1* gene from one parent and a permissive copy of chromosome 4 from the other parent. Because neither parent has both genetic changes, they will not have any symptoms of the disorder.

Some researchers think that mutations in the *SMCHD1* gene may also increase the severity of FSHD type 1. It is thought that the combination of a shortened D4Z4 region on chromosome 4 and the mutated *SMCHD1* gene increase the level of activation of the *DUX4* gene, resulting in greater muscle weakness and other severe symptoms (including respiratory difficulties) in the patient.

Demographics

FSHD is considered the third most common genetic disorder affecting skeletal muscle. The incidence of FSH muscular dystrophy is approximately 1 in 20,000. Some Dutch references report a higher incidence of 1 in 12,000. Individuals from all ethnic groups are affected.

Signs and symptoms

The severity of the symptoms of FSH muscular dystrophy is highly variable. Some people are debilitated, while others are minimally affected. Symptoms of progressive muscle weakness are usually first noticed in the teenage years, but may be noticed much later. For unknown reasons, more males than females with FSH muscular dystrophy develop symptoms by the age of 30 years. Specific muscle groups are affected. FSH muscular dystrophy does not lead to reduced sensation, nor does it affect intelligence.

Progressive muscle weakness of the shoulders/upper arms and face muscles are usually noticed first. The facial muscle weakness may be noticed as difficulty puckering the lips, smiling, sucking a straw, and closing the eyes while sleeping. The patient may have difficulty pronouncing the letters B, M, and P, which require moving or pursing the lips. Weakness may be asymmetrical; that is, one shoulder may be weaker than the other shoulder. The patient's shoulder blades may protrude, a condition

called scapular winging. The weakness of the shoulder muscles may make it difficult for the patient to lift the arms above shoulder level or throw a ball.

As the condition progresses, the muscles of the lower legs, abdomen, and hips may also become weak. The muscle weakness leads to such abnormal positioning as forward-sloping shoulders and exaggerated curvature of the spine. The patient may also develop a protruding abdomen as a result of weakened abdominal muscles. Although the weakness progresses continuously, the affected individual may perceive it as progressing rapidly at times and slowly at other times. This is because he or she notices the weakness when it results in loss of function. Reflexes are often weaker than normal. Twenty percent of affected individuals eventually require wheelchairs. Foot drop, a gait abnormality, is a common problem in patients with FSHD and increases the risk of dangerous falls.

Describing the weakness as shoulder weakness or facial weakness is an oversimplification. In FSH muscular dystrophy, very specific muscles are affected. Not all of the facial muscles are affected, and not all of the muscles of the shoulder are affected. For example, the biceps and triceps of the upper arm are affected before the deltoids, and the forearm is relatively unaffected.

Many individuals with early-onset FSH muscular dystrophy develop hearing loss of the higher frequencies. Some individuals experience significant hearing loss. Slight changes of the retina are also a symptom of FSH muscular dystrophy. These changes usually do not affect vision, however.

A subset of FSH muscular dystrophy patients are severely affected; as noted above, these individuals most likely have a combination of a shortened D4Z4 region on chromosome 4 and a mutated *SMCHD1* gene on chromosome 18. Individuals with severe infantile FSH muscular dystrophy are symptomatic at birth.

Diagnosis

The diagnosis of FSH muscular dystrophy is based on clinical history (symptoms), family history, and genetic testing. Many evaluations may be necessary to confirm the diagnosis. A thorough physical examination will be performed. Additional testing may include measuring the level of creatine kinase (CK) in the blood; special analysis of tissue obtained by muscle biopsy; and an electromyogram (EMG). Sometimes it is difficult to rule out other possible causes of the muscle weakness.

Molecular genetic testing is available for both types of FSHD. When FSHD type 1 is suspected, the test measures the length of the D4Z4 region of chromosome 4.

KEY TERMS

Creatine kinase (CK)—An enzyme that serves as a marker of the breakdown of muscle tissue. CK levels in blood can be tested to evaluate patients for muscular dystrophy and other disorders of muscle tissue.

De novo mutation—A mutation that arises in a child that is not present in either parent.

Digenic inheritance—A pattern of inheritance in which mutations in two (and only two) different genes are required for the manifestation of a genetic disorder. FSHD type 2 is an example of a genetic disorder with digenic inheritance.

Foot drop—A gait abnormality in which the affected person cannot raise the toes and front of the foot, or raise the foot at the ankle. Foot drop is an indication of a disease of the muscles or nerves; it is not a disease in itself.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Genome—All the DNA within one cell.

Methyl groups—Groups of one carbon and three hydrogen atoms attached to DNA. The number of methyl groups attached to a section of a chromosome influences the level of gene activity (repression or activation).

Methylation—The process in which methyl groups are added to DNA. Methylation typically acts to suppress a gene's ability to code for proteins.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Scapular winging—Abnormal protrusion of the shoulder blades as a result of weak shoulder muscles.

Subtelomere—The section of a chromosome immediately next to the telomere at the end of the chromosome.

Telomere—A specialized region at the end of a chromosome that prevents degradation of genetic material and also prevents the end of the chromosome from fusing with another chromosome.

When FSHD type 2 is suspected, genetic testing combines a screening test for hypomethylation in the D4Z4 region of chromosome 4 with a sequence analysis of the *SMCHD1* gene.

Genetic testing can be performed on fetal cells that are obtained by amniocentesis, performed after the 16th week of pregnancy, or chorionic villus sampling (CVS). CVS is usually performed between 10 and 12 weeks of pregnancy.

Because of the variable severity of FSHD symptoms as well as the different patterns of inheritance, assumptions should not be made about a patient's family history. A thorough clinical examination by an experienced physician may show that a person believed to be unaffected by the disorder actually has mild symptoms of it.

Treatment and management

There is no effective treatment, prevention, or cure for either type of FSH muscular dystrophy approved by the Food and Drug Administration as of 2021. Available treatments help affected persons with the effects of the disease but do not treat the disease itself. Supportive therapies include such orthotic devices as splints and braces, motorized wheelchairs or carts, and sometimes surgery. One surgical procedure that is recommended for some FSHD patients is to attach (fixate) the shoulder blades to the chest wall in order to stabilize the patient's shoulders and improve the range of motion in the patient's upper arms.

Physical and occupational therapy may be helpful to ease discomfort, adjust to physical changes, and lower the patient's risk of falling due to weakness of the ankles and calf muscles. Speech therapy may be necessary to help patients whose ability to articulate certain sounds has been affected by the weakness of facial muscles. Cognitive behavioral therapy (CBT) combined with regular exercise has been found to help relieve the chronic fatigue experienced by many patients with FSHD.

Researchers also continue to study various medications. Previous studies indicated that prednisone may improve muscle strength. However, this finding was not confirmed in more recent studies. Another medication, albuterol, was shown to be beneficial in early studies but the results of the completed study have not been posted.

Prognosis

The prognosis for both types of FSH muscular dystrophy is extremely variable. Prognosis cannot be predicted based on family history. Most people remain

ambulatory, but some do not. Progression is usually slow. One-third of affected individuals over 40 years of age have mild symptoms. A few people with FSH muscular dystrophy never develop muscle weakness. The typical course is weakness that becomes noticeable before the age of 20 years and progresses slowly but continuously throughout life.

Resources

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- "FSH Muscular Dystrophy." Johns Hopkins Medicine. <https://www.hopkinsmedicine.org/health/conditions-and-diseases/fsh-muscular-dystrophy> (accessed June 8, 2021).

ORGANIZATIONS

- FSHD Society, 75 North Main Street, Suite 1073, Randolph, MA 02368, (781) 301-6060, <https://www.fshdsociety.org/contact-us/>, <https://www.fshdsociety.org/>
- Muscular Dystrophy Association—USA, 161 N. Clark, Suite 3550, Chicago, IL 60601, (800) 572-1717, mda@mdausa.org, <https://www.mda.org>
- Muscular Dystrophy Family Foundation, PO Box 776, Carmel, IN 46082, (317) 615-9140, <http://mdff.org/contact-ushttp://www.mdff.org>
- Muscular Dystrophy UK, 61A Great Suffolk Street, London, United Kingdom SE1 0BU, 020 7803 4800, info@musculardystrophyuk.org, <http://www.musculardystrophyuk.org>

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Factor V deficiency see **Factor V Leiden thrombophilia**

Factor V Leiden thrombophilia

Definition

Factor V Leiden thrombophilia is a common genetic disorder that leads to a predisposition or increased chance of developing blood clots in the veins (venous thrombosis).

Description

Factor V Leiden thrombophilia is a disorder caused by an inherited change or mutation in the genetic instructions for making a substance called factor V. The factor V change leads to an increased chance of developing blood clots in blood vessels.

Blood clots form in two steps. In the first step, the body produces platelets that are "sticky" and can form initial plugs or clots when needed. However, the first platelets only form the first temporary plugs. To form a more lasting plug or clot, the platelets release chemicals to attract more platelets and other substances called clotting factors (or clotting proteins). In the second step, the platelets come together with the clotting proteins and form fibers. The fibers weave together and make the clot stronger and longer-lasting.

Individuals who are affected by factor V Leiden thrombophilia have a genetic mutation that makes a longer-lasting, "stickier" form of the clotting factor, or protein, called factor V. This different form of factor V is called factor V Leiden. The factor V Leiden clotting protein lasts longer in the blood because a chemical produced by the body called activated protein C (or APC), which is supposed to help break down the factor V clotting protein, cannot break down the factor V Leiden clotting protein as easily and quickly as it breaks down normal factor V. The factor V Leiden clotting protein breaks down ten times more slowly than an average clotting factor V and accordingly stays in the blood longer.

Since there is longer-lasting, extra-sticky factor V Leiden in the blood, individuals who are affected by factor V Leiden thrombophilia have an increased chance of having free-floating blood clots (thromboses) that can get stuck in the veins and other blood vessels. An alternative name used to describe this condition is hereditary resistance to activated protein C.

Genetic profile

Factor V Leiden thrombophilia occurs when a specific gene on the long arm of chromosome 1 is changed or mutated. This gene is called *F5*. Every person has approximately 30,000 genes that tell their bodies how to form and function. Each gene is present in pairs, since one is inherited from the mother, and one is inherited

from the father. Depending on the inheritance of the changed or mutated *F5* gene, factor V Leiden thrombophilia runs in families in a more severe and less severe form.

The less severe form of factor V Leiden thrombophilia is heterozygous and occurs when an individual inherits only one copy of the altered or mutated gene that causes factor V Leiden. The more severe form of factor V is homozygous and is caused by the inheritance of two non-working or mutated copies of the gene that causes factor V Leiden thrombophilia.

Heterozygous factor V Leiden is inherited in an autosomal dominant pattern. In an autosomal dominant condition, only one changed or mutated copy of the gene for a particular condition is necessary for a person to experience symptoms of the condition. If a parent has an autosomal dominant condition, there is a 50% chance of each child having the same or a similar condition. In heterozygous factor V Leiden thrombophilia, the chance of being affected by venous blood clots is four to eight times greater than for the general population.

Homozygous factor V Leiden thrombophilia is inherited in an autosomal recessive pattern. Such conditions are caused by the inheritance of two changed or mutated copies of a gene. Individuals who are affected by heterozygous factor V Leiden thrombophilia have only one copy of the altered gene. However, when two people with heterozygous factor V Leiden thrombophilia have children together, there is a 25% chance with each pregnancy for their child to inherit two copies, one from each parent. That child then would have two altered copies of the gene and therefore homozygous factor V Leiden thrombophilia. When an individual inherits two non-working copies of the gene that lead to homozygous factor V Leiden thrombophilia, his or her risk of being affected by blood clots stuck in the veins (venous thrombosis) is 80 times higher. Most individuals who are affected by homozygous factor V Leiden thrombophilia develop blood clots at a younger age than those affected by heterozygous factor V Leiden thrombophilia.

Demographics

Factor V Leiden thrombophilia is the most common inherited form of increased blood clotting in the general population. It is more common in the Caucasian population. In the general American and European populations, heterozygous factor V Leiden thrombophilia occurs in approximately 3 to 8 individuals per 100. In the same general American and European populations, homozygous factor V Leiden thrombophilia affects approximately 1 in 5,000 individuals. The frequency in African Americans, Asian Americans, Hispanic Americans, and

Native Americans is smaller than that in Caucasian Americans but is still present at approximately 0.45%–2% of individuals tested. Factor V Leiden thrombophilia is very rare in individuals who have only Asian, African, and indigenous Australian descent.

Signs and symptoms

The symptoms of factor V Leiden thrombophilia vary. Some affected individuals have no physical problems. Others will have complications including blood clots blocking blood vessels (thromboembolism), deep vein thrombosis, unexplained multiple miscarriages and stillborn infants, gallbladder dysfunction, strokes, and heart attacks. The most common physical sign of factor V Leiden thrombophilia is thromboembolism (a blockage in the veins caused by a free-floating clot, or embolus). Venous thromboembolism is most common in the deep veins of the legs (deep venous thrombosis, or DVT, of the legs). Non-specific and common factor V Leiden thrombophilia are suspected in individuals who have had multiple blood clots in the veins (venous thrombosis), more than three unexplained miscarriages, or a family history of individuals with multiple blood clots in the blood vessels.

Diagnosis

Diagnosis of factor V Leiden thrombophilia can be done through a blood coagulation screening test or DNA analysis of the gene that codes for factor V.

The blood coagulation screening test uses the breakdown protein APC in a resistance study to see how quickly the factor V is broken down as compared to other blood clotting factors. An individual with factor V Leiden thrombophilia has factor V that is resistant to being broken down, or is much more slowly broken down, by the APC protein. There are two types of APC resistance screening tests for factor V Leiden thrombophilia. The preferred test is the modified second-generation APC resistance study, because an extra step in the testing (dilution by plasma without factor V) makes it almost 100% accurate, even in pregnant women and patients being treated by medications such as heparin and warfarin.

The DNA or molecular analysis examines the *F5* gene to learn whether the gene is altered or mutated.

Prenatal diagnosis is not routinely offered because the disorder is fairly mild and effective treatment is available.

Potential complications

Factors that may increase the risk of developing abnormal blood clots include:

KEY TERMS

Deep vein thrombosis—A blood clot in one of the systemic veins deep in the body.

Heterozygous—Having two different versions of the same gene.

Homozygous—Having two identical copies of a gene.

Thromboembolism—A condition in which a blood vessel is blocked by a free-floating blood clot carried in the bloodstream.

Venous thrombosis—A condition caused by the presence of a clot in a vein.

- Inheriting two copies of the mutated factor V gene
- Prolonged sitting
- Taking estrogen, including oral contraceptives and hormone replacement therapy
- Pregnancy
- Serious surgeries or injuries (particularly leg fractures, abdominal surgery, and cancer)

DVT and PE are potential complications of factor V Leiden. Although factor V Leiden thrombophilia cannot be prevented, the risk of developing DVT or PE can be reduced in the following ways:

- Regular exercise
- Maintaining a healthy weight
- Frequent movement during travel by plane, train, or vehicle (especially if the trip is longer than four hours)
- Breaks at least once every two hours on a long road trip
- Wearing compression stockings

Treatment and management

The treatment and management of individuals affected by factor V Leiden thrombophilia are focused on prevention of floating blood clots (thrombosis) and thromboembolism. The management of affected individuals should be overseen by a hematologist who specializes in blood clotting disorders and a general practitioner or internist who can work closely with the hematologist.

At different times of life, different specialists may need to be added. For example, when a patient is pregnant, a perinatologist or high-risk obstetrician should work with the hematologist. Additionally, individuals who have had a deep vein clot or stroke may need to consult a vascular specialist and/or neurologist.

The physicians managing an affected individual's care should discuss with them the timing, risks, and benefits of taking birth control pills and taking blood thinning anticoagulant medications such as warfarin, aspirin, and heparin. Individuals who are affected by factor V Leiden thrombophilia should also be examined to make sure they do not have other blood clotting disorders in addition to factor V Leiden thrombophilia.

Prognosis

Individuals who are affected by factor V Leiden thrombophilia have a wide range of symptoms and signs. Some will never develop physical signs and symptoms of the disorder, and others will be more severely affected. Most affected individuals will not experience their first clotting event until adulthood. However, those with homozygous factor V Leiden thrombophilia have a significantly increased risk of having symptoms of the disease at a younger age. Treatment and close management of the disorder can reduce the risk of thromboembolism significantly.

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"Factor V Leiden thrombophilia." MedlinePlus Genetics. August 18, 2020. <https://medlineplus.gov/genetics/condition/factor-v-leiden-thrombophilia/> (accessed July 6, 2021).

ORGANIZATIONS

National Blood Clot Alliance, P.O. Box 825687, Philadelphia, PA 19182-5687, (703) 935-8845, (877) 466-2568, info@stoptheclot.org, <http://www.stoptheclot.org>

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Familial adenomatous polyposis

Definition

Familial adenomatous polyposis (FAP) is an inherited condition that typically presents with extensive adenomatous polyps of the colon. These polyps often develop into colorectal cancer in early adult life. Other symptoms are often present as well. These signs include polyps in the upper gastrointestinal tract, malignancies in the brain or thyroid, pigmented retinal lesions, and osteomas.

Description

FAP was first clearly described as a dominantly inherited colorectal cancer susceptibility by Lockhart-Mummery in an article published in 1925. FAP has since served as a paradigm for hereditary cancer and has taught much about the diagnosis, surveillance, and management of colon cancer. It is one of the most clearly defined and well-understood of the inherited colon cancer syndromes. FAP is thought to account for approximately 1% of all cases of colorectal cancer.

FAP is a disorder characterized by the development of hundreds to thousands of glandular colorectal tumors called adenomas or adenomatous polyps, meaning that they are benign growths made of the tissue that lines the inside of the colon. They are described as polyps because they protrude from mucous membranes. In FAP, these tumors generally develop by the second or third decade of life. They are found in the internal lining of the colon and the rectum, with a particular affinity for the left side of the colon or the rectosigmoid. By themselves, these polyps are benign, but they have the ability to become malignant, leading to colorectal cancer. If the polyps are not treated properly, it is almost certain that a person affected with FAP will develop colorectal cancer by the age of 40.

Other clinical findings that may be associated with FAP include polyps in the upper gastrointestinal tract, extraintestinal manifestations such as osteomas and epidermoid cysts, desmoid formation, retinal lesions, and malignant changes in other organs. Symptoms are thought to manifest anywhere between the ages of 16 and 50 years.

FAP is also known as familial polyposis coli (FPC) and adenomatous polyposis coli (APC). Gardner syndrome and Turcot syndrome are variants of FAP. Gardner syndrome is used to describe patients with FAP and the extracolonic symptoms of osteomas, soft tissue tumors, desmoids, and dental abnormalities. Turcot syndrome is

used when FAP is seen in conjunction with tumors of the central nervous system called medulloblastomas (cerebellar tumors that occur in childhood). Attenuated FAP (AFAP) is another variant of FAP. In this condition, individuals present with fewer polyps, usually fewer than 100 in number and often in the right colon. Patients with AFAP may have a later onset of cancer than those with classic FAP.

Genetic profile

FAP is inherited in an autosomal dominant pattern; thus an affected person has a 50% chance of passing the disease on to each of his or her children. It is almost 100% penetrant, meaning that nearly everyone who carries the gene mutation will show signs of the disorder. The majority of patients with FAP inherit the mutation from one of their parents. However, in approximately 25% of cases, there is no family history of the disorder and FAP occurs because of a new mutation in the affected individual.

The majority of cases of FAP are due to mutations of the *APC* gene, located on the long arm (or “q” arm) of chromosome 5. This gene encodes a protein that is important in cell adhesion and signal transduction. More than 300 different *APC* mutations have been described in FAP patients. Most *APC* mutations seen in individuals with FAP result in translation of a protein that is shorter than normal. This shortened protein cannot function properly.

Studies have shown that the type and location of the *APC* mutation seems to correlate to the clinical symptoms that a person manifests. For example, if the mutation is located near the center of the gene, colonic polyps tend to be more dense and numerous. A mutation toward the ends of the gene often leads to polyps that are fewer and more sparse, as in attenuated FAP. Additionally, mutations at one particular end (the 3' end) of the *APC* gene seem to be associated with a higher risk of desmoid formation. However, it is known that family members who carry identical mutations often have different clinical features. This finding suggests that modifying genes and/or environmental factors also influence the expression of the *APC* gene mutation.

The *APC* gene is a tumor-suppressor gene, meaning that its function is to control cell growth. When *APC* is mutated, it does not function correctly and allows cells to grow out of control. This results in tumors that may lead to cancer. Carriers of mutations in *APC* inherit a germline mutation in one allele of the gene. Thus, in every one of their cells, one gene does not make the *APC* protein, but the corresponding gene on the other chromosome continues to produce the functional protein.

Thus, tumor suppression continues. However, if a somatic mutation occurs in the remaining functional gene, no APC protein is made, tumor suppression fails, and tumors develop. These somatic mutations occur in various parts of the body at various times, leading to multiple tumors forming in distinct parts of the body over a period of time. In the case of FAP, many of these tumors are confined to the colon but can occur in other organs as well.

Demographics

Approximately 1 in 7,000 to 1 in 22,000 people are affected with FAP. It is seen in all racial and ethnic groups. Both sexes are affected equally.

Signs and symptoms

Colorectal

FAP is characterized by multiple (more than 100) adenomatous polyps of the colon and rectum. These generally develop after the first decade of life, but the age of onset of adenomas is variable. Fifteen percent of individuals with FAP will show these polyps by age 10, 75% by age 20, and 90% by the age of 30. More than 95% of affected individuals will have adenomatous polyps by the age of 35. Although these polyps are benign, it is inevitable that if left untreated, at least one of the hundreds of polyps will eventually progress to cancer. The majority of cancers appear by the age of 40, and over 90% appear by the age of 45. Symptoms of polyps and/or colorectal cancer may include rectal bleeding, change in bowel habits, iron deficiency anemia, or abdominal pain.

Upper gastrointestinal tract

Many individuals with FAP will develop adenomas in the upper gastrointestinal tract as well. The second portion of the duodenum is particularly prone to these polyps. These adenomas are benign, as they are in the colon, but about 5%–8% of patients with FAP will eventually develop cancer in this area. Duodenal cancer seems to cluster in certain FAP families while being absent in others. Adenomas of other portions of the small bowel may also occur but with lesser frequency.

In people affected with FAP, benign adenomas can also be seen in the stomach. Gastric cystic fundic gland polyps are also common. These are benign polyps that occur in the fundic gland of the stomach, an organ that secretes enzymes and mucus. It is rare for these polyps to become cancerous in individuals of Western origin. However, in Japanese and Korean families with FAP, the risk of gastric cancer is reported to be increased three- to four-fold over the general population.

Ocular, skeletal, and cutaneous

Approximately two-thirds of individuals with FAP will have congenital hypertrophy of the retinal pigment epithelium (CHRPE). These lesions are typically flat, oval, and pigmented. They can be detected by an ophthalmology examination. In FAP patients, these lesions are usually multiple, bilateral, or large. CHRPE does not affect vision, nor does it have the potential to become malignant. However, CHRPE is a very important finding for families with a history of FAP. If CHRPE runs in a family with FAP, all or nearly all affected individuals in the family will have this finding. It can be detected at birth and can thus identify susceptible family members at a young age.

Other manifestations of FAP include dental abnormalities, such as impacted teeth, supernumerary teeth, and congenitally missing teeth. Osteomas can occur, often in the jaw area or on the forehead. Soft tissue tumors, such as lipomas, epidermoid cysts, and fibromas, are observed in some patients with FAP as well.

Other tumors and malignancies

Abdominal desmoid tumors occur in approximately 15% of individuals with FAP. Desmoids are tumors made of connective tissue. Although they are not cancerous, approximately 10% grow very aggressively and can become life-threatening. They may lead to obstruction of blood vessels, the intestine, or ureters. They may also result in abdominal distention and associated pain and discomfort. Over 70% of these tumors develop in women aged 20–40 years, suggesting a hormonal role in their development. Additionally, they occur more commonly in those who have had prior abdominal surgery. Desmoids may occur as part of classical FAP, as part of Gardner syndrome, or sporadically, without the colonic findings of FAP.

Additionally, patients with FAP are at an increased risk for cancers in organs outside of the gastrointestinal tract. These include brain tumors, thyroid tumors, and hepatoblastoma. Hepatoblastoma is a malignant tumor of the liver and occurs in approximately 1.6% of patients with FAP in the first five years of life. Tumors of the adrenal cortex, biliary tract, and pancreas have also been reported.

Diagnosis

FAP can be diagnosed clinically in any individual with greater than 100 polyps in the colon or rectum. The diagnosis is usually made via flexible sigmoidoscopy. This procedure may be done on a routine basis or to investigate possible symptoms of colon polyps and/or colorectal cancer. Flexible sigmoidoscopy involves

inspecting the interior of the rectum and the sigmoid colon or the terminal part of the colon that leads to the rectum. Once polyposis has been established, complete colonoscopy may be necessary to further evaluate the extent of the polyps. Colonoscopy is a more invasive procedure that examines the interior of the entire colon and rectum, rather than only the terminal part.

In regard to a diagnosis in someone who does not yet have colon polyps, retinoscopy, or examination of the retina, can be useful in a family where CHRPE has been associated with FAP. In these families, CHRPE is almost 100% predictive of FAP; thus, if someone shows CHRPE on an ophthalmology exam, it is very likely that he or she is affected with FAP. Although genetic testing yields more certain predictive information, retinoscopy is a relatively inexpensive and noninvasive alternative diagnostic screening measure in families with a history of FAP associated with CHRPE.

Polyps may be first detected by the passage of occult (non-visible) blood in the stool by means of fecal occult blood testing. This testing is also inexpensive and noninvasive and if positive, could indicate that additional testing is needed.

FAP can also be diagnosed by genetic testing. This type of testing may be used to identify someone who is affected but does not yet show any symptoms of FAP. It can also confirm the diagnosis of FAP in someone who has polyposis discovered via flexible sigmoidoscopy. *APC* gene testing is most commonly performed by using a protein truncation test, which looks for the presence of shortened proteins caused by a mutation in the gene. This test identifies approximately 80% of those affected with FAP. The other 20% of patients likely have mutations that do not lead to a shortened protein. It is important to test an affected family member first to determine whether a detectable mutation is present. If a mutation is identified in this affected person, other at-risk family members can be tested for this particular mutation. However, if a mutation is not identified in the affected individual, it is likely that the mutation does not produce a shortened protein. In this case, protein truncation testing would not be informative for the rest of the family.

FAP can also be diagnosed by linkage analysis. This testing identifies approximately 95% of affected individuals; however, blood samples are required from numerous family members, including at least one affected individual. Thus, logistically, this procedure is more complicated than the protein truncation testing.

Treatment and management

There is no treatment for FAP because the genetic abnormality cannot be fixed. Management focuses on

routine surveillance of at-risk and affected individuals for early detection and treatment of colonic polyps and other manifestations.

For individuals diagnosed with FAP, either clinically or via linkage analysis or protein truncation testing, an annual sigmoidoscopy must be performed beginning around the age of ten years. Sigmoidoscopy is preferred because it is less invasive, safer, and will generally detect the polyps in FAP, since they are numerous and located throughout the colon. Colonoscopy may be the screening tool of choice if attenuated FAP is suspected since in this case, the adenomas are fewer in number and may be confined to the proximal region of the colon.

If polyposis is established, complete colonoscopy may be necessary to determine the extent of the polyposis and the timing of surgery. As for surgical intervention, total proctocolectomy (removal of the colon and rectum) is generally favored. In some cases, however, other options may be explored, such as total colectomy (removal of the colon only) with ileorectal anastomosis (the small intestine is attached to the upper portion of the rectum). Another option, a total colectomy with rectal mucosal proctectomy and ileoanal anastomosis, involves removing the entire colon and mucosal lining of the rectum. The ileum then attaches to the anus. Fecal continence is preserved, since the muscular wall and the sensory functions of the rectum are preserved.

All FAP patients require an annual medical examination with palpation of the thyroid and review of systems. Children with FAP should be screened for hepatoblastoma with liver palpation. In some cases, hepatic ultrasonography and determination of serum alpha-fetoprotein levels can be helpful as well. Upper endoscopy (visual examination of the upper gastrointestinal [GI] tract) should be completed every one to four years to evaluate for gastric and duodenal polyps. Duodenal polyps that increase in size or number or show signs of becoming cancerous may require treatment. This treatment may include evaluation by computed tomography or ultrasonography. If necessary, the polyps may be removed by laser or other procedures.

For at-risk relatives of affected individuals, regular screening should begin between the ages of 10 and 12 years. This screening can be accomplished by protein truncation testing. If the test result is a true negative (i.e., negative result in a person whose affected relative had a positive result), further screening is debatable. This test result should theoretically eliminate the risk of FAP but, in very few cases, laboratory errors or other circumstances may lead to an inaccurate test result. Thus, some experts suggest that flexible sigmoidoscopy should be

KEY TERMS

Benign—Referring to a noncancerous tumor that does not spread and is not life-threatening.

Duodenum—Portion of the small intestine nearest the stomach; the first of three parts of the small intestine.

Epidermoid cyst—Benign cystic tumor derived from epithelial cells.

Fibroma—A nonmalignant tumor of connective tissue.

Hypertrophy—Increase in the size of a tissue or organ brought on by the enlargement of its cells rather than cell multiplication.

Lipoma—A benign tumor composed of well-differentiated fat cells.

Malignant—A tumor growth that spreads to another part of the body, usually cancerous.

Osteoma—A benign bone tumor.

Somatic—Relating to the nonreproductive parts of the body.

performed at ages 18, 25, and 35 years in these individuals, with standard screening thereafter.

After colectomy, continued surveillance of patients with FAP is advised. Ileoscopy is recommended every three to five years. This procedure examines the ileum, or lowest third of the small intestine, and serves to rule out polyps, which may become cancerous with time. Surgical removal of desmoid tumors is invasive but often necessary to prevent recurrence. Various nonoperative treatments have been attempted, such as medication and radiation, none of which have yielded consistent results. Additionally, the examination of any remaining rectal tissue by proctoscopy is necessary every six months to assess for signs of rectal cancer.

As with any abdominal surgeries in people affected with FAP, there is a risk of developing desmoid tumors after the colectomy. If desmoids are suspected, computed tomography is the recommended imaging study. MRI may also be used in certain cases.

Surveillance of the upper GI tract, even after total proctocolectomy, is appropriate because of the incidence of tumors in this area previously discussed.

Prognosis

Without colectomy, the prognosis for individuals with FAP is very poor. Patients who have not undergone

colectomy develop colorectal cancer at an average age of 39 years. The majority of untreated people die from colorectal cancer by the age of 42 years. For those who do undergo a colectomy, prognosis is variable, depending on development and progression of other tumors. For example, desmoids can also be detrimental to those affected with FAP, accounting for 11%–31% of all mortality in these individuals.

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- Colorectal Cancer Network, <http://www.colorectal-cancer.net>
- Hereditary Colon Cancer Foundation, 3519 NE 15th Avenue, Unit 518, Portland, OR 97212, (334) 740-8657, info@HCCtakesGuts.org, <http://www.hcctakesguts.org>

Mary E. Freivogel, MS

Familial dysautonomia

Definition

Familial dysautonomia (FD) is a rare inherited disorder in which affected individuals experience multiple malfunctions of the autonomic nervous system (the part of the nervous system that regulates heart muscle, smooth muscle, and glands) as well as the sensory, motor, and central components of the nervous system. The disorder

is progressive with a continual loss of nerve cells of the sensory and autonomic nervous systems.

Description

Familial dysautonomia is an inherited disorder that occurs almost exclusively in people of Eastern European (Ashkenazi) Jewish descent. FD is one of a larger group of at least five hereditary sensory and autonomic neuropathies (HSANs), conditions that stem from abnormalities of the nervous system. FD was first described in 1949 by pediatricians Conrad Riley and Richard Day. They reported five children, all Jewish, who had an unusual set of reactions to mild anxiety, attributed to a disturbance of the autonomic nervous system. FD is also known as HSAN type III or Riley-Day syndrome. Decades of studies have determined the cause to be a genetic abnormality that causes poor development of nerve cells in the fetus, leading to a progressive loss of nerve cells of the autonomic and sensory nervous systems. The depletion of nerve cells in the autonomic system causes problems with unstable heart rate, blood pressure, and body temperature, as well as gastrointestinal dysfunction, poor motor coordination, and emotional instability. Abnormal development of the sensory nervous system results in poor perception of pain, heat, and cold. This causes affected individuals to injure themselves without being aware of it. This deterioration of the nervous system worsens throughout life and causes multiple health problems that lead to the death of 50% of those affected by the time they reach adulthood.

Genetic profile

FD is caused by mutations (genetic errors) in the *IKBKAP* gene that is found on human chromosome 9, specifically located at region 9q31. The disease is inherited as an autosomal recessive trait. This means that both parents have one copy of the mutant gene but do not have the disease. For these parents, there is a 25% chance with each pregnancy that the child will have the disease.

The *IKBKAP* gene has two known mutations, which together account for 100% of the Ashkenazi Jewish (AJ) cases of FD. There is also a third mutation causing FD that is rarely seen in the non-AJ population. This mutation's gene location has not yet been determined.

Demographics

The abnormal gene causing FD is rare in the general population but has a fairly high incidence in the Ashkenazi Jewish population, originating from Eastern Europe. Both males and females are affected. In the at-risk group, 1 in 27 people is thought to be a carrier of the abnormal gene, with a disease frequency of 1 in 3,700 live births.

Rarely, non-Jewish individuals affected with FD have been reported; a Norwegian child was diagnosed with FD in 1977.

Signs and symptoms

Sensory and autonomic nervous systems fail to develop properly in the fetus. Newborn babies with FD have poor or decreased muscle tone and have poor sucking and swallowing reflexes that make feeding difficult. Affected babies are prone to periods of abnormally low body temperature and are unable to produce adequate tears when crying.

Although symptoms vary markedly, by adolescence, affected children have a 90% likelihood of spinal curvature and experience weakness and leg cramping. They have difficulty concentrating and undergo personality changes including negativism, depression, irritability, and insomnia. Forty percent of affected people have regular vomiting crises in response to either emotional or physical stress. A crisis typically involves one to three days of compulsive vomiting, rapid heart rate, high blood pressure, profuse sweating, and red, blotchy skin.

Between crises, affected individuals may experience low blood pressure when rising to a standing position (postural hypotension). They often have unexplained fevers and may have convulsions in response to even mild infections. Uncoordinated swallowing, reflux of stomach contents, and a poor gag reflex result in food or fluids being misdirected into the trachea and lungs. Aspiration pneumonia (lung infections) often follows. Kidney function may deteriorate with age. Affected people have an abnormal response to low oxygen or high carbon dioxide in their blood. They do not experience the expected "air hunger," or urge to breathe, and may faint or have a seizure. Lack of tears, decreased blink frequency, and insensitivity of the eye to pain from foreign objects can cause inflammation and ulcers of the cornea.

A characteristic sign in those affected with familial dysautonomia is a lack of the sense of taste. This is due to the absence of taste buds on the tongue. Other sensory problems include an inability to feel pain or distinguish between hot and cold temperatures; sensory loss increases with age. Deep tendon reflexes in affected individuals are decreased. Poor speech and motor coordination result in abnormal gait, unsteadiness, tongue thrusting, and abnormal rhythmic facial movements. Growth is stunted, with an average adult height of 5 feet (1.5 meters). Puberty is delayed in both sexes. However, fertility and offspring of affected individuals are normal.

Diagnosis

The presentation of FD varies between affected people. However, of the many manifestations of the disease,

KEY TERMS

Aspiration pneumonia—Lung infection due to food or liquids accidentally getting into lungs.

Autonomic nervous system—The part of the nervous system that regulates heart muscle, smooth muscle, and glands.

Autosomal—Related to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Recessive—Genetic trait expressed only when present on both members of a pair of chromosomes, one inherited from each parent.

five signs are key to the diagnosis: flat, smooth tongue due to lack of taste buds; lack of red flare following histamine injection under the skin; decreased or absent deep tendon reflexes; absence of overflow tears with emotional crying; and parents of Ashkenazi Jewish background.

Other frequent signs are decreased response to pain and temperature, decreased corneal reflexes, unstable blood pressure, low blood pressure when standing erect, red blotching of the skin, and increased sweating. Further supportive evidence of the FD diagnosis includes feeding difficulties, repeated aspiration pneumonia, episodes of low body temperature, breath-holding spells, poor muscle tone, delayed motor development, repeated vomiting, spinal curvature, and poor growth. Prenatal diagnosis, screenings for carrier status, and genetic counseling are available.

Treatment and management

The identification of the FD gene as *IKBKAP* was reported in March 2001, and as the function of the gene is better understood, advancements in treatment are expected. Traditionally, treatment is preventive and supportive. Management of vomiting crises is attempted with drugs, replacement of body fluids, prevention of aspiration of stomach contents into lungs, control of blood pressure, and promotion of sleep. Care of the eyes includes

artificial tears, eyewashes, and topical antibiotics to avoid ulcers of the cornea. Early and adequate treatment of even mild infections is important to avoid triggering vomiting crises. Children should be protected from injury and watched for any unusual swellings or skin discolorations as a way of coping with decreased pain and temperature perception.

Physical and occupational therapy, braces, and other orthopedic aids are used for spinal curvature and poor motor coordination. Speech therapy, special feeding techniques, and respiratory care enhance quality of life. It is important to maintain adequate fluid intake and avoid situations such as high elevations, air travel, and diving underwater where oxygen concentration is decreased. Psychological intervention is helpful to alleviate emotional instability and mood swings in children, and depression, anxiety, and phobias in adults.

Prognosis

The disease process of familial dysautonomia cannot be prevented at present but 80% of affected individuals survive beyond childhood and 50% reach age 30. A few individuals with FD have lived into their fifties. With the determination of the exact location of the gene abnormality, prospects for new treatments and possible gene therapy are on the horizon.

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ORGANIZATIONS

Dysautonomia Foundation, 315 W. 39th St., Suite 701, New York, NY 10018, (212) 279-1066, (212) 279-2066, info@famdys.org, <http://www.familialdysautonomia.org>

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Familial endocrine adenomatosis see **Multiple endocrine neoplasia**

Familial fatal insomnia see **Prion diseases**

Familial idiopathic basal ganglia calcification

Definition

Familial idiopathic basal ganglia calcification (FIBGC) is a rare progressive neurological disorder that is often hereditary. Characterized by deposits of calcium in the basal ganglia and other parts of the brain, FIBGC causes worsening dementia and the loss of routine motor skills, among other symptoms.

Description

Though calcium is important for good health, this mineral can have harmful effects when it appears in parts of the body where it does not belong. In FIBGC, abnormal deposits of calcium build up in a region of the brain called the basal ganglia (mainly in a section called the globus pallidus) as well as in other parts of the brain. The basal ganglia is the technical name given to clusters of nerve cells that help to initiate and control movements of the body—for example, reaching for a cup of coffee or taking a step forward while walking. The presence of these calcium deposits (referred to as calcifications) interferes with the working of the brain, causing a variety of debilitating mental and physical symptoms that worsen over time. Aside from the basal ganglia, the calcium deposits associated with FIBGC often appear in other areas of the brain such as the cerebral cortex.

Two important effects of the disease are dementia and the loss of learned motor skills. People affected by FIBGC may become overly forgetful and easily confused or disoriented. They have trouble performing relatively simple tasks that require basic hand-eye coordination. Most people with the disease experience slurred speech and problems involving involuntary movements or poor coordination. In addition, personality changes and disorders of mood may develop. In one study of 18 people with FIBGC, half of the participants had symptoms of obsessive-compulsive disorder, major depression, or bipolar disorder. People with FIBGC may have psychotic

symptoms, including hallucinations (visual and auditory), a distorted perception of reality, and paranoid delusions.

As the disease progresses, it causes an increasing degree of paralysis. Muscles become stiff, and physical movement is restricted. Aside from these symptoms, people with FIBGC may experience specific movement disorders: slow, twisting movements of the hands and feet (athetosis) and jerky, rapid movements that resemble spasms (chorea). Vision may also be affected. Because the disease can weaken nerves that carry signals from the eyes to the brain, people with FIBGC may experience partial or almost complete vision loss. Ear infections have also been reported.

The underlying cause of FIBGC is unknown. For this reason, it is described as an idiopathic disorder. Less common names for the disease include Fahr disease, cerebrovascular ferrocalsinosis, non-arteriosclerotic cerebral calcifications, and striopallidodentate calcinosis.

Genetic profile

Research indicates that multiple genes are involved in FIBGC. Almost half of all known cases are caused by mutations in the *SLC20A2* gene, while a small number of cases are caused by mutations in the *PDGFRB* gene and in chromosomes 2, 7, 9, and 14.

The *SLC20A2* gene regulates production of a protein called sodium-dependent phosphate transporter 2 (PiT-2). This protein helps regulate phosphate homeostasis or phosphate levels within the body by transporting phosphate across the cell membrane and into the cell. Mutations in the *SLC20A2* that lead to FIBGC cause the gene to produce a PiT-2 protein that cannot carry phosphate into cells. As a result, phosphate levels in the bloodstream rise. When phosphate levels rise in the blood, they rise in the brain. This elevated phosphate combines with calcium and forms the calcium deposits in the brain that cause FIBGC.

FIBGC caused by mutations in the *PDGFRB* gene are a result of a failure to make a protein called PDGFRB protein, which is important in activating pathways that control many necessary cellular functions. The connection between mutations in the *PDGFRB* gene and FIBGC are not as well understood as those with mutations in the *SLC20A2* gene. Altered PDGFRB protein may affect the cells that line blood vessels in the brain, causing them to take in too much calcium, which could lead to the calcifications of FIBGC. It is also suspected that abnormal PDGFRB proteins could alter phosphate transportation, similar to the mutations in the *SCL20A2* gene, and this may lead to increased phosphate levels in the brain and to the development of calcifications in the brain.

The calcifications found in the basal ganglia of individuals with FIBGC may lead to the characteristics of

KEY TERMS

Calcification—A process in which tissue becomes hardened due to calcium deposits.

Cerebral cortex—The outer surface of the cerebrum made up of gray matter and involved in higher thought processes.

Cerebrum—The largest section of the brain, which is responsible for such higher functions as speech, thought, vision, and memory.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Dementia—A condition of deteriorated mental ability characterized by a marked decline of intellect and often by emotional apathy.

Idiopathic—Of unknown origin.

Neurological—Relating to the brain and central nervous system.

Parathyroid glands—A pair of glands adjacent to the thyroid gland that primarily regulate blood calcium levels.

the disease by disrupting the connection between the basal ganglia and other parts of the brain, specifically the frontal lobe. The frontal lobe is responsible for a person's ability to reason, plan, make decisions, and solve problems. These calcifications may also affect parts of the brain that control social behavior, mood, and motivation. While most people with FIBGC have greater calcification in the basal ganglia, not all people with FIBGC have significant calcification.

Demographics

FIBGC, which appears to affect men and women equally, can appear at any stage of life, from infancy to adulthood. Some people diagnosed with the disease have no family history of the condition, while in many cases FIBGC runs in families and affects members of several generations. In people with dominantly inherited FIBGC, symptoms usually appear anywhere between the ages of 30 and 60. The recessive form emerges at a younger age, between infancy and young adulthood.

Signs and symptoms

People with FIBGC have abnormal calcium deposits in the basal ganglia, primarily in the globus pallidus

region, and often in other parts of the brain. Loss of brain cells in these areas also occurs. The results of electrocardiogram (ECG) studies, which monitor heartbeats, are often abnormal in people with FIBGC. Other signs include malfunctioning parathyroid glands and low blood calcium levels.

The disease causes a variety of physical and psychological symptoms. The head of a person with FIBGC is often smaller and rounder than normal. The condition causes worsening dementia and loss of routine motor skills. Muscle stiffness, movement disorders, and paralysis may occur. Speech often becomes slurred. In some cases, FIBGC causes vision problems and ear infections. Symptoms of Parkinson's disease may develop as well.

Diagnosis

In simple terms, FIBGC is diagnosed when calcifications in the basal ganglia are associated with slurred speech, movement disorders, and other specific symptoms. Special imaging procedures such as a CT scan can detect the presence of calcium deposits. Symptoms can be determined by physical and psychological examinations. Friends or family members with relevant observations of the patient's behavior can also be helpful. Blood tests may be recommended to evaluate blood calcium levels and the parathyroid glands. The appearance of Parkinson-like symptoms is not essential to a diagnosis of FIBGC.

In the absence of other factors, calcium deposits in the basal ganglia do not necessarily indicate the presence of FIBGC. Such calcifications may be due to a metabolism disorder, infectious disease, or a genetic disorder other than FIBGC. In fact, sometimes these calcifications may be present without producing any symptoms or harmful effects, especially in people older than 60.

Treatment and management

There is no cure for FIBGC, which worsens over time. The process of calcification cannot be stopped or reversed. Where possible, clinicians focus on alleviating its various mental and physical effects. These may vary to some degree depending on the individual, even among members of the same family. Lithium carbonate, for example, may be recommended to control psychotic symptoms, while antidepressant medications are often used to combat depression. Ear infections associated with FIBGC can be treated with antibiotics and pain medication.

Prognosis

Due to its damaging effects on the brain and nervous system, FIBGC is eventually fatal.

QUESTIONS TO ASK YOUR DOCTOR

- How does familial idiopathic basal ganglia calcification cause its effect on the brain of a child?
- What is known about the genetic basis of familial idiopathic basal ganglia calcification?
- Are there treatments available that can be used to cure or reduce the effects of familial idiopathic basal ganglia calcification?
- What palliative treatments are available for a child with familial idiopathic basal ganglia calcification?

Resources

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- National Institute of Neurological Disorders and Stroke. NIH Neurological Institute, PO Box 5801, Bethesda, MD 20824, (301) 496-5751 or (800) 352-9424, <http://www.ninds.nih.gov>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06813, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Greg Annussek
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Familial infiltrative fibromatosis see **Hereditary desmoid disease**

Familial lipoprotein lipase deficiency

Definition

Familial lipoprotein lipase deficiency is a rare genetic disorder that interferes with fat metabolism. The disease is characterized by the accumulation of triglycerides and chylomicrons (fatty droplets) in the blood. Some common symptoms of this disorder include abdominal pain, nausea, vomiting, and small yellow lesions in the skin.

First described in 1932 by two German physicians, Max Bürger and Otto Grütz, familial lipoprotein lipase deficiency is also known by a number of other names including the following:

- Bürger-Grütz syndrome
- endogenous hypertriglyceridemia
- familial fat-induced hypertriglyceridemia
- familial hyperchylomicronemia
- familial LPL deficiency
- hyperlipoproteinemia type I
- hyperlipoproteinemia type Ia
- lipase D deficiency
- LIPD deficiency
- lipoprotein lipase deficiency, familial

Description

Both fatty tissue (also known as adipose tissue) and muscle normally produce the lipoprotein lipase enzyme. When a person has lipoprotein lipase deficiency, however, he or she is unable to make this enzyme or can make only very low quantities of it. As a result, fat accumulates in the blood. This accumulation of fats in the blood may lead to symptoms such as abdominal pain, nausea, and small yellow fat deposits called xanthomas that appear in the skin.

Genetic profile

Located on chromosome 8, the *LPL* gene carries the blueprint for making the enzyme called lipoprotein lipase. This enzyme breaks down two types of lipoproteins, which are proteins with lipid components (lipids are fats, oils, and other compounds that do not dissolve in water).

There are two types of lipoproteins: chylomicrons, which have the job of transporting fats from the intestine to the blood stream, and very-low-density lipoproteins (VLDLs), which are located in the blood and have the job of transporting fats and cholesterol from the liver to other places in the body. The role of lipoprotein lipase is

KEY TERMS

Autosomal recessive—Describes a genetic trait that appears only when two copies of a mutated gene are present.

Chylomicron—A small fatty droplet.

Lipase—An enzyme that catalyzes the breakdown of a lipid.

Lipids—A class of organic compounds defined by their tendency to dissolve in organic liquids, such as alcohol and ether, but not in water.

Lipoprotein—A complex molecule consisting of a lipid molecule joined with one or more protein molecules.

Prevalence—The number of individuals living with a particular illness within a particular population at any given time. Prevalence is often expressed in terms of the number of individuals per 100 or per 1,000 members of the population.

Triglyceride—A type of lipid consisting of a molecule of glycerol and three fatty acid fragments.

to liberate the fat from chylomicrons and VDLs so the fat can go on to either be used as energy or be stored. Lipoprotein lipase accomplishes this task with the help of another enzyme called apolipoprotein C-II.

When an individual has lipoprotein lipase deficiency, the genetic mutation causes little or no lipoprotein lipase to be produced. Without sufficient enzyme, fat-containing molecules do not break down as they should. They build up in the blood, triggering the symptoms associated with this disorder.

Not all *LPL* mutations are the same. Scientists know of more than 220 different mutations in the gene that can lead to familial lipoprotein lipase deficiency. In many cases, the *LPL* mutation causes one amino acid (amino acids are the building blocks of proteins) to be replaced by another. Specifically, the amino acid glutamic acid takes the place of the amino acid glycine at one position in the enzyme. That seemingly small change is enough to cause the reduction in enzyme function that eventually causes the symptoms of the disorder.

Familial lipoprotein lipase deficiency is an autosomal recessive disorder. It occurs when an individual inherits one mutated *LPL* gene from each parent. The parents may not have the condition and may instead only be carriers. Carriers are individuals who do not develop the disorder themselves but may pass the gene for the disorder on to their children. If both parents are carriers, each

of their children has a 50% chance of being a carrier and a 25% chance of acquiring the disorder. If both parents have lipoprotein lipase deficiency, all of their children will also acquire the disorder.

Demographics

The prevalence of this syndrome is estimated to be about one per million worldwide, although the condition is significantly more common in some parts of the province of Quebec in Canada. In Quebec, the disorder is likely traced to a common ancestor or small group of common ancestors who carried the mutated gene, which then passed down through subsequent generations, increasing in frequency over time.

Signs and symptoms

Symptoms of lipoprotein lipase deficiency generally first appear when the individual is in infancy or early childhood. Symptoms may include one or more (typically several) of the following:

Muscle and bone pain; the presence of xanthomas in the skin, typically on the arms, knees, buttocks, and trunk; jaundice (yellowish coloring of the skin and eyes); and repeated bouts of pancreatitis (inflammation of the pancreas), which may cause symptoms as diverse as abdominal pain, nausea, vomiting, chills, fever, and weakness.

Diagnosis

Initial diagnosis of familial lipoprotein lipase deficiency is based on the presence of symptoms of the disorder, with special attention to possible tenderness and inflammation of the pancreas; accumulation of fatty tissue under the skin, especially the eyelids; and swollen liver and spleen. Confirmatory tests involve a blood test to measure serum triglyceride levels and centrifugation, or spinning, of a blood sample in a centrifuge. Any serum triglyceride result greater than 2,000 mg/dL is suggestive of familial lipoprotein lipase deficiency, although such levels are characteristic of other metabolic genetic disorders as well. The appearance of a milky, fatty material during centrifugation is also suggestive of the condition. Finally, genetic tests are available to determine the existence of a mutation in the *LPL* gene responsible for familial lipoprotein lipase deficiency.

Treatment and management

No cure is available for familial lipoprotein lipase deficiency, but many of the symptoms are treatable. Patients are typically placed on an extremely low-fat diet that is limited to 20 grams of fat per day, or 15% of the individual's daily food intake. Most symptoms clear up after the patient goes on this diet. This diet is designed

QUESTIONS TO ASK YOUR DOCTOR

- How long will I have to remain on this low-fat diet?
- What is the likelihood that family members will also develop familial lipoprotein lipase deficiency?
- If I find out that my child has eaten high-fat foods, is there anything we can do after the fact to counter any potential effects?
- How will I know if my child's pancreatitis is severe enough to warrant a trip to the hospital?
- Are treatments or drugs available for use with familial lipoprotein lipase deficiency?
- Are there support groups or other resources for individuals with familial lipoprotein lipase deficiency and their families?

to keep the patient's blood triglyceride concentration to a level below 2,000 mg/dL. Continued monitoring of triglycerides will help ensure that the dietary measures are sufficient to control symptoms.

In addition, doctors may recommend that patients avoid other substances that are related to higher triglyceride levels. These include:

- Alcohol, and oral estrogens, which are hormones typically used in birth-control or hormone-replacement therapies
- Diuretics, which are so-called "water pills" that rid the body of excess water and cause an increase in urine production
- Isotretinoin, an acne treatment
- Sertraline hydrochloride (Zoloft), an antidepressant medication
- Heart medications known as beta blockers (also called beta-adrenergic blocking agents)

Acute pancreatitis may require a hospital stay. While in the hospital, patients receive intravenous fluids until the inflammation eases and the symptoms subside. This may take several days.

Brothers and sisters of a child who is diagnosed with the disorder should be tested for lipoprotein lipase deficiency, preferably in infancy, so that proper preventive measures can be taken as soon as possible. Adult partners who are carriers and are thinking about having children should consider genetic counseling to fully understand the risks for passing the disorder to their offspring and to receive information about prenatal testing for the disorder.

Prognosis

Individuals are born with familial lipoprotein lipase deficiency, and the first symptoms generally appear during infancy or childhood. No cure exists for this disorder, but those who are willing and able to make the necessary dietary adjustments normally survive the disorder well and live into adulthood. All signs and symptoms, including pancreatitis, skin lesions, and liver and spleen abnormalities disappear within a short time after a low-fat diet has been instituted. Although it is rare, some patients develop other conditions, such as diabetes mellitus, due to pancreatitis.

Resources

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- "Familial Lipoprotein Lipase Deficiency." UFHealth. April 8, 2019. <https://ufhealth.org/familial-lipoprotein-lipase-deficiency> (accessed June 8, 2021).

ORGANIZATIONS

- Genetic and Rare Diseases (GARD) Information Center, PO Box 8126, Gaithersburg, MD 20898-8126, 301-519-3194, 888-205-2311, gardinfo@nih.gov, <http://www.genome.gov/10000409>

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Familial Mediterranean fever

Definition

Familial Mediterranean fever (FMF) is an inherited disorder of the inflammatory response characterized by recurring attacks of fever accompanied by intense pain

in the abdomen, chest, or joints. Attacks usually last 12–72 hours and can occasionally involve a skin rash. Kidney disease is a serious concern if the disorder is not treated.

Description

FMF can be described as a disorder of “inappropriate” inflammation: An event that in a normal situation causes a mild or unnoticeable inflammation might cause a severe inflammatory response in someone with FMF. Certain areas of the body are at risk for FMF-related symptoms. A serosa is a serous (fluid-producing) membrane that can be found inside the abdominal cavity (peritoneum), around the lungs (pleura), around the heart (pericardium), and inside the joints (synovium). The symptoms of FMF are due to inflammation of one or more of the serosal membranes (serositis). Thus, FMF is also sometimes called recurrent polyserositis.

During an attack, large numbers of neutrophils, a type of white blood cell, move into the affected areas, causing painful inflammation and fever. These episodes may be accompanied by a skin rash or joint pain. In a few cases, chronic arthritis is a problem. Amyloidosis is a potentially serious condition in which proteins called amyloids are mistakenly produced and deposited in organs and tissues throughout the body. Left untreated, amyloidosis often leads to kidney failure, which is the major long-term health risk in FMF.

In most cases, the attacks of fever and pain are first noticed in childhood or adolescence. The interval between these episodes may be days or months and is not predictable. However, during these intervals people with FMF typically lead normal lives. It is not entirely clear what brings on an attack, but people with FMF often report mild physical trauma, physical exertion, or emotional stress just prior to the onset of symptoms. Treatment for FMF involves an oral medication called colchicine, which is highly effective for the episodes of fever and pain, as well as for amyloidosis and the kidney disease that can result from it.

FMF is also known by many other names. They include recurrent hereditary polyserositis, benign paroxysmal peritonitis, familial paroxysmal polyserositis, paroxysmal polyserositis, familial recurrent polyserositis, periodic fever, periodic amyloid syndrome, periodic peritonitis syndrome, Riemann periodic disease, Riemann syndrome, Siegal–Cattan–Mamou syndrome, and Wolff periodic disease.

There are two phenotypes of FMF, classified as type 1 FMF and type 2 FMF. Type 1 FMF is classified as having short episodes of inflammation and symptoms but is more recurrent in nature. The severity and signs and

symptoms of type 1 FMF are dependent on the individual. This is the classic type of FMF. Type 2 FMF is classified as having a diagnosis of amyloidosis only. In this type, no other signs or symptoms are present.

Genetic profile

FMF is a genetic condition inherited in an autosomal recessive fashion. Mutations in the *MEFV* gene (short for Mediterranean fever) on chromosome number 16 are the underlying cause of FMF. More than 80 *MEFV* mutations that cause FMF have been identified. Autosomal recessive inheritance implies that a person with FMF has mutations in both copies of the *MEFV* gene. All genes come in pairs, and one copy of each pair is inherited from each parent. If neither parent of a child with FMF has the condition, it means they both carry one mutated copy of the *MEFV* gene, but also one normal copy, which is enough to protect them from disease. If both parents carry the same autosomal recessive gene, there is a one in four chance in each pregnancy that the child will inherit both recessive genes, and thus have the condition.

The *MEFV* gene carries the instructions for production of a protein called pyrin, named for pyrexia, the medical term for fever. Most *MEFV* mutations change one of the protein building blocks (amino acids) used to make pyrin. The most common mutation replaces the amino acid methionine with the amino acid valine at protein position 694. *MEFV* mutations result in lower amounts of pyrin or a malformed pyrin protein that cannot function properly. As a result, pyrin cannot perform its proposed role in controlling inflammation, leading to an inappropriate inflammatory response.

Demographics

FMF is considered a rare disease worldwide. However, it is very common in Sephardic Jewish, Armenian, Arab, and Turkish people, with an estimated prevalence of about 1 in 200 individuals. Genetic testing has also recently identified numerous cases in additional Mediterranean populations including Ashkenazi Jews, Italians, Greeks, Spaniards, and Cypriots. Occasional cases are also increasingly reported in a wide range of other ethnicities, such as Northern Europeans and Japanese.

Signs and symptoms

The recurrent acute attacks of FMF typically begin in childhood or adolescence. Episodes of fever and painful inflammation usually last 12–72 hours. About 90% of people with FMF have their first attack by age 20. The group of symptoms that characterizes FMF includes the following.

KEY TERMS

Acute phase reactants—Blood proteins whose concentrations increase or decrease in reaction to the inflammation process.

Amyloid—A waxy translucent substance composed mostly of protein that forms plaques (abnormal deposits) in the brain.

Amyloidosis—Accumulation of amyloid deposits in various organs and tissues in the body such that normal functioning of an organ is compromised.

Colchicine—A compound that blocks the assembly of microtubules, which are protein fibers necessary for cell division and some kinds of cell movements, including neutrophil migration. Side effects may include diarrhea, abdominal bloating, and gas.

Exon—The region of a gene that contains the code for producing protein.

Leukocyte—A white blood cell. The neutrophils are a type of leukocyte.

Leukocytosis—An increase in the number of leukocytes in the blood.

Neutrophil—The primary type of white blood cell involved in inflammation. Neutrophils are a type of granulocyte, also known as a polymorphonuclear leukocyte.

Pericarditis—Inflammation of the pericardium, the membrane surrounding the heart.

Peritonitis—Inflammation of the peritoneum, the membrane surrounding the abdominal contents.

Pleuritis—Inflammation of the pleura, the membrane surrounding the lungs.

Pyrexia—The medical term denoting fevers.

Serositis—Inflammation of a serosal membrane. Polyserositis refers to the inflammation of two or more serosal membranes.

Synovitis—Inflammation of the synovium, a membrane found inside joints.

Fever

An FMF attack is nearly always accompanied by a fever, but it may not be noticed in every case. Fevers are typically 100°F–104°F (38°C–40°C). Some people experience chills prior to the onset of fever.

Abdominal pain

Nearly all people with FMF experience abdominal pain at one point or another, and for most it is the most

common complaint. The pain can range from mild to severe and can be diffuse or localized. It can mimic appendicitis, and many people with undiagnosed FMF have had appendectomies or exploratory surgery of the abdomen done, only to have the fever and abdominal pain return.

Chest pain

Pleuritis, also called pleurisy, occurs in up to half of the affected individuals in certain ethnic groups. The pain is usually on one side of the chest. Pericarditis would also be felt as chest pain.

Joint pain

About 50% of people with FMF experience joint pain during attacks. The pain is usually confined to one joint at a time and often involves the hip, knee, or ankle. For some people, however, the recurrent joint pain becomes chronic arthritis.

Myalgia

Up to 20% of individuals report muscle pain. These episodes typically last less than two days and tend to occur in the evening or after physical exertion. Rare cases of muscle pain and fever lasting up to one month have been reported.

Skin rash

A rash described as erysipelas-like erythema accompanies attacks in a minority of people and most often occurs on the front of the lower leg or top of the foot. The rash appears as a red, warm, swollen area about 4–6 in. (10–15 cm) in diameter.

Amyloidosis

FMF is associated with high levels in the blood of a protein called serum amyloid A (SAA). Over time, excess SAA tends to be deposited in tissues and organs throughout the body. The presence and deposition of excess SAA is known as amyloidosis. Amyloidosis may affect the gastrointestinal tract, liver, spleen, heart, and testes, but effects on the kidneys are of greatest concern. The frequency of amyloidosis varies among the different ethnic groups, and its overall incidence is difficult to determine because of the use of colchicine to avert the problem. Left untreated, however, those individuals who do develop amyloidosis of the kidneys may require a renal transplant or may even die of renal failure. The frequency and severity of a person's attacks of fever and serositis seem to have no relation to whether he or she will develop amyloidosis. In fact, a few people with FMF have been

described who have had amyloidosis but apparently no other FMF-related symptoms.

Other symptoms

A small percentage of boys with FMF develop painful inflammation around the testes. Headaches are a common occurrence during attacks, and certain types of vasculitis (inflammation of the blood vessels) seem to be more common in FMF.

Diagnosis

Individually, the symptoms that define FMF are common. Fevers occur for many reasons, and nonspecific pains in the abdomen, chest, and joints are also frequent ailments. Several infections can result in symptoms similar to FMF (Mollaret's meningitis, for instance), and many people with FMF undergo exploratory abdominal surgery and ineffective treatments before they are finally diagnosed. Membership in a less commonly affected ethnic group may delay or hinder the correct diagnosis.

In general, symptoms involving one or more of the following broad groups should lead to suspicion of FMF: unexplained recurrent fevers, polyserositis, skin rash, and/or joint pain; abnormal blood studies; and renal or other disease associated with amyloidosis. A family history of FMF or its symptoms would obviously be an important clue, but the recessive nature of FMF means there usually is no family history. The diagnosis may be confirmed when a person with unexplained fever and pain responds to treatment with colchicine since colchicine is not known to have a beneficial effect on any other condition similar to FMF. Abnormal results on a blood test typically include leukocytosis (elevated number of neutrophils in the blood), an increased erythrocyte sedimentation rate (rate at which red blood cells form a sediment in a blood sample), and increased levels of proteins associated with inflammation (called acute phase reactants) such as SAA.

As of 2021, *MEFV* was the only gene currently known to be associated with FMF. In the United States, several laboratories offer testing for the common mutation p.Glu148Gln in exon 2; mutation p.Pro369Ser in exon 3; and the eight common mutations in exon 10 observed in Mediterranean populations. Because most of the known *MEFV* mutations occur in exon 10, laboratories offering sequence analysis of select exons include exon 10 and variably include other exons.

Similar syndromes of periodic fever and inflammation include familial Hibernian fever and hyperimmunoglobulinemia D syndrome, but both are rarer than FMF.

QUESTIONS TO ASK YOUR DOCTOR

- Occasionally I have a mild fever accompanied by rather severe pain in my joints. How can I find out whether this condition is familial Mediterranean fever?
- What causes this condition?
- What can I do to avoid having episodes of familial Mediterranean fever?
- Should I expect this condition to improve or get worse over time?

Treatment and management

Colchicine is a chemical compound that can be used as a medication, and it is frequently prescribed for gout. Some years ago, colchicine was discovered to also be effective in reducing the frequency and severity of attacks in FMF. Treatment for FMF at this point consists of taking colchicine daily. Studies have shown that about 75% of FMF patients achieve complete remission of their symptoms, and about 95% show marked improvement when taking colchicine. Lower effectiveness has been reported, but there is some question about the number of FMF patients who choose not to take their colchicine between attacks when they are feeling well and thus lose some of the ability to prevent attacks. Compliance with taking colchicine every day may be hampered by its side effects, which include diarrhea, nausea, abdominal bloating, and gas. There is a theoretical risk that colchicine use could damage chromosomes in sperms and eggs or in an embryo during pregnancy, or that it might reduce fertility. However, studies looking at reproduction in men and women who have used colchicine have so far not shown any increased risks. Colchicine is also effective in preventing, delaying, or reversing renal disease associated with amyloidosis.

Studies have shown that an estimated 5%–10% of patients with FMF do not respond to colchicine treatment. Case studies have been published that show that tumor necrosis factor- α , IL-6, and IL-1 inhibitors are helpful for those who are indeed unresponsive to colchicines. The IL-1 blockers canakinumab and anakinra have been effective in clinical trials, decreasing the frequency and intensity of episodes of FMF flare-ups. The FDA approved the use of canakinumab (Ilaris) as a treatment for FMF in 2016.

Due to its nature as an inflammatory disease, anti-inflammatory pharmaceuticals such as NSAIDs, paracetamol, and dipyrrone are often utilized. Anti-inflammatory supplements such as curcumin, boswellia, and white willow

bark may also be helpful, as well as an anti-inflammatory diet that limits red meat, dairy, simple sugars, gluten, and processed foods.

Other medications may be used as needed to deal with the pain and fever associated with FMF attacks. Dialysis and/or renal transplant might become necessary in someone with advanced kidney disease. Given its genetic nature, there is no cure for FMF nor is there likely to be in the near future. Any couple that has a child diagnosed with FMF, or anyone with a family history of the condition (especially those in high-risk ethnic groups), should be offered genetic counseling to obtain the most up-to-date information on FMF and testing options.

Management of the genetic condition should also include surveillance via annual physical examination with urine spot tests and blood tests to ensure the provided treatment is indeed working and to ensure a rapid diagnosis of renal dysfunction should it occur.

Prognosis

For those individuals who are diagnosed early enough and take colchicine consistently, the prognosis is excellent. Most will have very few if any attacks of fever and polyserositis, and they will likely not develop serious complications of amyloidosis. The problem of misdiagnosing FMF continues, but education attempts directed at both the public and medical care providers should improve the situation. Future research should provide a better understanding of the inflammation process, focusing on how neutrophils are genetically regulated. That information could then be used to develop treatments for FMF with fewer side effects, and might also assist in developing therapies for other diseases in which abnormal inflammation and immune response are a problem.

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- "Familial Mediterranean Fever." NORD. <https://rarediseases.org/rare-diseases/familial-mediterranean-fever/> (accessed June 8, 2021).

ORGANIZATIONS

- March of Dimes, 1550 Crystal City Drive, Suite 1300, Arlington, VA 22202, (888) 663-4637, <https://www.marchofdimes.org>
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), 1 AMS Circle, Bethesda, MD 20892-3675, (301) 495-4484 or (877) 226-4267, (301) 718-6366, NIAMSinfo@mail.nih.gov, <http://www.niams.nih.gov>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>
- Norton and Elaine Sarnoff Center for Jewish Genetics, 30 S. Wells, Chicago, IL 60606, (312) 357-4718, jewishgeneticsctr@juf.org, <https://www.juf.org/cjg/>

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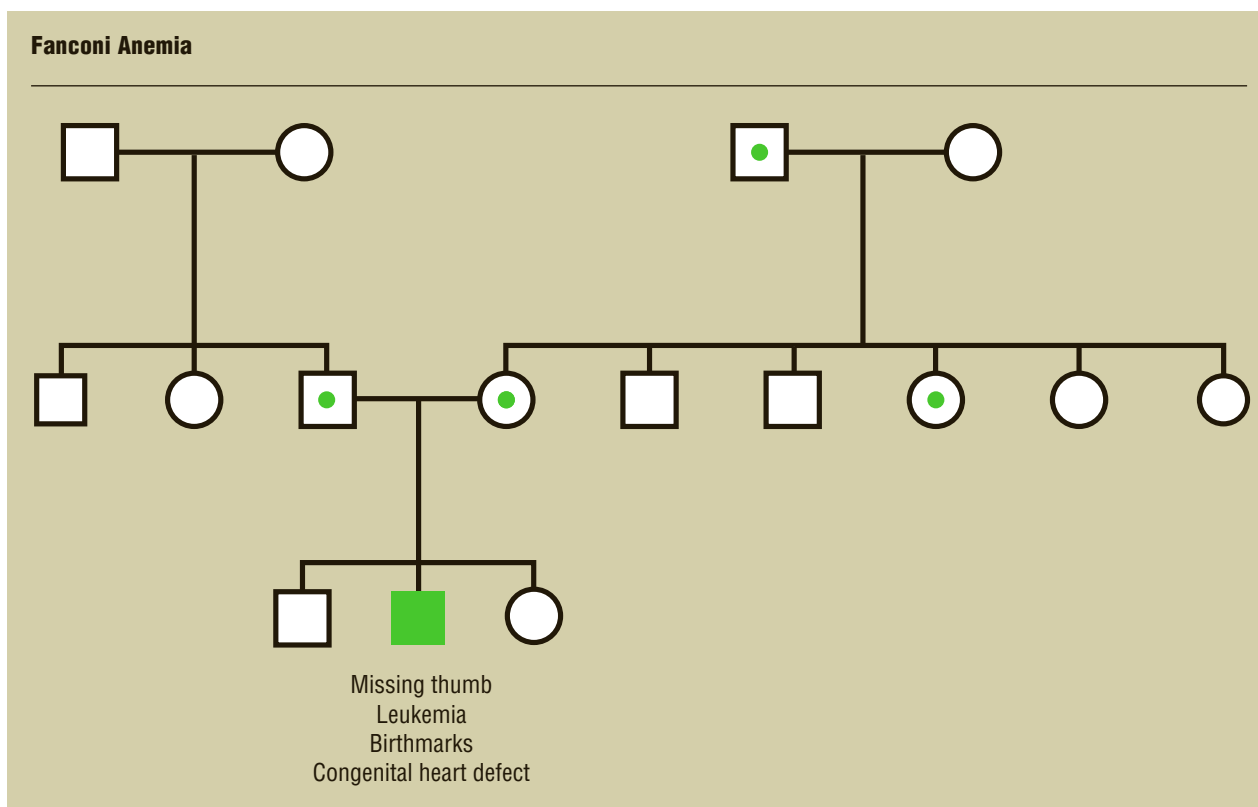
Fanconi anemia

Definition

Fanconi anemia is an inherited disorder characterized by a severe form of anemia and various other physical malformations. Patients with Fanconi anemia are susceptible to various types of cancer.

Description

Fanconi anemia (FA) was first described in 1927 by a Swiss pediatrician named Guido Fanconi (1892–1979). It is also called Fanconi pancytopenia, constitutional aplastic anemia, and aplastic anemia with congenital anomalies. It is a rare inherited bone marrow failure syndrome or form of aplastic anemia. Aplastic anemia is a life-threatening condition in which a person is unable to produce adequate amounts of red blood cells, white blood cells, or platelets. Red blood cells serve to carry oxygen to all areas of the body. White blood cells help to fight infection and disease. Platelets are responsible for clotting to help to heal wounds and control bleeding. Without adequate amounts of these important blood cells, patients affected with aplastic anemia are easily fatigued and susceptible to infections. Most cases of aplastic anemia develop throughout the course of a person's lifetime. However, in FA, the aplastic anemia is congenital, or present from birth.



Fanconi anemia: pedigree analysis chart (Gale)

FA is associated with various other findings in about 60% of patients. These include low birth weight, short stature, skeletal abnormalities, skin discoloration, small eyes, infertility, kidney problems, and heart defects. Additionally, people with FA experience a high incidence of leukemia and an increased incidence of other types of cancer, usually solid tumors.

The chromosomes in the cells of FA patients break and rearrange easily. Chromosomes are the information manuals of our cells. Genes are arranged on chromosomes in a linear fashion like beads on a string. Genes tell cells how to make proteins. These proteins perform many vital functions in the body. When chromosomes break, genes are disrupted and do not function correctly. Mutations in the genes lead to the encoding of abnormal proteins and various health problems associated with the defective proteins. The chromosome breakage in FA can be seen in the laboratory and is used to diagnose the disorder.

Genetic profile

At least 21 different genes were associated with FA as of 2021. A mutation in any one of these genes may cause the disorder.

Inheritance patterns

With the exception of one gene associated with Fanconi anemia, FA is inherited in an autosomal recessive pattern. This inheritance pattern means that for someone to be affected with FA, each of their parents must have a mutation in the same gene. Parents who carry the defective gene do not show symptoms of FA because they have a corresponding gene on the other chromosome that produces an adequate amount of protein. Thus they often do not know they are carriers until they have an affected child. If both parents carry the same defective gene, each of their children has a 25% chance of inheriting both abnormal genes and being affected with FA. Likewise, each child has a 25% chance of inheriting two functional copies of the gene and being unaffected. This leaves a 50% chance that the offspring will have one functional gene and one defective gene and will be an unaffected carrier of the disorder.

The exception to this autosomal recessive inheritance pattern is FA resulting from mutations in the *FANCB* gene, which is located on the short arm of the X chromosome at Xp22.2. Mutations in this gene account for about 2% of FA cases, and are inherited in an X-linked recessive pattern. In this pattern, male offspring of a mother carrying the defective gene on one of her X chromosomes will develop

FA because they do not have a second normal copy of the X-linked gene. Daughters are not affected unless they inherit a defective X chromosome from the father as well as the defective X chromosome from the mother.

FA gene mutations and the FA pathway

The known FA genes are as follows: the *FANCA* gene on the long arm of chromosome 16 at 16q24.3; the *FANCB* gene on the short arm of the X chromosome at Xp22.2; the *FANCC* gene on the long arm of chromosome 9 at 9q22.3; the *FANCD2* gene on the short arm of chromosome 3 at 3p26; the *FANCE* gene on the short arm of chromosome 6 at 6p21.31; the *FANCF* gene on the short arm of chromosome 11 at 11p15; the *FANCG* gene on the short arm of chromosome 9 at 9p13; the *FANCI* gene on the long arm of chromosome 15 at 15q26.1; the *FANCL* gene on the short arm of chromosome 2 at 2p16.1; the *FANCM* gene on the long arm of chromosome 14 at 14q21.2; the *BRCA2* gene on the long arm of chromosome 13 at 13q12.3; the *BRIP1* gene on the long arm of chromosome 17 at 17q22.2; the *PALB2* gene on the short arm of chromosome 16 at 16p12.2; the *RAD51C* gene on the long arm of chromosome 17 at 17q22; the *SLX4* gene on the short arm of chromosome 16 at 16p13.3; the *ERCC4* gene on the short arm of chromosome 16 at 16p13.12; the *BRCA1* gene on the long arm of chromosome 17 at 43q44; the *XRCC2* gene on the long arm of chromosome 7 at 7q36.1; the *MAD2L2* gene on the short arm of chromosome 1 at 1p36.22; the *RFWF3* gene on the long arm of chromosome 16 at 16q23; and the *UBE2T* gene on the long arm of chromosome 1 at 1q32.1. Eighty to 90% of cases of FA are caused by mutations in just three of these genes, *FANCA*, *FANCC*, and *FANCG*, because of their crucial role in DNA repair.

To understand how these genes are involved in the pathogenesis of FA, it is important to have an outline of the process of DNA repair in people with FA. The *FANCA*, *FANCC*, and *FANCG* genes code for proteins that function in a DNA repair process called the FA pathway. This pathway is activated when the process of DNA replication (copying) is interrupted by DNA damage. The type of damage most likely to activate the FA pathway is known as interstrand cross-links, or ICLs. ICLs occur when two nucleotides (the “building blocks” of DNA) on opposite DNA strands form abnormal attachments called cross-links. The most common causes of ICLs are toxic substances that build up in the body and certain cancer chemotherapy drugs. The formation of ICLs stops the process of DNA replication.

The FA pathway is a process with several stages in which it directs repair proteins to the area damaged by an ICL so that the DNA can continue replicating. The three most important FA genes, *FANCA*, *FANCC*, and *FANCG*, contain instructions needed for producing a

group of eight proteins called the FA core complex, which in turn activates two proteins called FANCD2 and FANCI. These two proteins then attract DNA repair proteins to the portions of DNA affected by ICLs. The repair proteins remove the cross-links, allowing DNA replication to resume.

Mutations in any of the *FANCA*, *FANCC*, and *FANCG* genes will cause the FA core complex to lose its ability to function, thus blocking the entire FA pathway. As a result, the ICLs accumulate over time, the damaged DNA is not repaired, and DNA replication eventually stops. The end result is either an abnormally high rate of cell death resulting from the lack of new DNA molecules, or uncontrolled cell growth caused by the absence of DNA repair. In Fanconi anemia, a high rate of cell death leads to the low level of blood cells and physical deformities seen in the disorder, while uncontrolled cell growth leads to myelodysplastic syndromes and acute myeloid leukemia.

Demographics

FA occurs equally in males and females. The total number of FA patients has not been fully documented; only about 2,000 cases of FA have been reported in the medical literature since 1927. It has been estimated, however, that between 1 in 100 and 1 in 600 people carry one of the defective FA genes. According to the Cincinnati Children’s Hospital Medical Center, 31 babies with FA are born in the United States in an average year.

FA is found in all ethnic groups worldwide but is relatively frequent in the Ashkenazi Jewish population. One in every 89 people in this population carries a mutation in the *FANCC* gene. Other groups with higher than average rates of mutations in the FA genes include the Afrikaners (descendants of nineteenth-century Dutch settlers) of South Africa, black Africans from sub-Saharan Africa, and the Roma people living in Spain.

Signs and symptoms

The signs and symptoms of FA generally appear in children between the ages of 3 and 12. In rare cases, symptoms do not present until adulthood. These symptoms vary in severity from case to case. Even within the same family, siblings who are both affected may show very different signs of the disorder.

Aplastic anemia is the first sign of FA in many patients. In some cases, it may be the only sign of the disorder. In aplastic anemia, the bone marrow does not produce an adequate number of red cells, white cells, or platelets. Known as pancytopenia, this deficiency can lead to several conditions. Anemia can result from the lack of red blood cells, leading to weakness, fatigue, and

KEY TERMS

Acute myelogenous leukemia (AML)—A life-threatening disorder of the bone marrow in which a large number of abnormal white blood cells accumulates in the marrow and reduces the production of normal red and white blood cells and platelets. It is also called acute myeloid leukemia.

Androgens—Synthetic male hormones given to patients with FA to improve their blood cell counts. They are effective in about 50% of patients.

Aplastic anemia—A disorder in which the bone marrow and its blood stem cells are damaged such that it cannot produce mature red blood cells, white blood cells, or platelets.

Café-au-lait spots—Light brown birthmarks on the skin that are usually harmless but may be associated with Fanconi anemia and several other syndromes. The name is French and means “coffee with milk,” which describes the color of the spots.

Chemotherapy—Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of the cancerous cells or by killing the cancer cells.

Congenital—Present at birth.

DNA replication—The process in which a DNA molecule forms two identical copies of itself.

FA core complex—A group of eight proteins encoded by FA genes that function as part of the FA pathway in DNA repair. The FA core complex has been described as a cellular “machine” for DNA repair.

FA pathway—The biological process that is activated when DNA replication is shut down by interstrand cross-links and other types of DNA damage.

Myelodysplastic syndromes—Disorders of the bone marrow in which immature blood cells called myeloblasts increase in number and prevent the effective production and maturation of normal red and white blood cells and platelets. About a third of untreated myelodysplastic syndrome cases progress to acute myelogenous leukemia.

Pancytopenia—A medical condition characterized by abnormally low levels of all three types of blood cells: red blood cells, white blood cells, and platelets.

Pathogenesis—The biological mechanism that leads to a disease or disorder, or the origin and development of the disease.

Radiation therapy—Treatment using high-energy radiation from x-ray machines, cobalt, radium, or other sources.

Tumor—An abnormal growth of cells. Tumors may be benign (noncancerous) or malignant (cancerous).

a pale appearance. Without enough white blood cells, the patient may be vulnerable to common germs and infections. The deficiency in platelets can cause easy bruising, nosebleeds, and possible internal bleeding.

Ten to 15% of patients with FA develop leukemia, specifically acute myelogenous leukemia (AML). Leukemia is a cancer of the blood system in which abnormal white blood cells grow rapidly in number and suppress the development of healthy blood cells. AML is a particularly aggressive type of leukemia and is difficult to treat successfully. Individuals with FA are very sensitive to the toxic drugs used to fight leukemia, which makes treatment even more difficult.

Some patients with FA develop myelodysplastic syndromes (MDS), which may be precursors of AML. Myelodysplastic syndromes are disorders of the bone marrow in which the development of mature blood cells is disturbed. Instead of red and white blood cells and platelets maturing normally and in sufficient numbers, the number of myeloblasts (immature blood cells) increases and the number of mature blood cells drops. As a

myelodysplastic syndrome progresses, the myeloblasts increase to the point where they invade the bone marrow, further lowering the production of mature blood cells. When the abnormal myeloblasts account for 20% or more of cells in the bone marrow, the disorder is defined as having progressed to AML.

Among the physical defects associated with FA, short stature is very common. Additionally, an affected child may be born with missing, misshapen, or extra thumbs, or an underdeveloped or missing bone in the arm. Approximately one-fifth of patients with FA exhibit other skeletal abnormalities, such as malformations of the hip, spine, or rib. About 25% of individuals with FA are born with abnormalities of the kidneys. Some are born with defects of the heart, stomach, esophagus, or intestinal tract. These problems may require immediate surgery at birth.

FA is also associated with hyperpigmentation, or a darkening of the skin, in approximately 65% of patients. This darkening may be present in the form of spots known as *café-au-lait* spots, or it may be more diffuse

over a larger portion of the body. Additionally, the head or eyes may be smaller than average and some patients may not grow properly. Learning disabilities are thought to be fairly common in FA as well. Hearing loss has been reported in 10% of patients.

As these individuals become older, other problems may appear. In males, it is common to see underdeveloped male organs and infertility. Females often have a delay in the start of their menstrual periods and a decrease in fertility. Menopause in women with FA may occur as early as age 30.

People with FA, especially those over the age of 20, are at a high risk of developing malignant solid tumors in the head, neck, intestines, urinary tract, liver, and esophagus. Women are also at an increased risk of cancers in their reproductive organs; this risk is related to the fact that mutations in the *BRCA2* gene are associated with ovarian and breast cancer as well as Fanconi anemia.

Diagnosis

FA is often suspected in early childhood because of its characteristic physical deformities—particularly the thumb and arm abnormalities—and the development of aplastic anemia. However, the definitive diagnostic test for suspected FA is a laboratory test, called a chromosome breakage test. White blood cells are isolated from a patient's blood sample and destructive chemicals are added to these cells. The chemicals used most often for the test are diepoxybutane (DEB) and mitomycin C (MMC). The chromosomes are then viewed under a microscope. If the person is not affected with FA, the chromosomes will appear normal. If the person is affected with FA, the chromosomes will be broken and rearranged. Skin cells can be tested in a similar fashion and will often show this chromosome breakage as well. This particular test can be completed prenatally if a family desires to know whether a child is affected before he or she is born. Cells obtained from the mother's placenta or cells floating in the amniotic fluid that surrounds the fetus in the womb can be used to detect chromosome breakage.

Molecular genetic testing was available as of 2021 for all known FA genes. It is recommended that the siblings of a person diagnosed with FA be tested for mutations as well and that genetic counseling be offered to the entire family.

Treatment and management

Once the diagnosis of FA has been made, several initial tests should be completed, including liver and kidney function studies, a formal hearing evaluation, a

QUESTIONS TO ASK YOUR DOCTOR

- What type of FA is present in my family?
- Which genes are involved?
- Is androgen therapy safe for girls and women with FA?
- What is the prognosis?
- Is bone marrow transplantation a possible treatment for the specific patient in my family?

developmental assessment, and an ultrasound examination of the kidneys and urinary system.

People affected with FA should be followed closely by a physician. Their blood cell and platelet counts should be monitored frequently. Symptoms caused by anemia and low platelet levels, such as bleeding, fatigue, chest pain, and dizziness, can be treated with transfusions as needed. Antibiotics are often given to fight infections. At times, hospitalization may be necessary to adequately tend to these complications. As patients get older, they should be monitored for any signs of solid tumors.

Due to either aplastic anemia or leukemia, many individuals with FA will eventually require a bone marrow transplant. The donor must be carefully matched to the patient. The prognosis for transplant is best for young patients who have a sibling donor with a matching tissue type. Bone marrow transplants, however, are not an option for many patients with FA because pre-treatment for these transplants requires chemotherapy and radiation therapy to prevent rejection of the transplant. Because FA makes some patients hypersensitive to chemotherapy and radiation treatment, bone marrow transplantation has a low rate of success in treating FA.

Between 50% and 75% of individuals with FA will respond to administration of androgens. These are artificial male hormones taken by mouth that can stimulate production of one or more types of blood cells. They are most effective in increasing the number of red blood cells but can increase the levels of platelets and white cells as well. These drugs prolong the lives of individuals with FA but are not a cure for the disorder. They also have side effects that include high blood pressure, headaches, nausea and vomiting, acne or oily skin, breast tenderness, and loss of menstruation in girls.

Various hematopoietic growth factors have been studied in relation to FA. These substances are already present in the body and serve to stimulate the production of blood cells and platelets. Scientists have developed a

way to manufacture these substances. They have been given to patients with FA and show promise in increasing the count of blood cells and platelets.

Prognosis

FA is an unpredictable illness. The average life expectancy for an affected individual was 30 to 33 years as of 2021, but any specific individual can have a life span above or below this average; some patients live into their 50s. Research discoveries have led to life-extending treatments and improved bone marrow transplant outcome. However, as patients live longer, they become at increased risk of developing other types of tumors. The most common causes of death in FA are bone marrow failure, leukemia, or solid tumors.

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Aplastic Anemia & MDS International Foundation, 4330 East West Highway, Suite 230, Bethesda, MD 20814, (800) 747-2820 or (301) 279-7202, <http://www.aamds.org>

Fanconi Anemia Research Fund, 360 E. 10th Avenue, Suite 201, Eugene, OR 97401, (888) 326-2664, (541) 687-4658, <http://www.fanconi.org>

National Cancer Institute, BG 9609 MSC 9760, 9609 Medical Center Drive, Bethesda, MD 20892-9760, (800) 422-6237, <http://www.cancer.gov>

National Heart, Blood, and Lung Institute (NHLBI), National Heart, Lung, and Blood Institute Building 3131 Center Drive, Bethesda, MD 20892, (877) 645-2448, <http://www.nhlbi.nih.gov>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810 (203) 744-0100, (203) 263-9938, <http://www.rarediseases.org>

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Fanconi-Bickel syndrome

Definition

Fanconi-Bickel syndrome (FBS) is a rare inherited disorder of carbohydrate metabolism caused by mutations in the gene known as *GLUT2*.

Description

Also known as glycogen storage disease type XI, the disease was first described by scientists G. Fanconi and Horst Bickel in 1949. Since then, only a few dozen cases of FBS have been studied—most in the United States, Europe, and Japan.

Onset of FBS is within the first year of life, with the overt symptom being a failure to thrive. At age two, an enlarged liver and kidneys are present and the child has rickets. The incidence of FBS has not been determined, but it is believed to occur in less than one in one million births.

Genetic profile

Fanconi-Bickel syndrome is believed to be an autosomal recessive disorder. This means that an individual with FBS would have to inherit an abnormal copy of the gene from both parents in order to show symptoms of FBS. People with only one abnormal gene are carriers and do not have the disorder. When both parents have the abnormal gene, there is a 25% chance with each birth that their child will inherit both abnormal genes and have the disease. There is a 50% chance with each birth that the child will inherit one abnormal gene and become a carrier of the disorder but not have the disease itself. There is a 25% chance each child will neither

KEY TERMS

Carbohydrate—Any of various natural compounds of carbon, hydrogen, and oxygen (as in sugars and starches) that are burned by the body for energy.

Diabetes mellitus—The clinical name for common diabetes. It is a chronic disease characterized by inadequate production or use of insulin.

Hyperlordosis—An exaggerated curve in the lower (lumbar) portion of the back.

Osteoporosis—Loss of bone density that can increase the risk of fractures.

Pancreas—An organ located in the abdomen that secretes pancreatic juices for digestion and hormones for maintaining blood sugar levels.

Pancreatitis—Inflammation of the pancreas.

Rickets—A childhood disease caused by vitamin D deficiency, resulting in soft and malformed bones.

inherit the abnormal gene and not have the disease nor be a carrier.

Demographics

Since there is so little research on Fanconi-Bickel syndrome, no clear pattern of demographics has been established. However, the disorder is known to affect both males and females. One common thread in some of the cases that have been studied has been consanguinity, meaning that FBS is found in the children of two persons of the same blood relation. In several of these cases the consanguinity is between two first cousins.

Signs and symptoms

In a 1987 study by researchers at the Research Institute for Child Nutrition in Dortmund, Germany, nine cases of Fanconi-Bickel syndrome were compared for clinical symptoms, behavior symptoms, and physical appearance. The initial symptoms reported were fever, vomiting, growth failure, and rickets between the ages of three and ten months. Later, these same patients showed signs of dwarfism, a protruding abdomen, enlarged liver, moon-shaped face, and abnormal fat deposits around the shoulders and abdomen. Also, cutting of teeth and puberty were delayed. Complications present included fractures and pancreatitis (an enlarged pancreas). Later in life, rickets and osteoporosis were constant features.

QUESTIONS TO ASK YOUR DOCTOR

- What is the genetic mechanism by which Fanconi-Bickel syndrome is inherited?
- At what age is the disorder normally manifested, and how is it originally diagnosed?
- How does the lifespan of a child with Fanconi-Bickel syndrome compared to a child in normal health?
- Are there books, pamphlets, or other written material to which I can turn for additional information about Fanconi-Bickel syndrome?

The German study, whose researchers included H. Bickel, co-discoverer of the syndrome, also used ultrasound to determine increased kidney size and growth in relation to body height. The most prominent finding was glucosuria (glucose, or sugar, in the urine). Polyuria (increased urination) was also a constant finding. The study noted that liver size was normal or slightly increased at birth in all nine cases but became greatly enlarged during infancy. The liver size and glycogen (a glucose storage molecule) content were reduced when the patients were placed on an antiketogenic (high carbohydrate) diet.

Other laboratory findings included fasting hypoglycemia (low levels of sugar in the blood), ketonuria (high levels of ketones in the urine), high hypercholesterolemia (high cholesterol), hypophosphatemia (high phosphate levels in the blood), and high levels of amino acids and protein in the urine. In a 1995 study at Children's Hospital in Philadelphia of an eight-year-old with Fanconi-Bickel syndrome, doctors reported additional symptoms of overworked kidneys, very small amounts of albumin (a class of water-soluble proteins) in the urine, and an increase in the number of cells in the inner part of the kidney that filters blood.

Diagnosis

Fanconi-Bickel syndrome can usually be identified in patients by neonatal screening for galactose, a type of sugar. Patients with FBS are intolerant of galactose. Other diagnostic factors include an impaired glucose tolerance test; x-ray to determine the pattern of rickets; urine tests to measure levels of glycose, phosphates, amino acids, and bicarbonate; and a liver biopsy to detect abnormal galactose oxidation.

Treatment and management

There is no effective treatment for Fanconi-Bickel syndrome. However, some of the symptoms can be treated with adequate supplementation of water, electrolytes, and vitamin D; restriction of galactose; and a diabetes mellitus-like diet (low sugar and low carbohydrate) presented in frequent small meals. These treatments can improve growth and give the patient a general sense of well-being.

Prognosis

The long-term prognosis has not been determined. It may depend on the severity of symptoms and early diagnosis and treatment of symptoms. The first person diagnosed with the disorder in 1949 was a four-year-old Swiss boy with consanguineous parents. At six months, the boy had excessive thirst, constipation, and was not thriving. He was treated with vitamin D and calcium supplements. At about age four, the boy had short stature, a protruding abdomen, an enlarged liver, facial obesity, osteopenia, and hyperlordosis. At age 12, the boy was found to be resistant to glycogen. In 1997 at age 52, the patient, without any treatment other than vitamin D and calcium supplements, was of short stature (4 ft. 8 in., 140 cm), weighed about 95 lb. (43 kg), had a moderately protruding abdomen, and a smaller than normal liver. Other than arthritis, he had no medical complaints. However, other people diagnosed as children with FBS had much shorter life spans. Long-term follow-up studies of nine persons with FBS showed severely retarded growth, partly compensated for by late onset of puberty.

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American Association of Kidney Patients (AAKP), 14440 Bruce B. Downs Blvd., Tampa, FL 33613, (813) 638-8100 or (800) 749-2257, (813) 636-8122, info@aakp.org, <http://www.aakp.org>

National Kidney Foundation, 30 East 33rd St., New York, NY 10016, (800) 622-9010, (212) 689-9261, info@kidney.org, <http://www.kidney.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Ken R. Wells

Fatty aldehyde dehydrogenase deficiency
(FALDH10 deficiency) see **Sjögren-Larsson syndrome**

Feingold syndrome

Definition

Feingold syndrome, previously known as oculo-digito-esophageal-duodenal syndrome (ODED), is a rare genetic disorder characterized by multiple conditions including various hand and foot abnormalities, small head (microcephaly), incompletely formed esophagus and small intestine (esophageal/duodenal atresia), an extra eye fold (short palpebral fissures), and learning disabilities.

Description

Individuals diagnosed with Feingold syndrome usually have a small head (microcephaly), fused toes (syndactyly), shortened fingers (mesobrachyphalangy), permanently outwardly curved fingers (clinodactyly), an extra eyelid fold (palpebral fissures), and learning delays. Other features can include backbone abnormalities (vertebral anomalies), an opening between the esophagus and the windpipe (tracheoesophageal fistula), and/or an incompletely formed esophagus or intestines (esophageal or duodenal atresia). The syndrome was first described by Dr. Murray Feingold in 1975. The underlying cause of the different features of Feingold syndrome is not fully understood. Feingold syndrome is also known as microcephaly mesobrachyphalangy tracheoesophageal fistula syndrome (MMT syndrome), and microcephaly-oculo-digito-esophageal-duodenal (MODED) syndrome.

KEY TERMS

Contiguous gene syndrome—A genetic syndrome caused by the deletion of two or more genes located next to each other.

Variable penetrance—A term describing the way in which the same mutated gene can cause symptoms of different severity and type within the same family.

Genetic profile

The genetic cause of Feingold syndrome is still being investigated. As of 2021, studies had identified alteration of the *MYCN* gene as causing this syndrome. This gene mutation has been linked to 47% of the cases of Feingold syndrome. The *MYCN* gene is located on the short arm of chromosome 2 and plays a major role in the development of structural tissue and organs during embryonic development. If this gene is mutated, these tissues and organs will not develop properly, leading to the signs and symptoms of this syndrome. However, it is still not clear if the features of Feingold syndrome are caused by a single mutation in one gene or the deletion of several side-by-side genes (contiguous genes).

This syndrome has also been linked to microdeletions in the *MIR17HG* gene on the long arm of chromosome 13 at 13q31, which encodes a micro RNA cluster known as miR-17/92. Some researchers refer to this form of the syndrome as Feingold syndrome type 2. As of 2021, about 25 patients worldwide have been identified with this type of Feingold syndrome.

Although the specific location and cause of Feingold syndrome is not fully determined, it is known that this syndrome is inherited in families through a specific autosomal dominant pattern. Every individual has approximately 30,000–35,000 genes that tell his or her body how to form and function. Each gene is present in pairs, with one inherited from the mother and one inherited from the father. In an autosomal dominant condition, only one nonworking copy of the gene for a particular condition is necessary for a person to experience symptoms of the condition. If a parent has an autosomal dominant condition, there is a 50% chance for each child to have the same or similar condition. Thus, individuals inheriting the same nonworking gene in the same family can have very different symptoms. For example, approximately 28% of individuals affected by Feingold syndrome have esophageal or duodenal atresia, while hand anomalies are present in almost 100% of affected individuals. The difference in physical findings within the same family is known as variable penetrance or intrafamilial variability.

Demographics

Feingold syndrome is a rare genetic condition. As of 2021, approximately 120 patients affected by Feingold syndrome had been reported in the literature. However, scientists believe that the syndrome has not been diagnosed in many affected individuals and suggest that it is more common than previously thought. The ethnic origin of individuals affected by Feingold syndrome is varied and is not specific to any one country or group.

Signs and symptoms

The signs and symptoms of Feingold syndrome vary from individual to individual. Most (86%–94%) individuals diagnosed with Feingold syndrome have a small head (microcephaly) and finger anomalies such as shortened fingers (mesobrachyphalangy), permanently curved fingers (clinodactyly), and/or missing fingers. Over half of affected individuals also have fused toes (syndactyly). Between 45% and 85% of individuals affected by Feingold syndrome have developmental delays and/or intellectual disability. Other features can include an extra eyelid fold (palpebral fissures), ear abnormalities/hearing loss, kidney abnormalities, backbone abnormalities (vertebral anomalies), an opening between the esophagus and the windpipe (tracheoesophageal fistula), and/or an incompletely formed esophagus or intestines (duodenal atresia seen in 20%–30%).

Diagnosis

Diagnosis of Feingold syndrome is usually made following a physical exam by a medical geneticist using x-rays of the hands, feet, and back.

Prenatal diagnosis of Feingold syndrome can sometimes be made using serial, targeted level II ultrasound imaging, a technique that can provide pictures of the fetal head size, hands, feet, and digestive tract. Ultrasound results indicative of Feingold syndrome include a “double bubble” sign suggesting incompletely formed intestines (duodenal atresia) and small head size (microcephaly). Diagnosis by ultrasound before the baby is born is difficult. Prenatal molecular genetic testing is available for those individuals who have a familial history with the syndrome.

Treatment and management

Since Feingold syndrome is a genetic disorder, no specific treatment is available to remove, cure, or fix all conditions associated with it. Treatment for Feingold syndrome is mainly limited to the treatment of specific symptoms. Individuals with incompletely formed intestinal and esophageal tracts require immediate surgery to try to extend and open the digestive tract. Individuals with learning difficulties or intellectual disability may benefit from special schooling and early intervention programs to help them learn and reach their potential.

QUESTIONS TO ASK YOUR DOCTOR

- What information is available about the genetic basis of this disorder?
- At what stage in fetal or postnatal development is it possible to diagnose Feingold syndrome, and on what is that diagnosis based?
- Are there currently any ongoing studies researching treatments for this genetic disorder and, if so, what results have they produced thus far?

Prognosis

Feingold syndrome results in a variety of different physical and mental signs and symptoms. Accordingly, the prognosis for each affected individual is very different.

Individuals who are affected by physical hand, head, or foot anomalies (with no other physical or mental abnormalities) have an excellent prognosis, and most live normal lives.

Babies affected by ODED who have incomplete esophageal or intestinal tracts will have many surgeries, and prognosis depends on the severity of the defect and survival of the surgeries.

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ORGANIZATIONS

- Federation of Esophageal Atresia and Tracheo-Esophageal Fistula Support Groups, Sommerrainstrasse 61, Stuttgart, Germany 70374, <http://www.we-are-eat.org>

Reach, PO Box 54, Helston, Cornwall UK TR13 8WD,
reach@reach.org.uk, <http://www.reach.org.uk>

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Fetal alcohol spectrum disorders

Definition

Prenatal exposure to alcohol can cause a broad range of disorders, together known as fetal alcohol spectrum disorders (FASD). FASD includes four categories of diagnoses, including fetal alcohol syndrome (FAS), partial FAS (pFAS), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBD). In addition, the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) includes the diagnosis of neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE). A person who meets the criteria for an FASD diagnosis will also fulfill the criteria for ND-PAE, according to the National Institute of Alcohol Abuse and Alcoholism (NIAAA). The most severe effects of drinking during pregnancy occur with fetal alcohol syndrome (FAS), a pattern of birth defects and learning and behavioral problems affecting individuals whose mothers consumed alcohol during pregnancy. The NIAAA notes that a study of more than 6,000 children in first grade in the United States found that from 1% to 5% of children in first grade have fetal alcohol spectrum disorders (FASDs). Sometimes, children whose parents are alcohol abusers are placed in foster care, and some of these children have FASD. In 2019, 16% of children newly placed in the foster care system by child protective services in the United States had parents with an identified alcohol issue.

FASD has lifelong effects. In a study of more than 3,000 subjects between 2003 and 2013, Sarah Soyeon Oh and colleagues found that people with FASD have a 52 times greater risk for being hospitalized for diseases of the nervous system.

Description

FAS is the most common preventable cause of intellectual disability. This condition was first recognized and reported in the medical literature in 1968 in France and in 1973 in the United States. Alcohol is a teratogen, the term used for any drug, chemical, maternal disease, or other environmental exposure that can cause birth defects or functional impairment in a developing fetus. For this reason, doctors advise against drinking any alcohol during



Fetal alcohol spectrum disorders. (Shutterstock/lumruay)

pregnancy. Some features of FASD may be present at birth, including low birth weight, prematurity, and microcephaly (small head). Characteristic facial features may be present at birth or may become more obvious over time. Signs of brain damage include delays in development, behavioral abnormalities, and intellectual disability, but affected individuals exhibit a wide range of abilities and disabilities. It has only been since 1991 that the long-term outcome of FASD has been known. Learning, behavioral, and emotional problems are common in adolescents and adults with FAS.

Genetic profile

According to author Nina Kaminen-Ahola, FASD is partly a genetic disorder in that alcohol causes rearrangements and changes to the child's chromosomes while in utero. There are also gene-environment interactions to the fetus caused by the use of alcohol during pregnancy. Not all individuals from alcohol-exposed pregnancies have obvious signs or symptoms of FAS; individuals of different genetic backgrounds may be more or less susceptible to the damage that alcohol can cause. The dose of alcohol, the time during pregnancy that alcohol is used, and the pattern of alcohol use all contribute to the different signs and symptoms that are found in the child.

Demographics

There is no racial or ethnic predilection for FAS. Individuals from different genetic backgrounds who are exposed to similar amounts of alcohol during pregnancy may show different symptoms of FAS. The reported rates of FAS vary widely and depend on the population studied and the monitoring methods used.

Signs and symptoms

Classic features of FAS include short stature, low birth weight and poor weight gain, an abnormally small head (microcephaly), and a characteristic pattern of facial features. In infants and children, these may include small eye openings (measured from inner corner to outer corner), epicanthal folds (folds of tissue at the inner corner of the eye), small or short nose, low or flat nasal bridge, smooth or poorly developed philtrum (the area of the upper lip above the colored part of the lip and below the nose), thin upper lip, and small chin. Some of these features are nonspecific, meaning that they can occur in other conditions or be appropriate for age, racial, or family background. Other major and minor birth defects that have been reported include cleft palate, congenital heart defects, strabismus, hearing loss, defects of the spine and joints, alteration of the hand creases, and small fingernails and toenails. Since FAS was first described in infants and children, the disorder is sometimes more difficult to recognize in older adolescents and adults. Short stature and microcephaly remain common features, but weight may normalize, and the individual may actually become overweight for his or her height. The chin and nose grow proportionately more than the middle part of the face, and dental crowding may become a problem. The small eye openings and the appearance of the upper lip and philtrum may continue to be characteristic. Pubertal changes typically occur at the normal time.

Newborns with FAS may have difficulties with feeding due to sucking difficulties, irregular sleep-wake cycles, decreased or increased muscle tone, or seizures or tremors. Delays in achieving developmental milestones, such as rolling over, crawling, walking, and talking, may become apparent in infancy. Behavior and learning difficulties typical in the preschool or early school years include poor attention span, hyperactivity, poor motor skills, and slow language development. Attention deficit-hyperactivity disorder is a common associated diagnosis. Learning disabilities or intellectual disability may be diagnosed during this time. Arithmetic is often the most difficult subject for a child with FAS. During middle-school and high-school years the behavioral difficulties and learning difficulties can be significant. Memory problems, poor judgment, difficulties with daily living skills, difficulties with abstract reasoning skills, and poor social skills are often apparent by this time. It is important to note that animal and human studies have shown that neurologic and behavioral abnormalities can be present without characteristic facial features. These individuals might not be identified as having FAS but might fulfill criteria for alcohol-related diagnoses as set forth by the Institute of Medicine.

KEY TERMS

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Congenital—Refers to a disorder that is present at birth.

IQ—Abbreviation for "intelligence quotient." Compares an individual's mental age to his or her true or chronological age and multiplies that ratio by 100.

Microcephaly—An abnormally small head.

Miscarriage—Spontaneous pregnancy loss.

Placenta—The organ responsible for oxygen and nutrition exchange between a pregnant mother and her developing baby.

Strabismus—An improper muscle balance of the ocular muscles, resulting in crossed or divergent eyes.

Teratogen—Any drug, chemical, maternal disease, or exposure that can cause physical or functional defects in an exposed embryo or fetus.

In 1991, Streissguth and others reported some of the first long-term follow-up studies of adolescents and adults with FAS. In the approximately 60 individuals they studied, the average IQ was 68, with 70 being the lower limit of the normal range. However, the range of IQ was quite large, as low as 20 (severely intellectually disabled) to as high as 105 (normal). The average achievement levels for reading, spelling, and arithmetic were fourth grade, third grade, and second grade, respectively. The Vineland Adaptive Behavior Scale was used to measure adaptive functioning in these individuals. The composite score for this group showed functioning at the level of a seven-year-old. Daily living skills were at a level of nine years, and social skills were at the level of a six-year-old.

In 1996, Streissguth and others published further data regarding the disabilities in children, adolescents, and adults with FAS. Secondary disabilities, that is, those disabilities not present at birth and that might be preventable with proper diagnosis, treatment, and intervention, were described. These secondary disabilities included: mental health problems; disrupted school experiences; trouble with the law; incarceration for mental health problems, drug abuse, or criminal acts; inappropriate sexual behavior; alcohol and drug abuse; problems with employment; dependent living; and difficulties

parenting their own children. In that study, only seven out of 90 adults were living and working independently and successfully. In addition to the studies by Streissguth, several authors in various countries have now reported on long-term outcomes of individuals diagnosed with FAS. In general, the neurological, behavioral, and emotional disorders become the most problematic for the individuals. The physical features change over time, sometimes making the correct diagnosis more difficult in older individuals, without old photographs and other historical data to review. Mental health problems, including attention deficit, depression, panic attacks, psychosis, and suicide threats and attempts, were present in over 90% of the individuals studied by Streissguth.

Diagnosis

FAS is a clinical diagnosis, which means that there is no blood, x-ray, or psychological test that can be performed to confirm the suspected diagnosis. The diagnosis is made based on the history of maternal alcohol use and a detailed physical examination for the characteristic major and minor birth defects and characteristic facial features. It is often helpful to examine the siblings and parents of an individual suspected of having FAS, either in person or by photographs, to determine whether findings on the examination might be familial or whether other siblings may also be affected. Sometimes, genetic tests are performed to rule out other conditions that may present with developmental delay or birth defects. Individuals with developmental delay, birth defects, or other unusual features are often referred to a clinical geneticist, developmental pediatrician, or neurologist for evaluation and diagnosis of FAS. Psychoeducational testing to determine IQ and/or the presence of learning disabilities may also be part of the evaluation process.

Treatment and management

Most of the birth defects associated with prenatal alcohol exposure are correctable with surgery. Children should have a psychoeducational evaluation to help plan appropriate educational interventions. Common associated diagnoses such as attention deficit-hyperactivity disorder (ADHD), depression, or anxiety should be recognized and treated appropriately. The disabilities that present during childhood persist into adult life. However, some of the secondary disabilities may be avoided or lessened by early and correct diagnosis, better understanding of the lifelong complications of FAS, and intervention. According to the Centers for Disease Control and Prevention (CDC), early intervention as soon as possible is best, such as from birth to age three. The younger or older child may also benefit from speech therapy and physical therapy. Medications such as

QUESTIONS TO ASK YOUR DOCTOR

- My spouse and I plan to adopt a baby from foster care who may have fetal alcohol syndrome. What medical problems should we expect to develop as a result of this condition?
- What types of treatments are available for fetal alcohol syndrome?
- Is there a way of knowing what the long-term prognosis will be for a child with FAS?
- Is fetal alcohol syndrome a condition that can be transmitted genetically?

stimulants may help with hyperactivity, and antipsychotics may be used for anxiety, aggression, or other problematic behaviors.

The CDC, through a collaborative effort, seeks to identify, develop, and evaluate effective strategies for intervening with children with FAS and their families. Through these interventions, researchers are trying to help children with FAS develop their full potential, prevent secondary conditions, and provide education and support to caregivers and families. Some possibly hopeful findings were revealed in a study by Jeffrey R. Wozniak and colleagues, of children with FASD who were administered choline, a dietary supplement. In this study of 31 children with FASD, 15 were given choline, and 16 were given a placebo. Four years later, at age nine, the children who had been given the choline had a significantly higher non-verbal intelligence, as well as significant improvements in their visual-spatial skills, working memory, and verbal memory. The treated children also had fewer behavior symptoms of ADHD. Further research is needed to determine whether choline supplementation is effective in children with FASD.

Clinical trials

Clinical trials on FAS and FASDs are also currently sponsored by the National Institutes of Health (NIH) and other agencies. In 2021, NIH reported 17 ongoing or completed studies.

A few examples include the following:

- An assessment of the effectiveness of an attachment-focused intervention for preschool children with FAS. (NCT01536184)
- A study to determine whether atomoxetine hydrochloride improves inattention, hyperactivity, and impulsivity

problems in children exposed to alcohol during birth. (NCT00417794)

- An evaluation of the types of parenting training that will most benefit children with FAS. (NCT02210455)

Clinical trial information is constantly updated by NIH (<http://clinicaltrials.gov>).

Prognosis

The prognosis for FAS depends on the severity of the defects and the level of brain damage present at birth. Miscarriage, stillbirth, or death in the first few weeks of life may occur in very severe cases. Major birth defects associated with FAS are usually treatable with surgery. Some of the factors that have been found to reduce the risk of secondary disabilities in FAS individuals include diagnosis before age six, stable and nurturing home environments, never having experienced personal violence, and referral and eligibility for disability services. In a study in Canada of individuals with FASD with a mean age of 16, researchers Svetlana Popova and colleagues found a high level of psychological and developmental disabilities (78%) in the subjects, as well as substance use (50%), and also involvement in the child welfare system (75%) and the criminal justice system (30%). Subjects older than age 20 had the greatest percentage of past alcohol use (39%). The researchers also found that 78% had mental health issues. The long-term data helps in understanding the difficulties that individuals with FAS encounter throughout their lifetimes and can help families, caregivers, and professionals provide the care, supervision, education, and treatment geared toward their special needs.

Prevention of FAS is the key. Prevention efforts must include public education efforts aimed at the entire population (not just at women of child-bearing age); appropriate treatment for women with high-risk drinking habits; and increased recognition and knowledge about FAS by professionals, parents, and caregivers. All FASDs are 100% preventable if a woman does not drink alcohol while she is pregnant.

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March of Dimes, 1550 Crystal Drive, Suite 1300, Arlington, VA 22202, (888)-MODIMES, (888) 663-4637, <https://www.marchofdimes.org>

National Organization on Fetal Alcohol Syndrome (NOFAS), 1200 Eton Court, NW, Third Floor, Washington, D.C. 20007, (202) 785-4585, Information@nofas.org, <https://www.nofas.org>

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Revised by Christine Adamec

Fetal facies syndrome see **Robinow syndrome**

FG syndrome

Definition

FG syndrome (FGS) is a genetic disorder characterized by intellectual disability, low muscle tone (hypotonia), enlarged cranium, constipation, and anal abnormalities.

Description

FGS refers to a rare genetic condition that has a variety of physical and mental symptoms. Most individuals affected by FGS have symptoms including intellectual disability, low muscle tone, brain abnormalities (partial agenesis of the corpus callosum), seizures, large head, characteristic facial features, large intestinal and anal abnormalities, constipation, short stature, joints that tend to stay in one place (fixed), broad big toes, and light and dark skin streaking. The syndrome was first described by Opitz and Kaveggia in 1974 based on physical findings and family history. All of these features appear to be caused by mutated or changed genes on the X chromosome. Although the full effect of the mutation or change in the gene is not fully understood, the mutations are believed to interrupt the genes' normal functions in the brain, digestive tract, and muscle tissue.

Other names for FGS include Opitz-Kaveggia syndrome and Keller syndrome.

Genetic profile

FGS is caused by mutations on the long arm of the X chromosome. Studies in 1998 and 2000 found that individuals affected by FGS can have a mutation on the X chromosome in two different locations on the long arm (q) of the X chromosome: Xq12-Xq21 (called FGS1) and Xq28 (called FGS2). When a set of symptoms are caused by gene mutations at different locations, the disorder is called heterogeneous. Although a gene mutation causing FGS can appear in an individual for the first time without being found in the affected individual's parents, most cases of FGS are inherited.

Since both possible gene mutations are found on the X chromosome, FGS is inherited in an X-linked recessive pattern. Every individual has approximately 30,000–35,000 genes that tell his or her body how to form and function. Each gene is present in pairs, with one inherited from the mother and one inherited from the father. Females have two X chromosomes, while males have a single X chromosome and Y chromosome. In other words, females receive two copies of the genetic information stored on the X chromosome. When a female inherits the gene for an X-linked recessive condition, she is known as a carrier. She usually has no problems related to that condition because the gene on her other X chromosome continues to function properly and "masks" the

KEY TERMS

Agenesis—Lack or failure of development.

Cell differentiation—The act of a cell becoming a specific type of cell.

Hypotonia—Decreased muscle tone.

X-linked—A gene on the X chromosome as given by the mother.

abnormal gene. However, males inherit only one copy of the information stored on the X chromosome. When a male inherits the gene for an X-linked recessive condition, he will experience the symptoms associated with that condition. The mutated or changed genes that cause FGS are located on the X chromosome; thus, the full-blown disorder primarily affects males carrying the mutated or changed gene on their one X chromosome. When a condition is X-linked, the gene for the condition travels through the family on the X chromosome. In X-linked genetic conditions, the risk for a carrier female to have an affected son is 50%, while the risk to have a carrier daughter is also 50%. An affected male has a 100% chance of having carrier daughters and no chance to have an affected son.

Individuals inheriting the same mutated gene in the same family can have very different symptoms. For example, approximately 38% of individuals affected by FGS have anal anomalies, like a missing anal opening (imperforate anus), while intellectual disability is present in 97% of individuals affected by FGS. The difference in physical findings within the same family is known as variable penetrance or intrafamilial variability.

As of 2013, studies had pointed out a possible genetic link between the *MED-12* gene and FGS. The *MED-12* gene is a member of a larger complex that plays a role in cell growth and differentiation. It is also a suppressor for other genes such as *SHH*, which plays a role in the timing of cell growth. If this gene is not translated or transcribed correctly, growth abnormalities will occur during the embryonic stage. Studies have concluded that a possible missense mutation or a frameshift mutation of this gene directly leads to FGS as well as other intellectual disability and growth abnormality syndromes such as Lujan syndrome and Ohdo syndrome. Other X-linked genes known as of 2021 to be involved in the spectrum of FG signs and symptoms include *FLNA*, *BRWD3*, *FMRI*, *CASK*, *MECP2*, *ATRX* and *UPF3B*.

Demographics

FGS can appear in any ethnic population. It has been described in individuals of Japanese, American, European,

African, and other ethnic backgrounds. FGS is not believed to be more common in one specific population. The prevalence of FGS is not currently known, although several hundred cases have been reported throughout the world. This information may be skewed, however, due to the similarities of FGS and other disorders.

Signs and symptoms

Individuals affected by FGS can be affected by a variety of symptoms. Most affected individuals have signs of FGS such as intellectual disability, low muscle tone and physical development, seizures, large heads, big foreheads, a front cowlick of hair, wide-spaced eyes, extra eye folds (short, palpebral fissures), constipation, and an outgoing, talkative personality. Other fairly common signs of FGS include anal abnormalities (imperforate anus), brain abnormalities (partial agenesis of the corpus callosum), hearing impairments, broad thumbs and big toes, small ears, fine/thinning hair, fused fingers, minor backbone abnormalities, cleft lip and palate, heart defects, and fetal fingertip pads.

Diagnosis

Diagnosis of FGS is usually made from physical examination by a medical geneticist. The physical examination looks for the combined characteristic features, low muscle tone, intellectual disability, and other related signs and symptoms. Genetic testing for mutations in the *MED12* gene is also available as of 2021. Diagnostic criteria to differentiate FGS from Lujan syndrome (LS) have been developed. Although FGS and LS share similar characteristics such as intellectual disability, muscle weakness, and brain abnormalities, FGS can be clinically differentiated from LS by its characteristic facial features and digestive tract dysmorphia, whereas LS syndrome has a separate set of characteristic facial features without digestive tract dysmorphia.

Treatment and management

FGS is a genetic disorder and does not have a specific therapy that removes, cures, or fixes all signs of the disorder.

Management and treatment for FGS mainly focuses on the treatment of specific symptoms. More specifically, individuals with incompletely formed anal openings and serious heart defects would need surgery to try to correct the problems. Individuals affected by FGS who have intellectual disability benefit from special schools and early intervention programs.

Prognosis

The prognosis of an individual affected by FGS depends on the severity of the symptoms by which he or she is affected. For example, approximately one-third of

QUESTIONS TO ASK YOUR DOCTOR

- Are there support groups for me and my child?
- What will daily life be like with FGS?
- Will my child be able to attend school and develop cognitive function?
- How severe is my child's case of FGS?
- What is the prognosis of my case?
- What are the treatment options available to us?
- What are the chances that any future children of ours will develop this genetic syndrome?

individuals affected by FGS will die before two years of age due to the severity of heart defects and anal abnormalities.

Most individuals affected by FGS who do not have severe physical problems, such as serious heart defects and anal abnormalities, are still affected by intellectual disability.

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ORGANIZATIONS

- The Arc, 1825 K St. NW, Suite 1200, Washington, DC 20006, (202) 534-3700 or (800) 433-5255, (202) 534-3731, <http://www.thearc.org>

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Fibroblast growth factor receptor-related conditions

Definition

Fibroblast growth factor receptors (FGFRs) are a family of proteins involved in cell division, growth, maturation, differentiation, and healing. These receptors receive signals from other proteins outside the cell wall called fibroblast growth factors (FGFs). In humans and other mammals, fibroblast growth factors are important in the development of muscle tissue, limb growth and lengthening, blood vessel development, craniofacial development, and cell specialization.

When an FGF protein attaches to a fibroblast growth factor receptor, the receptor initiates a series of chemical reactions inside the cell that enable the cell to mature, to take on specialized functions, or to undergo certain other changes. Mutations in the genes that code for fibroblast growth factor receptors lead to various genetic disorders marked by short stature, premature fusion of the bones of the skull, craniofacial anomalies, and the speeded-up progression of certain types of cancers. There are four known genes that code for FGFRs: *FGFR1*, *FGFR2*, *FGFR3*, and *FGFR4*.

Description

Fibroblast growth factor receptors

Fibroblast growth factor receptors (FGFRs) are a family of proteins that play critical roles in cell division, maturation, and specialization, as well as the formation of blood vessels (angiogenesis) and embryonic development. As a group, FGFRs are very similar to each other in their structure and function. All are transmembrane proteins composed of three distinct parts: a binding site on the exterior of the cell membrane, an active site on the interior of the cell membrane, and a connecting section spanning the cell membrane and joining the inner and outer components.

Fibroblast growth factors (FGFs) attach to the binding site of the extracellular portion of the FGFR protein. As of 2021, there were at least 23 known human FGFs, ten of which bind to and interact with FGFRs. Two FGFs must first bind with each other; as a pair, they fit into the FGFR binding site, forming an FGF/FGFR complex. FGF pairing and FGF/FGFR binding is non-specific, with any two FGFs coupling and binding any FGFR.

When the binding site is empty and no FGF is bound, the FGFR is inactive and cellular growth continues unchecked. When an FGF pair binds, the FGF/FGFR complex sends a signal that travels the length of the

FGFR-related dwarfism syndromes

Syndrome*	Incidence	Gene	Common mutations**
Achondroplasia (ACH)	1/15,000—1/40,000	FGFR3	Gly380Arg
Hypochondroplasia (HCH)	Unknown	FGFR3	Asn540Lys
Thanatophoric dysplasia type I (TD1)	1/60,000 (TD1 and TD2)	FGFR3	Arg248Cys
Thanatophoric dysplasia type II (TD2)	See above	FGFR3	Lys650Glu
Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN)	3 reported cases	FGFR3	Lys650Met

*Please see the entry of the specific disease for further information and an exact description of the disorder.

**This represents common mutations and is not a complete list of mutations.

FGFR-related dwarfism syndromes (Gale)

FGFR protein, resulting in the stimulation of the active site on the inside of the cell membrane.

The active site of the FGFR stimulates molecules within the cell through the biochemical process of phosphorylation. Each activated molecule goes on to affect another molecule, thereby propagating the original signal and, much like the domino effect, triggering a cascade of events. The process continues, molecule by molecule, until the signal reaches the nucleus of the cell, ultimately resulting in the inhibition of cell growth.

FGFR genes

A different *FGFR* gene codes for each of the four types of FGFR proteins (Table 1). Genes are the genetic material passed down from generation to generation that tells a person's body how to work and how to grow. Genes are packaged into chromosomes, with hundreds of genes on each chromosome. Individual cells contain 46 chromosomes, which may be matched into 23 pairs. One of each pair is inherited from the egg of the mother, and one of each pair is inherited from the sperm of the father.

A mutation—a change in an *FGFR* gene—also changes the structure of the FGFR protein, which then affects the protein's function. Most *FGFR* gene mutations are thought to cause the protein receptors to become overly active. These defective receptors stimulate the activation cascade independent of FGF binding. This process causes a strong slowing-down effect on growth, which is readily observed in the symptoms of affected individuals. Common features of the disease include abnormalities of the limbs, skin, head, and face.

Other mutations in FGFR genes are associated with certain cancers, resulting in uncontrolled cell division, speeding up tumor growth, and the formation of new blood vessels that feed cancerous tumors.

FGFR Genes

Gene	Chromosome	Protein product
FGFR1	8p11	FGFR1
FGFR2	10q26	FGFR2
FGFR3	4p16	FGFR3
FGFR4	5q35	FGFR4

FGFR Genes (Gale)

The four FGFR genes in humans are *FGFR1*, located on the short arm of chromosome 8 at 8p11.23-p11.22; *FGFR2*, located on the long arm of chromosome 10 at 10q26; *FGFR3*, located on the short arm of chromosome 4 at 4p16.3; and the *FGFR4* gene, located on the long arm of chromosome 5 at 5q35.2.

Inheritance patterns

FGFR-related syndromes are inherited in an autosomal dominant pattern. That is, although individuals inherit two copies of each FGFR gene, only one copy must be mutated for a person to be affected with a disorder. Some individuals with an FGFR-related disorder have a parent affected by the same disease, in which case the disease is said to be familial. Other individuals are the first person in their family to be affected. These cases are considered sporadic, meaning they arose from a new mutation in the affected person's DNA.

Whether familial or sporadic, all affected individuals have a 50% chance of passing on the disease to a child in any future pregnancy. The overall risk for the offspring can change if an affected person has a child with an individual affected by the same disease.

Genetic testing

Prenatal testing is available for all of the FGFR-associated syndromes. Some cases are diagnosed based on clinical presentation, while others are diagnosed by DNA

FGFR-related Craniosynostosis Syndromes

Syndrome*	Incidence	Gene	Common mutations**
Muenke syndrome	Unknown	FGFR3	Pro250Arg
Crouzon syndrome	1.6/100,000	FGFR2	25 mutations
Crouzon with Acanthosis Nigricans	Unknown	FGFR3	Ala391Glu
Jackson-Wiess syndrome	Unknown	FGFR2	Cys342Arg, Ala344Gly
Apert syndrome	1/100,000	FGFR2	Pro250Arg, Ser252Trp
Pfeiffer types 1–3	1/100,000 (collective)	FGFR1, FGFR2	Pro250Arg
Beare-Stevenson cutis gyrata	<10 cases reported	FGFR2	Ser372Cys, Tyr375Cys

*Please see the entry of the specific disease for further information and an exact description of the disorder.
**This represents common mutations and is not a complete list of mutations.

FGFR-related craniosynostosis syndromes (Gale)

mutation analysis. Chorionic villus sampling (CVS) or amniocentesis may be used when there is a known familial mutation. If there is no family history of FGFR-related disease, but prenatal examination by ultrasound gives rise to concern, prognosis and diagnosis are traditionally based on clinical findings after birth.

A newer and less invasive method of prenatal genetic testing involves analysis of cell-free DNA in maternal blood; this method has been used successfully to test for achondroplasia and thanatophoric dysplasia. Molecular genetic testing is available for mutations in all four *FGFR* genes.

Diseases related to *FGFR* genes

Genetic disorders associated with *FGFR* genes fall into several major categories: craniosynostoses, which are disorders in which the child’s skull is misshapen due to abnormally early closure of the cranial sutures; dwarfism syndromes; and certain types of cancer.

FGFR1-related conditions

The *FGFR1* gene is thought to have important functions in the development of the fetus’s nervous system as well as controlling the growth of the long bones in the arms and legs. Mutations in this gene are linked to the following disorders:

- Kallmann syndrome type 2, also known as isolated gonadotropin-releasing hormone (GnRH) deficiency (IGD). Kallmann syndrome (KS) is a rare disorder with several different inheritance patterns marked by failure to begin or fully complete puberty as a result of impaired secretion of gonadotropins—hormones necessary for normal growth and sexual development. About 50% of patients diagnosed with KS have a diminished (hyposmia) or completely absent sense of smell (anosmia). The role of the *FGFR1* gene in KS type 2 is evident in the autosomal dominant pattern of inheritance and the fact that children with this subtype of KS frequently have malformations of

the hands, such orofacial abnormalities as cleft palate, and dental agenesis (failure of some or all permanent teeth to develop)—features that do not appear in other subtypes of KS. Mutations in the *FGFR1* gene account for about 10% of all cases of Kallmann syndrome.

- Pfeiffer syndrome type 1. Five percent of cases of Pfeiffer syndrome type 1, a type of craniosynostosis, results from the substitution of a single amino acid in the *FGFR1* protein at position 252, resulting in prolonged cell signaling that leads to premature closure of the sutures in the infant’s skull, together with misshapen facial features and abnormalities of the bones in the hands and feet. Children with type 1 Pfeiffer syndrome typically have an underdeveloped midface region, widely spaced eyes (hypertelorism), an abnormally small upper jaw, and dental abnormalities.
- Osteoglophonic dysplasia. Osteoglophonic dysplasia is a rare disorder of bone growth characterized by craniofacial abnormalities and dwarfism. It results from a gain-of-function mutation in the *FGFR1* gene in which prolonged cell signaling results in premature fusion of the cranial sutures and disruption of the normal growth of the bones in the arms and legs. The term “osteoglophonic” refers to the hollow areas in the bones that show up as holes on x-ray imaging. Only about 17 cases of this disorder had been reported in the medical literature as of 2021.
- Cancers. Mutations in the *FGFR1* gene are associated with a type of cancer of the blood called 8p11 myeloproliferative syndrome, a condition in which abnormal numbers of white blood cells are produced. Most cases of the syndrome develop into acute myelogenous leukemia (AML), but some develop into lymphoma. 8p11 syndrome results from a translocation between the *FGFR1* gene on chromosome 8p and the *ZMYM2* gene on the long arm of chromosome 13 at 13q11. The exchange of material between the two chromosomes results in the *FGFR1* gene merging with the *ZMYM2* gene. This fusion leads to uncontrolled cell

growth and division, as the *FGFR1* gene's signaling function is continuously "turned on" without any stimulation by fibroblast growth factors.

The *FGFR1* gene has also been found to be abnormally active in certain types of stomach, prostate, pancreatic, ovarian, testicular, and head and neck cancer. The gene's increased activity in these cancers is associated with the rapid growth of tumors and poorer outcomes for patients diagnosed with these cancers.

FGFR2-related conditions

Craniosynostosis is the hallmark of a major group of disorders caused by mutations in the *FGFR2* gene. Craniosynostosis refers to the premature fusion of some or all of the bones of the skull due to early closure of the cranial sutures. During normal development, the bones of the skull do not completely fuse until the first to second year of life. This delayed fusion allows for passage through the narrow birth canal at delivery and for maximum brain growth during early developmental years.

Not all forms of craniosynostosis are related to mutations in the *FGFR* genes; there are more than 150 genetic disorders that involve craniosynostosis which are not related to *FGFR* mutations. The collective incidence of all forms of craniosynostosis is 1 in 2,000 to 1 in 2,500 live births.

There are seven craniosynostosis syndromes related to mutations in the *FGFR2* gene: Apert syndrome, Crouzon syndrome, Beare-Stevenson syndrome, Jackson-Weiss syndrome, most cases of Pfeiffer syndrome type 1, Pfeiffer syndrome type 2, and Pfeiffer syndrome type 3. Types 2 and 3 of Pfeiffer syndrome are considerably more severe than type 1.

Most *FGFR2*-related syndromes display some form of craniosynostosis, or distinctive facial features, and most display hand and foot deformities, Crouzon syndrome being the exception. Syndromes range from severe (neonatal death) to mild (no or only minor clinical manifestations). The characteristic facial features observed include underdevelopment of the midface, protruding eyes, down-slanting eyes, small beaked nose, protruding lower jaw (prognathism), and eyes that are unusually far apart (hypertelorism). Hand and foot anomalies are distinct for each syndrome and are sometimes used to distinguish among the disorders. One of the puzzling features of disorders caused by mutations in the *FGFR2* gene is that some specific mutations in this gene cause Crouzon syndrome in some families and Pfeiffer syndrome in others. The reason for this anomaly was not known as of 2021.

A disorder caused by mutations in the *FGFR2* gene that does not include craniosynostosis is lacrimo-auriculo-dento-digital (LADD) syndrome. LADD syndrome is a rare disorder characterized by

abnormalities of the tear duct system (lacrimo-), ears (auriculo-), teeth (dento-) and fingers (digital). It may be caused by mutations in the *FGFR3* as well as the *FGFR2* gene. Children with this syndrome typically have misshapen ears as well as hearing loss, and abnormally low saliva production as well as small teeth.

FGFR3-related conditions

Mutations in the *FGFR3* gene are associated with several types of dwarfism.

Achondroplasia was the first disease associated with FGFRs, and *FGFR3* is the only gene known to be associated with it. It is the most common form of inherited disproportionate short stature, with an incidence of 1 in 15,000 to 1 in 40,000 live births. More than 80% of cases of achondroplasia are sporadic, with a strong link to advanced paternal age. The disorder is caused by a gain-of-function mutation in the *FGFR3* gene. It is characterized by abnormal bone growth that results in short stature with disproportionately short arms and legs, a large head, and characteristic facial features that include a prominent forehead (frontal bossing) and an underdeveloped midface. Intelligence and life span are usually normal, although there is an increased risk of death in infancy from compression of the spinal cord and/or upper airway obstruction.

Hypochondroplasia is a form of short-limbed dwarfism also caused by a mutation in the *FGFR3* gene. Although it appears clinically as a mild form of dwarfism, hypochondroplasia is caused by mutations in the *FGFR3* gene that differ from those that cause achondroplasia. Children with hypochondroplasia typically have abnormally large heads (macrocephaly); broad but short hands and feet; and short, thick necks. They are at increased risk of epilepsy and intellectual disabilities.

Thanatophoric dysplasia (TD) types I and II and severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) dysplasia are the most severe forms of *FGFR*-related dwarfism. Both types of thanatophoric dysplasia are fatal with death occurring before birth or during early infancy; the term "thanatophoric" comes from two Greek words that mean "death-bearing." All reported cases of TD have been caused by *de novo* mutations of the *FGFR3* gene, as the children do not live long enough to reproduce. The most noticeable feature of thanatophoric dysplasia is a cloverleaf-shaped skull known by the German term *Kleeblattschädel*.

Only a small number of cases of SADDAN dysplasia have been reported. Although SADDAN dysplasia is much like thanatophoric dysplasia in its presentation, affected individuals survive past infancy. Patients with SADDAN dysplasia are severely affected both mentally and physically, with the most noticeable physical feature

KEY TERMS

Acanthosis nigricans—A brownish-black hyperpigmentation of the skin, most often found in the folds of the body. It can be caused by genetic disorders as well as by certain malignancies and endocrine disorders.

Acute myelogenous leukemia (AML)—A life-threatening disorder of the bone marrow in which a large number of abnormal white blood cells accumulate in the marrow and reduces the production of normal red and white blood cells and platelets. It is also called acute myeloid leukemia.

Angiogenesis—The process in which existing blood vessels give rise to new blood vessels. Angiogenesis is important in wound healing but also plays a critical role in the growth of malignant tumors.

Anosmia—Lack or loss of the sense of smell.

Congenital—Refers to a disorder which is present at birth.

Cranial suture—Any one of the seven fibrous joints between the bones of the skull.

Craniosynostosis—A condition in which one or more of the fibrous joints (sutures) in an infant's skull turns to bone prematurely. As a result, the shape of the head is affected as the infant continues to grow, and the facial features are often deformed.

Dental agenesis—Failure of the teeth to form normally during embryonic development. The complete absence of all the teeth is called anodontia.

Dwarfism—In general, a condition in which a person is considerably shorter than normal when fully grown (below an adult height of 4 feet 10 inches) as a result of an endocrine disorder, skeletal abnormality, or genetic disorder. There are about 200 different conditions that can cause dwarfism.

Fibroblast growth factors (FGFs)—A family of proteins that signal through growth factor receptors to regulate cell division, cell proliferation, and wound healing in humans and many other species.

Fibroblasts—The active cells in connective tissue, responsible for synthesizing collagen and maintaining the structural integrity of connective tissue. Fibroblasts play an important role in wound healing.

Frontal bossing—The medical term for an unusually prominent forehead, typically accompanied by a heavy brow ridge.

Gain-of-function mutation—A mutation that results in enhanced or new activity on the part of the protein encoded by the gene.

Gonadotropins—Polypeptide hormones that (in humans) include luteinizing hormone (LH) and follicular-stimulating hormone (FSH). The gonadotropins act on the sex glands (ovaries in females, testes in males) and are essential to normal sexual maturation in humans.

Growth factors—Naturally occurring proteins that stimulate cell growth, differentiation, and healing. Most growth factors function in cell signaling.

Hypertelorism—Unusually widely spaced eyes.

Macrocephaly—Having an abnormally large head.

Phosphorylation—The addition of a phosphate group to a protein molecule. Protein phosphorylation plays an important role in many biological processes, including the activation of growth factor receptors.

Polymorphism—A variation in a gene or chromosome that occurs with fairly high frequency in the general population.

Prognathism—Abnormal protrusion of either the upper or lower jaw.

Translocation—A chromosomal abnormality that results from an exchange of material between two chromosomes from different pairs (nonhomologous chromosomes). Translocation may result in the fusion of two different genes.

being the brownish-black discoloration of their skin, a condition known as acanthosis nigricans. Both SADDAN dysplasia and thanatophoric dysplasia types I and II have their own distinct *FGFR3* gene mutations.

Muenke syndrome is a rare form of craniosynostosis associated with hearing loss and a risk of learning disabilities as well as malformations of the skull and facial features. Hypertelorism is common in children with this syndrome, as are flattened cheekbones and an enlarged head (macrocephaly). Muenke syndrome is thought to

affect about 1 child in 30,000 and to account for 8% of all cases of craniosynostosis. It requires molecular genetic testing to distinguish it from other forms of craniosynostosis, however, as its clinical features are not sufficiently distinctive.

FGFR4-related conditions

Although mutations in the *FGFR4* gene had not been linked to any forms of dwarfism or craniofacial disorders as of 2021, certain polymorphisms (variations that are

QUESTIONS TO ASK YOUR DOCTOR

- Should our family consider genetic testing for *FGFR*-related syndromes?
- What is the risk of cancer associated with these syndromes?
- What are the chances of having more than one child with an *FGFR*-related disorder?
- What kinds of treatments are available for children with these syndromes?

common in the general population) in this gene are associated with rapid tumor progression in patients diagnosed with some types of cancer. One polymorphism, found in 50% of people worldwide, involves the substitution of an amino acid called arginine for glycine at position 388 in the amino acid chain of the *FGFR4* protein. Although this variation has no known effects in healthy adults, it worsens the outcome in patients with breast, head and neck, colon, and prostate cancers.

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ORGANIZATIONS

- Children's Craniofacial Association, 13140 Coit Road, Suite 517, Dallas, TX 75240, (214) 570-9099 or (800) 535-3643, contactCCA@ccakids.com, <http://www.ccakids.com>
- Craniosynostosis and Positional Plagiocephaly Support (CAPPS), 114 N Elm Street, Massapequa NY 11758, (516) 232-7015 or (888) 572-5526, <http://cappskids.org>

- FACES: The National Craniofacial Association, PO Box 11082, Chattanooga, TN 37401, (800) 332-2373 or (423) 266-1632, <http://www.faces-cranio.org/index.htm>
- Little People of America (LPA), 617 Broadway #518, Sonoma, CA 95476, (888) LPA-2001, <http://www.lpaonline.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

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Fifth digit syndrome see **Coffin-Siris syndrome**

First-trimester pregnancy screening

Definition

First-trimester pregnancy screening includes blood and urine tests and ultrasound exams to determine whether the fetus is at higher risk for birth defects and whether the mother and child are at higher risk for other potentially harmful conditions. Most first-trimester tests and procedures are not diagnostic, but they might indicate the need for further screening or diagnostic testing. In some cases, screening may indicate the need for immediate intervention or treatment.

Purpose

Laboratory tests and ultrasound (high-frequency sound waves that create images of the fetus) are first-trimester pregnancy-screening procedures that do the following:

- screen for genetic disorders caused by inherited gene mutations or chromosomal abnormalities
- screen for birth defects (congenital anomalies) that may be caused by medications, chemicals, or infections
- assess the mother's general health
- screen for maternal conditions and infections that pose a risk for the mother or baby
- detect Rh incompatibility

Some first-trimester screening tests may be performed only if a woman is at a higher risk of having a baby with a genetic disorder; however, in most cases of congenital anomalies, the parents have no risk factors, and the cause of the abnormality is unknown. Most available first-trimester tests screen for chromosomal abnormalities in the fetus, especially trisomy (an extra



Early pregnancy ultrasound. (Shutterstock/Reshetnikov_art)

chromosome), which is the most common chromosomal abnormality. The risk of trisomy increases with increasing maternal age: when the mother is age 35, the risk of a chromosomal abnormality is one in 192; at age 40, it is one in 66. The most common chromosomal condition is Down syndrome, or trisomy 21—all or part of an extra chromosome 21. Screening also usually includes trisomy 13 (Patau syndrome, an extra chromosome 13), trisomy 18 (Edwards syndrome, an extra chromosome 18), and Turner syndrome, the most common monosomy (absence of a chromosome), in which a female has a damaged or missing X chromosome.

In 2021, researchers discovered a relationship between a protein called pregnancy-associated plasma protein(PAPP-A) and risk for gestational diabetes, a common complication of pregnancy. Insulin resistance associated with gestational diabetes is a health problem for pregnant women, who can pass some of the metabolic changes on to their newborns. PAPP-A has been found in the circulating blood of pregnant women and has been associated with some birth defects. The protein is thought to affect an insulin growth factor that promotes healthy tissue growth. Low levels of PAPP-A are related to higher chance of insulin resistance and gestational diabetes later in pregnancy.

Some inherited genetic disorders are more common in certain racial or ethnic groups, and first-trimester screening for these disorders is usually performed only when the mother or father belongs to one of those groups. Examples include the following:

- sickle cell disease in African Americans
- cystic fibrosis (CF) in non-Hispanic whites
- Tay-Sachs disease in people of Ashkenazi Jewish, Cajun, or French Canadian ancestry

Description

Screening for genetic disorders

First-trimester screening for genetic disorders measures certain substances in the mother's blood and images the fetus by ultrasound. The two main types are combined first-trimester screening and integrated screening.

Combined screening is the most widely used first-trimester procedure and is typically performed at 11–14 weeks of pregnancy. It includes a blood test for human chorionic gonadotropin (hCG) and PAPP-A and an ultrasound exam for possible trisomies. Detection of hCG in the blood or urine indicates pregnancy and is the basis of home-pregnancy testing.

Quantitative hCG measures the hCG level in the mother's blood and, in conjunction with progesterone levels, is used to diagnose an ectopic pregnancy that is outside of the uterus, as well as to help diagnose and monitor women at risk for miscarriage. Levels of hCG rise much more slowly with ectopic or failing pregnancies. In such cases, hCG tests may be performed over several days. Chromosomal defects, such as trisomy, tend to significantly increase hCG levels and decrease PAPP-A levels. A targeted ultrasound exam, called nuchal translucency, can detect fluid and increased space at the back of the fetus's neck, which sometimes indicates Down syndrome or another trisomy. Doctors can check hCG levels additional times early in pregnancy if there are signs that the pregnancy is not progressing as it should.

The results of hCG and PAPP-A tests and nuchal translucency ultrasound are combined to determine the risk of a chromosomal defect. This screening detects 82% to 88% of cases of Down syndrome. Combined screening is appropriate for women who want their screening results as early in pregnancy as possible. Combined screening is also appropriate for women who, in the event of a positive screening result, would choose to have a diagnostic test called chorionic villus sampling (CVS) in the first trimester and may choose to terminate an affected pregnancy.

Integrated screening for trisomies and neural tube defects involves a PAPP-A blood test and nuchal translucency ultrasound in the first trimester, followed by “quad screening” in the second trimester. Quad screening includes blood tests for alfa-fetoprotein (AFP) for neural tube defects, and hCG, estriol, and inhibin-A for trisomies. (Neural tube defects, such as spina bifida, cannot be screened for in the first trimester.) Integrated screening detects 94% to 96% of cases of Down syndrome. It is appropriate for women who want the most accurate screening test. It is also appropriate when CVS is not available and for women who would consider having

diagnostic amniocentesis in the event of a positive screen but who would not consider CVS in the first trimester because of the slightly higher risk of complications. If nuchal translucency ultrasound is not available, quad integrated screening or triple integrated screening (AFP, hCG, and estriol) detects 85% to 88% of cases of Down syndrome. Women who are already in their second trimester of pregnancy have the option of triple or quad screening but not integrated screening.

A newer screening test for chromosomal abnormalities analyzes cell-free fetal DNA in maternal blood. It can be performed as early as 10 weeks of gestation. This test is recommended for women at high risk for having a child with a chromosomal abnormality because of maternal age, family history, an ultrasound finding, or a positive blood-screening test. DNA screening can significantly reduce the need for invasive diagnostic testing by CVS or amniocentesis. It is considered much more accurate than standard screening tests, with significantly higher detection of Down syndrome and significantly fewer false positives for all three trisomies.

Carrier tests screen for genes in the mother and father that can cause genetic disorders in the child. Carrier tests can be performed before or during pregnancy. They are performed if the mother or father has a genetic disorder, a family history of a genetic disorder, or a previous child with a genetic disorder, or if he or she is a member of a racial or ethnic group at increased risk for certain genetic disorders. Because cystic fibrosis is so common, CF carrier screening is offered to all women of reproductive age.

Other screening tests

The following first-trimester pregnancy screening tests are standard for all women:

- A complete blood count (CBC) determines the numbers of different types of cells in the blood: low red blood cell counts can indicate anemia, white blood cell counts indicate the mother's ability to fight off infection, and platelet counts indicate the clotting ability of the mother's blood.
- The mother's blood type, including the presence or absence of Rh (rhesus) factor, is determined. Rh factor is a protein that is present on the surface of the red blood cells of most—but not all—people. If a mother is Rh-negative, and her fetus is Rh-positive, she may produce antibodies that attack the fetal red blood cells. This occurrence can be prevented by treating the mother with immune serum.
- Urinalysis detects red and white blood cells in the urine, which may indicate a urinary tract infection, and glucose, which may indicate diabetes. Protein levels in the urine are determined for comparison with levels later

in pregnancy, when high levels of urine protein suggest the risk of pre-eclampsia, a life-threatening condition in the mother.

- Urine cultures are used to screen for urinary tract infections.
- A glucose-screening test is performed on women with risk factors for diabetes or those who had gestational diabetes mellitus during a previous pregnancy.
- Maternal blood is screened for antibodies to rubella (German measles), which indicate past infection or vaccination against the disease. Rubella in early pregnancy can cause birth defects. Since women without the antibodies cannot be vaccinated until after giving birth, they must avoid anyone who is infected with this highly contagious virus.
- Hepatitis B and C infections can be passed to the fetus. All pregnant women are screened for hepatitis B, and those with risk factors are screened for hepatitis C.
- All pregnant women are screened for syphilis and chlamydia, because those infections can cause complications in the mother and infant. Infected women are treated during pregnancy and then retested.
- Women are screened for gonorrhea if they have risk factors for infection, such as being under age 25 or living in an area with high gonorrhea rates.
- All women are screened for HIV, which causes AIDS. HIV can be transmitted to the baby before or during birth, but medications and other steps greatly reduce the risk of transmission.
- Women are screened for tuberculosis (TB) if they are at high risk for the disease, live in close contact with someone with TB, or are infected with HIV.

Precautions

First-trimester pregnancy-screening tests pose no risk to the mother or fetus. Screening tests for birth defects, however, are not diagnostic—they merely indicate whether the fetus is at normal or increased risk for a birth defect. Screening test results depend on both the nuchal translucency technique and on an accurate determination of gestational age. If the gestational age is wrong, the test results may not be accurate.

Furthermore, screening cannot detect all fetal abnormalities. A positive screening test result is generally followed by a diagnostic test. Women may choose to substitute diagnostic tests for screening tests, especially if the parents have a family history of birth defects or a previous child with birth defects, or if they belong to certain ethnic groups. The American College of Obstetricians and Gynecologists recommends that diagnostic tests—CVS in the first trimester or amniocentesis in the

KEY TERMS

Amniocentesis—A procedure performed between 16 and 18 weeks of pregnancy, in which a needle is inserted through a woman's abdomen into the uterus to draw out a small sample of the amniotic fluid from around the fetus; either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about various genetic disorders and other medical conditions in the fetus.

Carrier testing—Testing performed to determine whether someone possesses one changed copy and one unchanged copy of a particular gene.

Chorionic villus sampling (CVS)—A procedure involving removal of a small placenta sample during pregnancy to obtain fetal chromosome results.

Combined first-trimester screening—Blood tests for pregnancy-associated plasma protein A and human chorionic gonadotropin and an ultrasound exam for chromosomal abnormalities.

Complete blood count (CBC)—A measurement of blood levels of red blood cells, white blood cells, and platelets.

Cystic fibrosis (CF)—A respiratory disease characterized by chronic lung disease, pancreatic insufficiency, and an average age of survival of 20 years. Cystic fibrosis is caused by mutations in a gene on chromosome 7 that encodes a transmembrane receptor.

Down syndrome—A chromosomal disorder caused by the presence of all or part of an extra 21st chromosome.

Edwards syndrome—Trisomy 18; a genetic disorder caused by an extra chromosome 18 that can be screened for in the first trimester.

Gestational diabetes—This type of diabetes (a condition that negatively affects how the body uses carbohydrates) occurs in pregnant women who did not have diabetes before becoming pregnant. It can lead to health problems and pregnancy and birth complications.

Human chorionic gonadotropin (hCG)—A protein produced in early pregnancy; fetal chromosomal abnormalities can significantly increase hCG levels in maternal blood.

Integrated screening—Blood tests and ultrasound in the first trimester, followed by blood tests for three or four proteins in the second trimester, to screen for chromosomal abnormalities and neural tube defects.

Nuchal translucency ultrasound—Specialized ultrasound imaging that looks for a larger-than-normal space and fluid at the back of the first-trimester fetal neck to screen for chromosomal abnormalities.

Patau syndrome—Trisomy 13; an extra chromosome 13.

Pregnancy-associated plasma protein A (PAPP-A)—An early pregnancy protein in maternal blood and urine; fetal chromosomal abnormalities can cause decreased PAPP-A levels.

Rh factor—Rhesus factor; a protein on the surfaces of red blood cells of many people; if a fetus is Rh-positive, and the mother is Rh-negative, the mother must be treated with immune globulin to prevent the production of antibodies that could cross the placenta and attack the fetal blood cells.

second trimester—and/or targeted ultrasound be offered to all women in place of screening tests, regardless of risk factors. However, CVS and amniocentesis are invasive procedures that carry a very small risk of miscarriage or other complications.

If a woman is pregnant with multiple fetuses, blood tests for Down and Edwards syndromes are less reliable. That is because the levels of PAPP-A and free beta hCG increase, and the proteins from an affected fetus may be more difficult to detect in the mother's blood. However, nuchal translucency ultrasound assesses each fetus independently.

Preparation

Screening for birth-defect risk is a personal choice. Many women want as much information as possible about

their baby's health and want to ease any anxieties. Detection of a birth defect in the first trimester provides time to consider options. These may include terminating the pregnancy or preparing to care for a child with a birth defect and arranging for specialized medical care during and after the child's birth. Other women would not consider terminating an affected pregnancy and would rather not know about any problems beforehand.

Some women decide against screening tests because they know they would not choose to have an invasive diagnostic test if the screening test were to indicate a higher risk of an abnormality. Other women choose to forego the uncertainty of a screening test and have a diagnostic test instead. Pregnant women and their families may find it useful to consult a genetic counselor before deciding to have first-trimester screening for birth defects.

QUESTIONS TO ASK YOUR DOCTOR

- What type of first-trimester pregnancy screening do you recommend?
- What information is obtained from first-trimester screening?
- What does it mean if my screening results are negative?
- What are my options if the screening results are positive?
- What are the advantages and disadvantages of having diagnostic testing instead of screening?

A woman's risk factors are assessed in preparation for first-trimester screening. A questionnaire may ask about personal and family histories of birth defects, ethnicity, maternal age of 35 or older, and pre-existing diabetes.

Aftercare

Some screening tests may be performed or repeated later in the pregnancy. The CBC is repeated later. An Rh-negative mother with an Rh-positive baby will be tested later for Rh antibodies to determine whether she requires immunoglobulin. Glucose screening for gestational diabetes and screening for group B streptococcus infection are also performed later in pregnancy. As of 2021, researchers were studying whether PAPP-A and glucose levels at various points during pregnancy might better tell how gestational diabetes develops.

Results

Results of first-trimester pregnancy screening are available in about one week. The health care provider and possibly a genetic counselor will explain the results and offer options for any follow-up, such as diagnostic tests. Results of combined screening are generally provided as a risk number: If the risk is higher than a predetermined cut-off value, such as one in 300 or higher, the result is considered positive, with the baby at risk for a chromosomal abnormality. Women with higher-than-normal risk values are offered CVS in the first trimester, amniocentesis in the second trimester, or, rarely, fetal blood testing. However, CVS or amniocentesis is generally offered to all women, regardless of screening results. A genetic counselor can help women assess the benefits and risks of diagnostic testing. Counseling also may be helpful for addressing issues raised by pregnancy termination or caring for a child with a genetic disorder.

Combined first-trimester screening identifies about 85% of fetuses with Down syndrome and up to 75% of those with Edwards syndrome. About 5% of results are false positives. Certain other screening systems are somewhat different. With contingent sequential screening for Down syndrome, trisomy 18, and neural tube defects, the following is true: If the first-trimester combined screening result is negative, no further testing may be offered; if the result is positive, a diagnostic test is offered; if the result is intermediate, a second-trimester screening test is offered. This system diagnoses 88% to 94% of cases of Down syndrome. With stepwise sequential screening for Down syndrome, trisomy 18, and neural tube defects, the following is true: If first-trimester screening is negative, a second-trimester screening test is offered; if the first-trimester screen is positive, a diagnostic test is offered. This system diagnoses 95% of cases of Down syndrome.

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ORGANIZATIONS

American College of Obstetricians and Gynecologists, 409
12th Street, SW, Washington, D.C. 20024-2188, (202)
638-5577, (800) 673-8444, <http://www.acog.org>

Eunice Kennedy Shriver National Institute of Child Health and
Human Development, NICHD Information Resource
Center, P.O. Box 3006, Rockville, MD 20847, (800)
370-2943, NICHDInformationResourceCenter@mail.nih.gov, <http://www.nichd.nih.gov>

March of Dimes, 1550 Crystal Drive, Suite 1300, Arlington, VA
22202, (888) 663-4637, <http://www.marchofdimes.org>

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Fluorescence in situ hybridization

Definition

Fluorescence in situ hybridization (FISH) is a powerful technique used to identify the presence of specific chromosomes or parts of chromosomes through the attachment (hybridization) of fluorescent DNA probes to available chromosomal DNA. The fluorescent DNA sequence used to attach to the cellular DNA is called the probe and is created in the experimental laboratory. Sometimes an RNA sequence is used as the probe instead of DNA. Examining the labeled cellular DNA under special lighting reveals the presence or absence of a fluorescent signal that indicates specific genes. FISH can be used on tissue preparations, on blood or bone marrow smears, directly on cells, or on nuclear isolates.

Description

In situ is Latin for “in the original place,” which, in the case of FISH, means inside a human cell or tissue. To hybridize with something means to attach to it in a very selective, specific manner. In situ hybridization (ISH) is the attachment of a very specifically designed DNA probe to cellular DNA (the original place). FISH uses a DNA probe that can be labeled with a fluorescent compound and emits colored light when it is exposed to specific light wavelengths under a microscope. FISH can detect specific DNA or RNA sequences that are present in a human cell by taking advantage of DNA’s double-stranded nature.

FISH and DNA structure

In a normal human cell, DNA is compartmentalized in an area known as the cell’s nucleus. Within this nucleus, the preferred conformation of DNA is two strands wrapped around each other and twisted. This twisted structure is known as the DNA helix. DNA is made up of chemical bases that are represented by the letters C, T, G, and A. This is the DNA alphabet that makes up each strand of DNA. The letters of each strand pair up in a specific manner when twisting to form the helix. All the T bases pair with A bases, and all the G bases pair with C bases. Different combinations of these bases are put together in three-letter “words” called codons. The arrangement of the words is what determines what a gene will encode for, gives the gene its meaning, and therefore tells the body how to grow and develop. DNA is transcribed into RNA, the beginning of expression of DNA in a cell. To express the product that the gene is encoding, RNA is translated into proteins that function in many capacities for life.

FISH takes advantage of the tendency of DNA to form base pairs with its corresponding letters. The DNA inside a cell can be experimentally exposed and temporarily unraveled from its helical structure. To denature DNA means to take the unraveling a step farther and undo the bonds between the bases from the two strands. Once the single-stranded bases are exposed, carefully designed DNA sequences that can be fluorescently labeled can be used to probe the cell’s set of DNA or RNA. At specific temperatures and under standardized laboratory conditions, the probe is able to hybridize with (pair up with) and therefore label the cellular DNA. This technique can be used to search for specific gene sequences in human tissue that would cause clinical complications. FISH can also reveal the actual location of a DNA sequence on a chromosome.

The FISH technique

The general procedure for FISH involves fixing samples of chromosomes or human tissue onto a piece of glass known as a slide (it slides into place on the viewing platform of a microscope when the sample is ready to examine). To prepare the tissue on the slide for hybridization, it is treated with chemicals to permeabilize (open up) the cells and expose the DNA. The chemicals also denature the DNA so that it is single-stranded and ready for the probe. A specific chemical hybridization solution containing the probe is applied to the slide so that the probe can hybridize with cellular DNA. This hybridization solution controls the degree of specificity to which the probe hybridizes to the target sequence. Factors such as the temperature, pH, and salt concentration can be changed to control the specificity of the hybridization. When the probe is made of RNA or is being

KEY TERMS

Aneuploidy—Having too many or too few copies of a specific chromosome; the most common forms are trisomy (three) and monosomy (one); two copies of a chromosome is normal.

Chromosome—A thread-like structure of DNA and associated proteins called chromatin that carries multiple genes.

DNA—Deoxyribonucleic acid, inheritable material that constitutes the building blocks of life.

Fluorochrome—A fluorescent compound used for visualization in FISH.

Gene—A sequence of chromosomal DNA that functions as a hereditary unit and encodes for the production of a functional product.

Locus (plural: loci)—Position occupied by a gene on a chromosome.

Nuclear isolate—An isolated preparation of the contents of the nucleus of a cell, which contains the DNA.

RNA—Ribonucleic acid, the intermediate step between DNA and its final expression product. DNA is transcribed into RNA and RNA is translated into protein.

Transcription—The process by which DNA is changed into RNA.

Translation—The process by which RNA is changed into protein.

hybridized to RNA, special precautions must be taken because single-stranded RNA is less stable than DNA and easily degraded. Any excess probe is washed away.

Probes can be labeled directly with an attached fluorescent molecule; or indirectly, when a specific fluorescent-labeled antibody or labeled binding protein is used to detect a tag attached to the probe sequence. Using the indirect method, the probe itself only contains an attachment point for the fluorescent antibody or binding protein. With this method, the probe by itself is not fluorescent. Once the fluorescent binding molecules are applied, the slide can be viewed on a special microscope designed for fluorescence. The microscope applies a beam of light, set at a specific light wavelength, to the DNA on the slide. The fluorescent tags on the DNA emit colored light in response to specific wavelengths. The fluorescent molecules do not fluoresce under sunlight.

Fluorescent labeling

Fluorescent compounds are known as fluorochromes. An example of a fluorochrome that may be used is fluorescein isothiocyanate (FITC). FITC can be attached, or conjugated, to an antibody for the tag on the DNA probe. FITC can fluoresce only under specific narrow wavelengths of light and does not fluoresce in sunlight. Sunlight contains many wavelengths of light measured in nanometers (nm). Short wavelengths less than 400 nm are types of ultraviolet light that have very high energy. The visible spectrum of light ranges from 400–780 nm. The infrared long wavelengths of light lie between 780 nm–1 mm. FITC compounds are designed to fluoresce only when specific narrow ranges of wavelengths are shining on them. The wavelength required varies from compound to compound. A dark room and a special microscope equipped with such lighting are used for this purpose. Fluorescent labeling can allow two or more different probes to be visualized at the same time because they fluoresce with different colors and can be distinctly visualized. Special filters have been developed to allow simultaneous visualization of several fluorescent molecules at once. When many gene loci (locations) on a chromosome are being labeled, the process is referred to as a chromosome paint. Fluorescent dyes are subject to photobleaching (fading) and so are not permanent preparations. Digital imaging systems can store the fluorescent images permanently and make quantitative measurements.

Once the DNA has been visualized, many types of information can be revealed. FISH is an extremely powerful technique used for many applications in medical research and diagnosis. FISH can be used to determine chromosome structure, chromosome deletions, and chromosomal gene mapping; to detect the expression of genes when probing RNA; to localize viral DNA sequences; to diagnose viral diseases based on the presence of viral DNA sequences; and to localize genes involved in cancer formation, forensics, and sex determination.

FISH applications in medicine

There are specific types of genetic disorders whose detection and diagnosis have been revolutionized by the FISH technique in accuracy, time, and cost. FISH findings have been determined as so important, that the standing committee for the International System on Cytogenetic Nomenclature (ISCN) established a specific genetic nomenclature just to describe FISH findings. Deletion syndromes, such as Prader-Willi syndrome, were first characterized by high-resolution analysis of chromosomes. Because the deletions in some of these disorders are small and difficult to detect, they are referred to as

microdeletion syndromes. The FISH technique has revolutionized the detection and diagnosis of microdeletion syndromes. In some cases, the prevalence of these diseases had not been realized before FISH.

FISH has had a great impact on the characterization of chromosome structural abnormalities that are difficult to diagnose. Given a patient with a genetic disease that has multiple possible gene mutations, FISH, with multiple fluorochromes, can be used to determine the precise nature of the chromosomal rearrangements. FISH can be used to literally map out the exact chromosomal structure in DNA samples from such patients to a level of accuracy previously unknown. This kind of diagnosis would not have been confirmed prior to the advent of FISH. FISH studies can also be used to screen for fetal aneuploidies (too many or too few of one type of chromosome), such as Down syndrome.

FISH is used in cancer analysis. Exploration of the acquired chromosomal abnormalities found in cancer cells is an important area of research. Techniques other than FISH usually require growing sample cells in laboratories for study, a task that can prove very difficult. Because FISH can be used on nondividing cells, it can greatly augment standard research techniques. FISH studies are also being used to look for early relapse and residual disease in cancer patient bone marrow transplants from opposite sex donors. The success of transplant engraftments is monitored by dual fluorochrome FISH studies that can label and differentiate between the proportions of female XX and male XY cells in bone marrow and blood.

FISH is used in gene mapping of specific chromosomes and chromosomal regions. The DNA sequences within a chromosome can be determined by labeling FISH probes with multiple different fluorochromes and distinguishing their hybridization color patterns. Chromosomes are composed of DNA and associated proteins. The combination of DNA and protein found in chromosomes is called chromatin. In a new technique called fiber FISH, chromosome-specific chromatin fibers are stretched out on a glass slide and hybridized with gene locus-specific probes. Fiber FISH achieves higher levels of fine-resolution mapping of DNA sequences than normal FISH.

FISH is a powerful technique. Because of its high accuracy, time efficiency, and relatively low cost, it is quickly becoming the preferred method by which to accomplish many clinical and research applications.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Maria Basile, PhD

Focal dermal hypoplasia

Definition

Focal dermal hypoplasia, previously known as Goltz syndrome, is a rare genetic skin condition. It is a dominant X-linked trait that primarily affects females because it is usually lethal in males before birth.

Description

Focal dermal hypoplasia (FDH) was first described by R. W. Goltz in 1962. It is a genetic disorder that affects the appearance and function of the skin, causing characteristic localized (focal) patches of thin or absent (hypoplasia) skin (dermal). FDH is a member of a larger family of genetic disorders known as the ectodermal dysplasias, which include abnormalities of the skin, hair, teeth, nails, and/or the sweat glands. In FDH, the skin abnormalities include areas where the skin is completely absent or thin (lesions), discolored, itchy, or blistered. Hair may be missing in patches, and the teeth are usually poorly formed. Nails also may be unusual in appearance. In addition to these characteristics, individuals with FDH can have skeletal malformations and eye problems.

The obvious symptoms of FDH are the result of improper functioning of the skin, an organ whose

KEY TERMS

Anophthalmia—Congenital absence of the eyes.

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Coloboma—A birth defect in which part of the eye does not form completely and appears to be cleft or notched.

De novo mutations—A genetic mutation that is seen for the first time in the affected person, not inherited from the parents.

Dermis—The layer of skin beneath the epidermis.

Ectodermal dysplasia—A hereditary condition that results in the malformation of the skin, teeth, and hair. It is often associated with malfunctioning or absent sweat glands and/or tear ducts.

Epidermis—The outermost layer of the skin.

Goltz syndrome—Focal dermal hypoplasia (FDH).

Hyperhidrosis—Excessive perspiration that may be either general or localized to a specific area.

Hypohidrosis—Insufficient perspiration or absent perspiration that may be either general or localized to a specific area.

Hypoplasia—Incomplete or underdevelopment of a tissue or organ.

Papilloma—Any benign localized growth of the skin or the linings of the respiratory and digestive tracts. The most common papillomas are warts.

X-linked dominant—A gene or trait located on an X chromosome that is expressed in preference to the same gene on the other X chromosome; X-linked mutations are often lethal in males because males have only one X chromosome.

multiple functions are often overlooked. The skin consists of two layers: the outer skin (epidermis) and the inner skin (dermis). The epidermis layer protects the body from environmental threats such as temperature variations, bacterial infections, and toxic chemicals. The dermis contains cells that manufacture the protein collagen. Collagen makes up about one-fourth of all the protein in the human body and plays a vital role in wound healing, skin and muscle support, and bone formation. With FDH, type IV collagen in the dermis is abnormally formed and may be present as loose collagen bundles and fibers with loss of regular bands. The epidermis is deformed or completely absent. The importance of collagen in many of the body's tissues explains the varied

symptoms of FDH, which are observed in parts of the body as different as the bones, skin, hair, and fingernails.

Genetic profile

FDH is caused by mutations in the *PORCN* gene on the short arm (p) of the X chromosome at position 22.3 (Xp22.3). It is inherited as an X-linked dominant trait with close to 100% fetal mortality in males, since males have only one X chromosome. The gene mutations may be inherited from a parent, but they most often occur as a sporadic or *de novo* mutation in the egg or sperm cell, fertilized egg, or early embryo, so the parents are unaffected. Males who do survive generally have milder symptoms because they have a *de novo* mutation that occurred later in development, so the mutated gene is present in only some of their cells. The *PORCN* gene produces a protein that modifies Wnt proteins, which are important components of the signaling pathways that regulate fetal development of the skin, bones, and other structures. *PORCN* gene mutations prevent the production of functional *PORCN* protein. Without *PORCN*, the unmodified Wnt proteins appear to be unable to move out of cells to participate in signaling during early development.

Demographics

FDH is presumed to be rare, but its prevalence is not known. It occurs with equal frequency in all races and across all geographic regions. Because it is an X-linked dominant condition, about 90% of surviving patients are female.

Signs and symptoms

FDH is characterized by localized areas of malformed skin (skin lesions) that appear underdeveloped, streaked, or absent. The skin may lack color (pigmentation) in the affected areas or may be streaked with lines (linear pigmentation). The affected areas may look and feel inflamed or irritated, with itching, blistering, reddening, swelling, and even crusting and bleeding. Fatty deposits (papillomas) are usually present in sensitive skin areas, such as the gums, lips, tongue, armpits, vaginal opening, and anus. Nodules of yellowish fatty tissue can grow on the affected skin, particularly in skin folds.

People with FDH often have excessive skin growth on the palms of the hands and on the soles of the feet. Because of this overgrowth of skin layers, increased sweating (hyperhidrosis) often occurs in these areas. Similarly, because of an undergrowth of skin in other parts of the body, many affected people do not sweat normally (hypohidrosis) throughout the rest of their body.

QUESTIONS TO ASK YOUR DOCTOR

- Can you explain the genetic basis of focal dermal hypoplasia?
- Did my daughter inherit focal dermal hypoplasia?
- What are the primary symptoms associated with focal dermal hypoplasia?
- What is my child's prognosis?
- Can you recommend an organization or other resources for additional information about focal dermal hypoplasia?

Additionally, people with FDH may have patches of hair loss on the scalp and pubic region. The teeth are often malformed, mispositioned, or absent, and cavities are commonplace because of missing or incomplete tooth enamel.

Unusual bone formations are also associated with FDH. Missing or extra fingers or toes, webbed fingers or toes, permanently bent fingers or toes, and fusion of bones in the fingers or toes have all been observed. Other skeletal abnormalities, such as curvature of the spine, underdevelopment or protrusion of the lower jaw, and fused vertebrae, may be present.

Individuals with FDH are likely to exhibit facial asymmetry, underdeveloped ears, wide-set eyes, and a pointed chin. Hearing loss, either at birth or developing later, is common, due to underdevelopment of the ears. Many eye abnormalities have been observed with FDH. These range from missing eyes (anophthalmia) and incomplete formation of the eye (coloboma) to clouding of the cornea, drooping eyelids, and crossed eyes. The mucous membranes of the nose and throat may also be affected. Intellectual disability occurs in some cases.

Diagnosis

FDH is generally diagnosed by characteristic skin abnormalities coupled with the characteristic fatty deposits in the gums, lips, armpits, vagina, and/or anus. It is distinguished from the other possible ectodermal dysplasias by lack of pigmentation of the skin in some of the affected areas, abnormal sweating, lack of cysts in the eyes, and the presence of tear ducts. The papillomas in the genital areas are often misdiagnosed as genital warts, but FDH patients will test negative for human papillomavirus (HPV), which causes common genital warts.

Genetic testing for FDH, including prenatal diagnosis, is possible as of 2021.

Treatment and management

Treatment and management of FDH varies depending on the symptoms. Dermatological treatments, such as skin creams, as well as more targeted treatments, are usually indicated. Some affected individuals require dental work or surgery. Others require respiratory therapy to keep the nose and throat clear. Certain skeletal deformations may be corrected with orthopedic surgery. Because of the associated abnormal sweating patterns, affected individuals must avoid heat and strenuous exercise.

Prognosis

FDH is usually lethal in male fetuses. With medical treatment, females with FDH can expect a normal lifespan.

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ORGANIZATIONS

- Ectodermal Dysplasia Society, Unit 1 Maida Vale Business Centre, Leckhampton, Cheltenham, Gloucestershire UK GL53 7ER,

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Fragile site (FRAXE) see **Fragile X syndrome**

Fragile site mental retardation 1 (FMR1) see
Fragile X syndrome

Fragile X syndrome

Definition

Fragile X syndrome is the most common form of inherited developmental disability. Individuals with this condition have developmental delay, variable levels of intellectual disability, and behavioral and emotional difficulties. They may also have characteristic physical traits. In general, males have moderate intellectual disability, and females have mild intellectual disability.

Description

Fragile X syndrome with intellectual disability is a neurodevelopmental disorder. It is also known as Martin-Bell syndrome, Marker X syndrome, and FRAXA syndrome. Fragile X tremor/ataxia syndrome (FXTAS) is classified as a neurodegenerative disorder. Both syndromes are caused by mutations in the *FMR1* gene located on the X chromosome. *FMR1* produces the fragile X mental retardation protein (FMRP). This protein binds to RNA and is presumed to be involved in the translation of messenger RNA (mRNA) during protein synthesis and to play an important role in brain development.

Genetic profile

Each cell in the body contains 23 pairs of chromosomes, one member of each pair inherited from each parent. These chromosomes consist of genetic material (DNA) needed for the production of proteins for growth, development, physical/intellectual characteristics, and metabolism. The first 22 pairs of chromosomes are the same in males and females. The remaining two chromosomes are called the sex chromosomes (X and Y). The sex chromosomes determine whether a person is male or

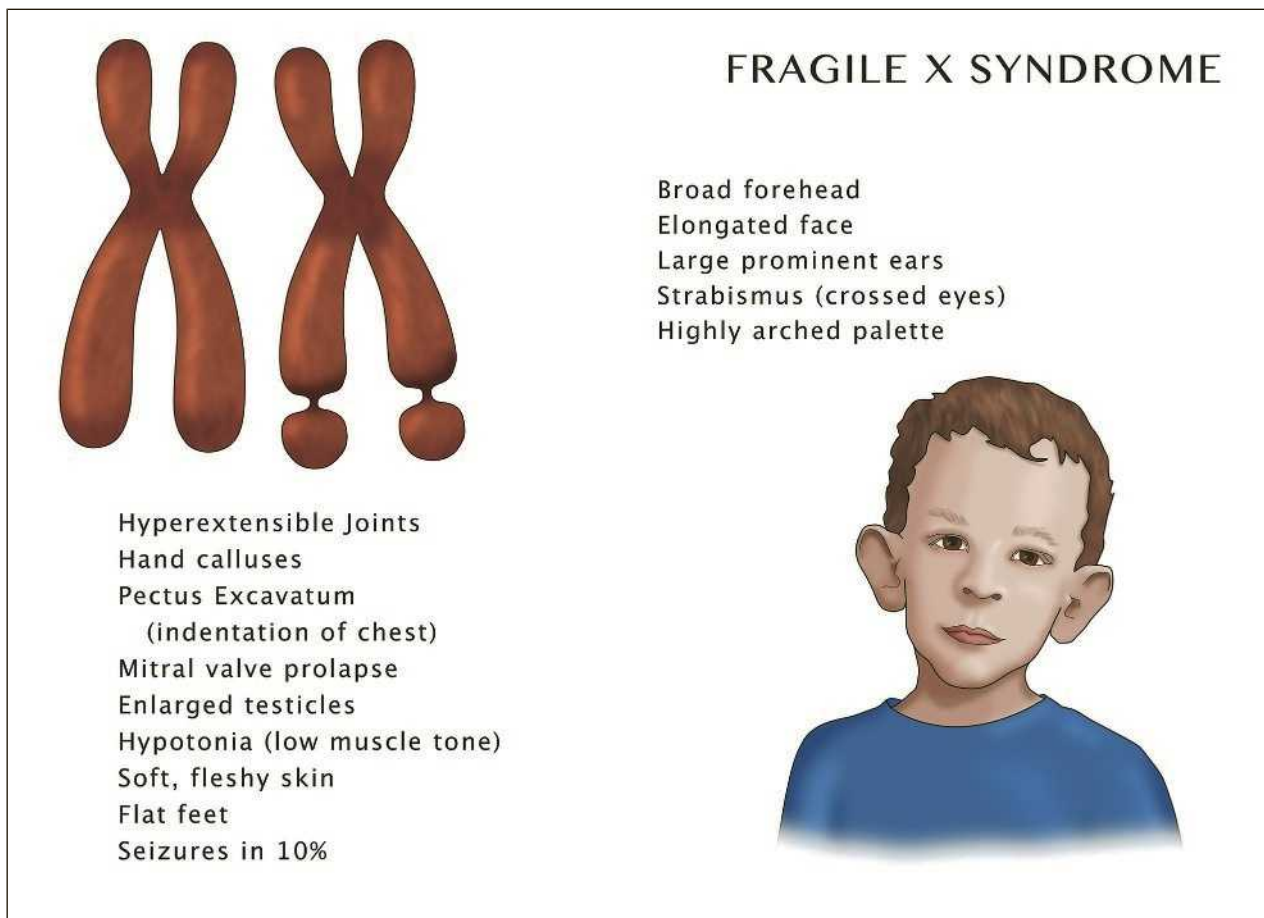


Illustration of an X chromosome with an extra portion dangling, which is the anomaly known as fragile X. (Monica Schroeder/Science Source)

female. Males have only one X chromosome, which is inherited from the mother at conception, and they receive a Y chromosome from the father. Females inherit two X chromosomes, one from each parent.

Fragile X syndrome is caused by a mutation in a gene called *FMR1*, which is located on the X chromosome. The fragile X mutation involves a short sequence of DNA in the *FMR1* gene. This sequence is designated CGG. Normally, the CGG trinucleotide sequence is repeated between six and 54 times. People who have repeats in this range do not have fragile X syndrome and are not at increased risk to have children with fragile X syndrome. Those who are affected by fragile X syndrome with intellectual disability have expanded CGG repeats of more than 200 in the first exon (protein-coding region) of the *FMR1* gene (the full mutation). CGG repeats of 55–200 cause premutations and FXTAS.

People who carry a premutation do not usually have developmental delays or behavioral symptoms; however, they are at risk for having children with FXTAS or fragile X syndrome with intellectual disability, because the size



Fragile X syndrome symptoms. (Monica Schroeder/Science Source)

of the premutation can expand over succeeding generations. Since the *FMR1* gene is located on the X chromosome, males are more likely to develop symptoms than females, because males have only one copy of the X chromosome. Males who inherit the full mutation are expected to have mental impairment. A female's normal X chromosome may compensate for her chromosome with the fragile X gene mutation. Females who inherit one full mutation have an approximately 50% risk of mental impairment. The phenomenon of expanding trinucleotide repeats in successive generations is called anticipation. More than 99% of cases of fragile X syndrome are caused by CGG repeat expansions; fewer than 1% of cases are caused by point mutations or deletions in the *FMR1* gene.

Fragile X syndrome is inherited in an X-linked dominant manner. When a man carries a premutation on his X chromosome, it tends to be stable and usually will not expand if he passes it on to his daughters. (He passes his Y chromosome to his sons.) Thus, all of his daughters will be premutation carriers. When a daughter who carries a premutation has children, the premutation becomes

unstable and can expand as she passes it on. Therefore, a man's grandchildren are at greater risk of developing the syndrome. There is a 50% risk of a premutation carrier female transmitting the mutation with each pregnancy. The likelihood of the premutation expanding is related to the number of repeats present; the higher the number of repeats, the greater the chance that the premutation will expand to a full mutation in the next generation.

All mothers of children with a full mutation are carriers of an *FMR1* gene expansion. Another aspect of fragile X syndrome is mosaicism in 15% to 20% of those affected by the condition. Mosaicism means that only some of the cells in the body have the fragile X mutation. This is caused by a trinucleotide repeat expansion or premutation expansion occurring in a cell of the early embryo or developing fetus. Only cells that come from the cell with the mutation are affected.

Researchers continue to study the possible causes of fragile X syndrome. In 2020, researchers at Tokyo University found that specific groups of molecules might contribute to the abnormal development of neural stem

KEY TERMS

Artificial intelligence—Abbreviated as AI, artificial intelligence is the ability of computers or computer-driven devices to make decisions with real-time data based on machine learning.

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Fragile X tremor/ataxia syndrome (FXTAS)—A movement disorder caused by 55–200 CGG repeats in the *FMR1* gene.

Mosaicism—A condition in which an individual's cells are not all genetically identical.

Premature ovarian insufficiency (POI)—Premature ovarian failure; the cessation of ovarian function before age 40.

Premutation—A change in a gene that precedes a mutation; this change does not alter the function of the gene.

Trinucleotide repeat expansion—A sequence of three nucleotides that is repeated too many times in a section of a gene.

cells in fetal brains. Learning more about molecular pathways that contribute to fragile X syndrome will help with assessing risk in individuals.

Demographics

Fragile X syndrome affects males and females of all ethnic groups. It is estimated that there are about one in 7,000 males affected with fragile X syndrome. There are approximately half as many females with fragile X syndrome as males (one in 11,000); however, the carrier frequency in unaffected females is one in 100 to one in 600. The average age of children at diagnosis of fragile X syndrome is 35 to 42 months.

Signs and symptoms

Individuals with fragile X syndrome appear normal at birth, but their development is delayed. Most boys with fragile X syndrome have mental impairment. The severity of mental impairment ranges from learning disabilities to severe intellectual disability. Behavioral problems include attention deficit and hyperactivity at a young age. Some may show aggressive behavior in adulthood. Short attention span, poor eye contact, delayed and disordered speech and language, emotional instability, and unusual hand mannerisms (hand flapping or hand biting) are also seen

frequently, as are behavioral characteristics such as whirling and spinning. These symptoms are noticeably similar to symptoms of autism spectrum disorder.

Characteristic physical traits appear later in childhood. These traits include a long and narrow face, prominent jaw, large ears, and enlarged testes. In females who carry a full mutation, the physical and behavioral features and intellectual disability tend to be less severe. About 50% of females who have a full mutation are intellectually disabled. Females may develop premature ovarian insufficiency (POI) or premature ovarian failure, in which the ovaries cease functioning before age 40, with irregular menstrual periods and menopausal symptoms.

Children with fragile X syndrome may have frequent ear and sinus infections. Near-sightedness and lazy eye are also common. Many babies with fragile X syndrome have trouble with sucking, and some experience digestive disorders that cause frequent gagging and vomiting. A small percentage of children with fragile X syndrome have seizures. Children with fragile X syndrome tend to have loose joints that may result in joint dislocations. Some children develop a curvature in the spine, flat feet, and a heart condition known as mitral valve prolapse.

Diagnosis

A child with signs of speech, language, or motor developmental delays of unknown cause might be tested for fragile X gene mutations, especially if there is a family history of the condition. Definitive identification of fragile X syndrome is made by genetic testing to assess the number of CGG sequence repeats in the *FMR1* gene. Genetic testing for the fragile X mutation can be performed on the developing fetus before birth through amniocentesis or chorionic villus sampling (CVS); this test detects 99% of trinucleotide repeat expansions in the *FMR1* gene. Prenatal testing will only be performed after the fragile X carrier status of the parents has been confirmed and the couple has undergone genetic counseling.

A spring 2021 study from the University of Wisconsin-Madison reported that use of artificial intelligence (AI) leads to an earlier diagnosis of fragile X syndrome. The researchers input information from medical records of 1.7 million patients and matched several other diagnoses that are common among those who have the genetic condition, such as certain heart conditions. Through machine learning, the AI diagnosis can occur five years earlier on average, alerting doctors to risk sooner. The AI diagnosis still was being studied in 2021.

Treatment and management

There is no cure for fragile X syndrome. Management includes speech therapy, occupational therapy, physical

QUESTIONS TO ASK YOUR DOCTOR

- What is the prognosis for my child with fragile X syndrome?
- What is the risk that we will have another child with fragile X syndrome?
- Is preimplantation or prenatal genetic testing available for fragile X syndrome?
- Are there any treatments for fragile X syndrome?

therapy, and special education. Mainstreaming children with fragile X syndrome into regular classrooms is encouraged because they do well imitating the behavior of others. Drugs may be used as needed to treat hyperactivity, seizures, and other problems. Establishing a regular routine, avoiding overstimulation, and using calming techniques may also help in the management of behavioral problems. Children with a defective heart valve should see a heart specialist and take medications before surgery or dental procedures. Children with frequent ear and sinus infections may need medications or have special tubes placed in their ears to drain excess fluid.

Prognosis

Early diagnosis and intensive intervention offer the best prognosis for individuals with fragile X syndrome. Adults with fragile X syndrome may benefit from vocational training and may need to live in a supervised setting. Lifespan is typically normal.

Resources

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ORGANIZATIONS

Arc of the United States, 1825 K Street, NW, Suite 1200, Washington, D.C. 20006, (800) 433-5255, <http://www.thearc.org>

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), P.O. Box 3006, Bethesda, MD 20847, (866) 760-5947, NICHDInformationResourceCenter@mail.nih.gov, <https://www.nichd.nih.gov>

National Fragile X Foundation, 1861 International Drive, Suite 200, McLean, VA 22102, (800) 688-8765.

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Revised by Teresa Odle, BA, ELS

Francois dyscemicphalic syndrome see
Hallermann-Streiff syndrome

Fraser syndrome

Definition

Fraser syndrome is a rare autosomal recessive genetic disorder that primarily affects the eyes, genitalia, and urinary tract.

Other names for Fraser syndrome include:

- Cryptophthalmos syndactyly syndrome
- Cryptophthalmos syndrome
- Cryptophthalmos with other malformations
- Fraser-Francois syndrome
- Meyer-Schwickerath syndrome
- Ullrich-Feichtiger syndrome

Description

Fraser syndrome is named for Canadian geneticist C. R. Fraser, who first described the syndrome in 1962. Individuals affected with Fraser syndrome appear to have

hidden eyes because the skin of their eyelids is partially or fully sealed shut. This condition is called cryptophthalmos and is classified into three types: complete, in which the eyelid is completely fused over an existing eye; incomplete, in which the eyelid is only partially fused over the underlying eye; and abortive, in which the eyelid is completely fused and the underlying eye does not form.

Approximately half of all individuals affected with Fraser syndrome have abnormalities of the genitals, while 37% have renal (kidney) problems, including the absence of one or both kidneys. Some individuals also have abnormalities of the larynx or voice box, of the middle and outer ear, and of the fingers and toes.

Genetic profile

Fraser syndrome is caused by mutations in the *FRAS1*, *FREM2*, or *GRIP1* genes. Nearly half of all cases of Fraser syndrome are caused by mutations in the *FRAS1* gene. *FREM2* and *GRIP1* gene mutations are responsible for a small percentage of cases.

FRAS1 and *FREM2* genes produce FRAS1 and FREM2 proteins and are part of a group of proteins called the FRAS/FREM complex. These proteins are responsible for helping produce the FRAS and FREM complex, which are thin sheets of tissue, called basement membranes that support cells in many tissues in the body. These complexes are extremely important during fetal development, particularly in connecting the top layer of the skin to the tissues beneath. They are also important in the proper development of other organs and tissues, such as the kidneys.

Mutations in the *FRAS1* and *FREM2* genes prevent formation of the FRAS/FREM complex and cause the FRAS/FREM complex to be missing in basement membranes of the skin. When this occurs, the top layer of skin is detached, causing blisters to form during development. These blisters are likely responsible for the abnormalities of the eyes, fingers, and toes seen in Fraser syndrome. Scientists have not yet discovered how the lack of the FRAS/FREM complex may cause the kidney and genital abnormalities seen in Fraser syndrome.

The genetic mutations that cause Fraser syndrome are inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each have one copy of the mutated gene, making them carriers. Carriers generally do not show signs and symptoms of the condition, but if two carriers have children, they have a 25% chance of passing on the condition with symptoms to their child.

Demographics

Fraser syndrome is very rare, occurring in less than 1 of every 100,000 births. It has been reported that the frequency of the syndrome is over 100 times higher in the Roma (gypsy) population as in the non-Roma population.

As in all recessive genetic disorders, both parents must carry the gene mutation in order for their child to have the disorder. Approximately 15% of individuals diagnosed with Fraser syndrome have been observed in cases where the parents are related by blood. Parents with one child affected by Fraser syndrome have a 25% likelihood that their next child will also be affected with the disease.

Signs and symptoms

Fraser syndrome is characterized by hidden eyes resulting from either partial or complete fusion of the eyelids. This condition may be observed on only one side (unilaterally), but it is generally observed in both eyes of affected individuals (bilaterally). In most cases the underlying eyes are not fully formed, which causes small eyes called microphthalmia. In some cases of Fraser syndrome the underlying eyes are completely absent.

Individuals with Fraser syndrome have abnormal or absent tear ducts and widely spaced eyes, a condition called hypertelorism. Blindness from birth is quite common in affected individuals. However, in cases where there is a functioning visual pathway to the retina, the inner light-sensitive layer of the eye, partial vision has been observed.

Approximately half of those individuals affected with Fraser syndrome have syndactyly, a partial or complete fusion of the fingers or toes. In cases of Fraser syndrome, the observed syndactyly is most often of the third and fourth digits of the hands or feet. An extra finger or toe situated outside the normal fifth digit, called postaxial polydactyly, and webbing of the fingers or toes are also symptoms seen in individuals with Fraser syndrome. The only other bone abnormality seen with any high frequency is a greater than normal width of the cartilaginous joint between the pubic bones in the front of the pelvis.

Abnormalities of the middle and/or outer ear occur in approximately 50% of affected individuals. These symptoms range from malformations and closures of the outer structures of the ear, called the pinna or the auricle, to an absence of the auditory canal (Eustachian tube). In cases where the Eustachian tube is absent, connective tissue fills the space where the auditory canal should be and bone covers what would be the opening of the auditory canal to the outer ear. As a result of these abnormalities, some individuals may be deaf or have hearing problems.

KEY TERMS

Autosomal recessive—Genetic transmission of a trait or condition in which two copies of a gene must be present.

Cerebrospinal fluid—The fluid that surrounds the brain and spinal cord.

Cryptophthalmos—Condition in which the eyelid does not form correctly.

Diaphragm—Dome-shaped muscle and fiber that separates the torso into two sections, thoracic and abdominal.

Eustachian tube—Small tube that connects the middle ear to the throat.

Hypospadias—Congenital anomaly in which the opening of the penis is located underneath the penis rather than at the tip.

Mesentery—Tissue that attaches the intestines to the abdominal wall.

Microphthalmia—Abnormally small eyes.

Scrotum—The sac of skin that holds the testicles.

Syndactyly—Fusion of fingers or toes.

Urethral atresia—Abnormal closure of the tube that leads from the bladder to the outside of the body.

Approximately 85% of those affected with Fraser syndrome have abnormalities of the nose. The most common nasal abnormalities are blockage or narrowing of the nasal cavities that open into the mouth and throat by excess bone or by membranous tissue. Forking of the tongue and cleavage of the internal nasal passage are also seen.

Blockage and narrowing of the larynx is commonly associated with Fraser syndrome. Occasionally an abnormal web-like structure is seen in the vocal apparatus that causes an inability of speech if not corrected.

Abnormalities of the digestive system, otherwise known as the gastrointestinal or GI tract, are also common. These abnormalities include an incomplete development of the mesentery, or membrane that connects the small intestine to the back wall of the abdominal cavity; malrotation of the small intestine; umbilical hernia, a protrusion of parts of the large intestine through an abnormal opening in the abdominal wall near the navel; and defects of the diaphragm, the large muscle that separates the upper and lower parts of the abdomen.

Approximately 50%-80% of all individuals with Fraser syndrome have abnormalities of the genitalia. Affected females may have partial or complete fusion of the labia, the folds of skin on either side of the vagina;

an abnormally large clitoris; a malformation of the fallopian tubes, the paired tubes that connect the ovaries to the uterus; and/or an abnormally shaped uterus. Affected females beyond puberty may not have a menstrual cycle. Affected males may have undescended testicles, a condition where one or both testicles may fail to descend into the scrotum; hypospadias, a condition where the urinary opening is on the underside of the penis rather than at the tip; micropenis, an abnormally small penis; and/or urethral atresia, a condition where the urinary opening of the penis may be fused completely closed.

Another complication of Fraser syndrome is malformations of one or both kidneys. These malformations may include renal dysplasia, hypoplasia, or renal agenesis, conditions in which one or both kidneys may be small, located in the wrong place, or completely absent.

Both the navel and the nipples may develop in irregular locations. The navel can be located lower than normal and the nipples are generally wider set. A hairline that extends forward over the temples is an additional cosmetic symptom of Fraser syndrome.

Many infants with Fraser syndrome have hydrocephaly, a condition in which too much cerebrospinal fluid (CSF) collects in the brain. Some cases have been found in which the left ventricle, one of the normal cavities within the brain, is not present. Dandy-Walker malformation, an abnormal condition of the brain in which the fourth ventricle of the brain may become blocked and too much CSF collects, has also been associated with Fraser syndrome. These brain abnormalities can all cause developmental delays and intellectual disability.

Diagnosis

The symptoms of Fraser syndrome have been classified into four major and eight minor characteristics. A patient is diagnosed with Fraser syndrome rather than another genetic syndrome by the presence of at least two of the four major characteristics of the syndrome accompanied by at least one of the eight minor characteristics of the syndrome, or by the presence of one major characteristic and at least four minor characteristics.

The four major characteristics of Fraser syndrome include:

- Cryptophthalmos – hidden eyes
- Syndactyly – fused or partially fused fingers and/or toes
- Genital abnormalities
- Affected sibling(s)

The eight minor characteristics of Fraser syndrome include malformations of the:

- Nose
- Ears

QUESTIONS TO ASK YOUR DOCTOR

- What treatment is available for my child?
- What other specialists will my child need to see?
- Will my child need surgery?
- Are there support groups available for children with Fraser syndrome or their parents?
- What are the chances that my next child will have Fraser syndrome?

- Voice box
- Abdominal wall (umbilical hernia)
- Kidneys (renal agenesis, atresia, or dysplasia)
- Fingers and toes (syndactyly)
- Cleft tongue (or other oral clefts)
- Developmental/intellectual disability

Prenatal diagnosis of Fraser syndrome is possible as early as 18 weeks of fetal development and is accomplished by the observance via ultrasound of a combination of some or all of the following conditions: blockage of urine flow out of the bladder; small eyes; fused or partially fused fingers and/or toes; pulmonary obstruction, a blockage of the lungs resulting from an absence or closure of the voice box (laryngeal atresia); ascites, the accumulation of thin, watery fluid, called serous fluid, in the abdominal cavity; fetal hydrops, a blood disorder that prevents proper formation of the hemoglobin, the oxygen carrying part of blood; nuchal edema, a presence of an abnormally high amount of fluid in the tissues comprising the nape of the neck; and oligohydramnios, an absence of amniotic fluid due to an incomplete development of the kidney.

A molecular genetic test for mutations in the *FREM2* gene is available as of 2021. The test can be performed on a sample of amniotic fluid, fetal blood, fresh tissue, bone marrow, or a buccal swab.

Treatment and management

Genetic counseling is particularly important in the prenatal treatment and management of Fraser syndrome. This is because the severity of symptoms and appearance of an infant with this syndrome is likely to be very similar in a sibling also born with the disease.

Surgery is almost always necessary to correct the improperly fused tissues of the eyelids, ears, nose, and genitals. Most affected individuals are blind at birth; however, if some visual function is observed to be present such as a wincing reaction to strong light, partial vision is possible

after surgery to repair the damaged eyelids. Recently, corneal transplant surgery has been used to achieve improvements in vision. In cases of anophthalmia, missing eye(s), reshaping of the eye socket may be necessary and a glass eye is fitted for cosmetic purposes. Many infants diagnosed with Fraser syndrome are also deaf or partially deaf at birth. Special programs for the hearing and vision-impaired are necessary for these affected persons.

The most serious and life-threatening abnormalities associated with Fraser syndrome are those of the kidneys and the larynx. In some cases, the laryngeal malformations cannot be repaired, which leads to either stillbirth or death shortly after birth. This is particularly true of laryngeal atresia. Corrective surgery is often possible in cases of laryngeal stenosis, narrowing of the larynx.

If both kidneys are absent, renal agenesis, the affected individual is usually stillborn. In cases of unilateral renal agenesis, renal dysplasia, or renal hypoplasia, the affected individual may require kidney dialysis or a kidney transplant. The abnormalities of the small intestine that are associated with Fraser syndrome are generally correctable through surgery.

Prognosis

The type and severity of the kidney and voice box malformations that may result in Fraser syndrome usually determine the prognosis. Overall, 25% of all babies born with Fraser syndrome are stillborn. Another 20% die within the first year of infancy, often in the first few weeks of life. The cause of death is usually lack of kidney function or blockage of the larynx. Kidney and larynx defects tend to be either very slight or absent in the surviving 55% of Fraser syndrome affected individuals, but developmental delay is observed in most patients.

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ORGANIZATIONS

Children’s Craniofacial Association, 13140 Coit Road, Suite 517, Dallas, TX 75240, (214) 570-9099 or (800) 535-3643, (214) 570-8811, contactCCA@ccakids.com, <http://www.ccakids.com>

National Kidney Foundation, 30 E. 33rd St., New York, NY 10016, (800) 622-9010, <http://www.kidney.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06813, (203) 744-0100 or (800) 999-6673, (203) 797-9590, <https://rarediseases.org/rare-diseases/fraser-syndrome>

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FRDA-1 *see* **Friedreich ataxia**

Freeman-Sheldon syndrome

Definition

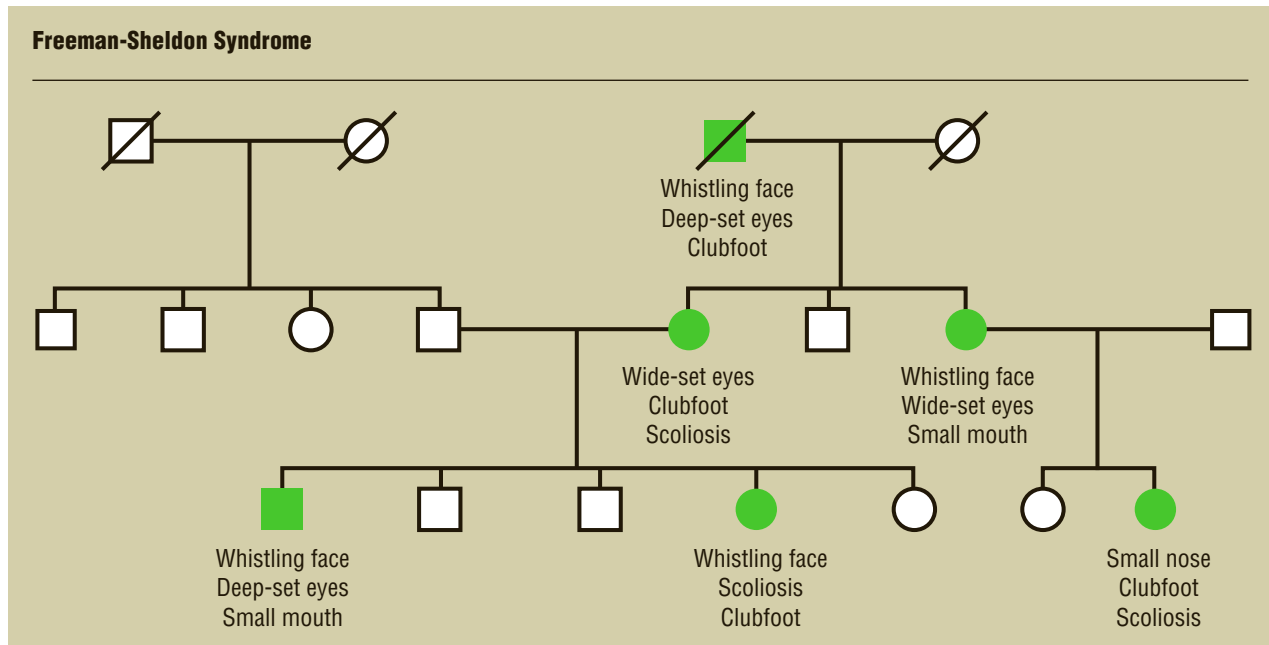
Freeman-Sheldon syndrome (FSS) is a very rare genetic disorder characterized by an abnormally small puckered mouth (microstomia), which gives the appearance of a person whistling. For this reason, Freeman-Sheldon syndrome is also known as whistling-face syndrome. FSS

may also be referred to as Freeman-Burian syndrome; distal arthrogryposis type 2A (DA2A); windmill-vane hand syndrome; or craniocarpotarsal dystrophy. It is considered the most severe form of a group of disorders known as the distal arthrogryposes. FSS has also been defined as a congenital myopathy, which means that weakness of the skeletal muscles in affected children is present from birth.

Description

Ernest Freeman and Joseph Sheldon, two British physicians, first described this distinctive disorder in 1938. The syndrome is characterized by skeletal malformations in the hands and feet as well as facial abnormalities.

In addition to the small mouth, characteristics of FSS include a flat, mask-like face; underdeveloped nose cartilage; abnormally widely spaced eyes (hypertelorism); an abnormally small jaw (micrognathia); contracted muscles (contractures) in the joints in the fingers and hand; permanently bent fingers (camptodactyly); and clubbed feet. Most of the features of FSS are caused by muscle weakness. In addition to those characteristics, individuals with FSS may have crossed eyes, drooping upper eyelids (ptosis), scoliosis, hearing loss, and walking difficulties. In one case series, 80% of the children diagnosed with FSS required assistive devices (canes, walkers, etc.) in order to walk. Health is generally good, and life expectancy is normal; however, about 31% of children with FSS suffer from mild mental retardation.



Freeman-Sheldon syndrome: pedigree analysis chart (Gale)

KEY TERMS

Arthrogryposis (plural, arthrogryposes)—The medical term for joint contractures in two or more areas of the body. The English word is derived from two Greek words that mean “joint” and “curving” or “hooked.”

Camptodactyly—A congenital disorder in which one or more fingers are permanently bent. It is a classic sign of FSS as well as of several other genetic syndromes.

Congenital—Present at birth.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

De novo mutation—A genetic mutation that is not inherited from either parent.

Distal—Referring to body parts that are furthest from the center of the body.

Dysphagia—Difficulty in swallowing.

Electromyography (EMG)—A diagnostic test of the responsiveness of skeletal muscle that involves placing electrodes either on the skin above a muscle or in the muscle, and measuring the electrical activity in the muscle. The level of activity is recorded on a monitor.

Hypertelorism—Abnormally widely spaced eyes.

Malignant hyperthermia—A rare potentially fatal condition triggered by exposure to certain inhalational anesthetics, in which the body’s metabolism speeds up and overwhelms its ability to regulate body temperature.

Micrognathia—An abnormally small jaw.

Microstomia—The medical term for an abnormally small mouth.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Myopathy—The general medical term for weakness of the skeletal muscles present in the muscle tissue itself rather than in the nerves supplying the muscles.

Myosin—Any of a family of proteins involved in muscle contraction, cell movement, and other motor processes.

Ptoxis—Drooping of the upper or lower eyelid.

Scoliosis—An abnormal side-to-side curvature of the spine.

Genetic profile

FSS has several different inheritance patterns. In many cases, the syndrome follows an autosomal dominant inheritance pattern. With this pattern of inheritance, the syndrome appears when a child inherits one defective gene from one parent. In some families, however, FSS follows an autosomal recessive inheritance pattern. In these cases, the condition appears only when a child receives the same defective gene from each parent. This syndrome can also occur sporadically, that is, neither parent passes on the gene responsible for FSS. These cases of FSS result from *de novo* mutations.

In 2006, mutations in the *MYH3* gene on the short arm of chromosome 17 at 17p13.1 were identified as the cause of most cases of FSS. This gene codes for a protein that belongs to the family of myosins, which are proteins involved in cell movement and muscle contraction. Mutations in the *MYH3* gene interfere with normal development of muscle tissue in the fetus, leading to the myopathy, contractures, arthrogryposis, and other signs of FSS.

There are also a few reported cases of FSS in which there is no mutation in the *MYH3* gene. The cause of these cases was unknown as of 2021.

Demographics

Freeman-Sheldon syndrome is extremely rare; about 100 cases have been reported in the medical literature since the disorder was first described in 1938. The frequency is estimated at less than one person per million. It affects males and females in equal numbers. As far as is known, FSS affects children in all races and ethnic groups; cases have been reported in Japan, Morocco, Turkey, and India as well as Europe and North America.

Signs and symptoms

Doctors can recognize Freeman-Sheldon syndrome at birth. Babies born with FSS usually have distinct abnormalities of the head, face, hands, and feet.

Facial abnormalities usually include an extremely small and puckered mouth, a full forehead, prominent cheeks, and thin, pursed lips. The middle part of the face may be flat, giving the baby a mask-like appearance. There may be a high palate, unusually small jaw, abnormally small tongue, and a raised mark or dimpling in the shape of an “H” or “V” on the chin. Other common facial abnormalities associated with FSS include widely

QUESTIONS TO ASK YOUR DOCTOR

- How will FSS affect my child's quality of life?
- Are we likely to have a second child with the syndrome?
- What are the treatment options?
- Will my child always need to use a walker or cane in order to walk?

spaced, deep-set eyes (hypertelorism), crossed eyes (strabismus), and down-slanting eye openings.

Infants born with FSS may have malformations of the hands or feet, including clubbed feet. The muscles in the joints of the fingers and hands may be contracted.

Characteristics of FSS are often linked with other problems such as impaired speech, swallowing and eating difficulties (dysphagia), failure to thrive, and vomiting. Children may fail to grow and gain weight at the expected rate, and there may be respiratory problems. Although most of the characteristics of FSS will be discovered fairly early in life, scoliosis (curvature of the spine) may be diagnosed later in childhood or adolescence as the child grows.

Diagnosis

Because many of the characteristics of FSS are present at birth, doctors can recognize and diagnose FSS following birth based on these characteristics. Other diagnostic techniques that have been used after birth to evaluate infants whose congenital defects are less obvious include CT scanning of the head to indicate the presence and severity of craniofacial and dental abnormalities. Electromyography may be used to evaluate the strength of the muscles in the hands, feet, and jaw. FSS has also been diagnosed prenatally using ultrasound imaging.

Molecular genetic testing for mutations in the *MYH3* gene was available as of 2015 in Europe as well as in the United States. Because FSS can run in families, parents of children with FSS may wish to seek genetic counseling.

Treatment and management

Most children with Freeman-Sheldon syndrome require orthopedic or plastic surgery to correct their hand problems, clubbed feet, and tight mouth. Plastic surgery can improve the function and appearance of the mouth and nose. Craniofacial surgery can reshape the frontal bone and increase eyelid openings. The thumb may be repositioned to improve hand function.

A potential surgical complication in FSS patients is malignant hyperthermia—a life-threatening problem with inhaled anesthetic agents in which uncontrolled metabolism in skeletal muscle overwhelms the body's ability to regulate its temperature. A muscle biopsy prior to surgery can minimize this risk, as can a less invasive test that involves intramuscular injection of a small amount of halothane.

Children with FSS may also benefit from psychological counseling as they grow older in order to cope with the social complications that may result from their physical limitations or abnormal facial features.

Prognosis

Life expectancy for infants diagnosed with Freeman-Sheldon syndrome is normal. Infants and children with FSS may be referred to physical and speech therapists. Physical therapy may help children improve the use of their hands, and it also can improve ambulation (walking). Speech therapy may improve tongue movement, which helps speech and swallowing. Assistive devices are often recommended to aid muscular function.

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ORGANIZATIONS

- FACES: The National Craniofacial Association, PO Box 11082, Chattanooga, TN 37401, (423) 266-1632 or (800) 332-2373, <http://www.faces-cranio.org/index.htm>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

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Friedreich ataxia

Definition

Friedreich ataxia (FA, sometimes abbreviated as FRDA) is an inherited, progressive nervous system disorder causing loss of balance, coordination, and mobility. The disorder was first described by Nikolaus Friedreich, a German medical professor, in 1863.

Description

Ataxia is a condition marked by impaired coordination. FA is a progressive ataxia that typically starts around puberty and slowly progresses into adulthood. The nervous system is the affected system, with a deterioration of the cerebellum and peripheral sensory nerves, thus affecting both movement and sensation.

Genetic profile

FA is an autosomal recessive disorder, which means that two defective gene copies, one from each parent, must be inherited in order to develop symptoms. A person with only one defective gene copy is called a carrier and will not show signs of FA, but he or she has a 50% chance of passing along the gene to offspring with each pregnancy. Couples in which both parents are carriers of FA have a 25% chance with each pregnancy of conceiving an affected child.

The gene for FA is called *FXN*. It is located on chromosome 9 and codes for a protein called frataxin. Normal frataxin is found in the cellular energy structures called mitochondria, where it is involved in regulating the transport of iron. Due to the role that mitochondria have in the life of a cell, a decrease or dysfunction of this protein will result in cell death. Cell death occurs more frequently in the cells of the peripheral (outside of the brain) nervous system, which is why this disorder is classified as a nervous system disorder.

In approximately 96% of patients with FA, both copies of the frataxin gene are expanded with nonsense information known as a triple repeat of a particular sequence of DNA bases called GAA. Normally, the GAA base sequence is repeated between six and 30 times, but those with FA have between 100 and 1,300 copies. About 4%



A businessman with Friedreich ataxia and hand degeneration text-messaging on a mobile phone. (*Disability Images/Science Source*)

of patients have been found to have the triple repeat in only one copy of the frataxin gene and a different gene change in the other copy. Longer GAA repeats are generally associated with more severe disease, but the severity of disease in a particular individual cannot be predicted from the repeat length. The extra DNA or other gene change interferes with normal production of frataxin, thereby impairing iron transport. FA symptoms are thought to develop at least in part because defects in iron transport prevent efficient use of cellular energy supplies. Extra iron builds up in the mitochondria, leading to the accumulation of damaging chemicals called free radicals.

The nerve cells that are most affected by FA are those in the spinal cord involved in relaying information between muscles and the brain. Tight control of movement requires complex feedback among the muscles promoting a movement, those restraining it, and the brain. Without this control, movements become uncoordinated, jerky, and inappropriate for a desired action.

Demographics

FA is the most common inherited ataxia, affecting between one in 22,000 to one in 50,000 people or roughly 3,000 to 5,000 people in the United States. It is found in individuals of European, Middle Eastern, and North African descent and is rare in other ethnic groups. Approximately 1% of Caucasian individuals carry one defective copy of the gene for frataxin. Approximately 25% of individuals diagnosed with FA are later diagnosed with diabetes mellitus.

Signs and symptoms

Symptoms of FA usually first appear between the ages of eight and 15, although onset as early as 18 months or as late as 40 years is possible. The first symptom is

KEY TERMS

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Mitochondria—Eukaryotic cellular organelles that produce energy for the cells through cellular respiration and are rich in fats, proteins, and enzymes.

usually gait incoordination. For instance, a child with FA may graze doorways when passing through, trip over low obstacles, or show general clumsiness when walking. Unsteadiness when standing still and deterioration of position sense are common. Foot deformities and walking off the heels (toe walking) often result from uneven muscle weakness in the legs. Muscle spasms and cramps may occur, especially at night.

Ataxia in the arms usually follows within several years, leading to decreased hand-eye coordination. Arm weakness does not usually occur until much later. Speech and swallowing difficulties are common. The loss of reflexes in the lower legs is common. Diabetes mellitus, a condition characterized by elevated blood sugar, may also occur. Nystagmus, or eye tremor, is common in FA, along with some loss of visual acuity. Hearing loss may also occur. A side-to-side curvature of the spine (scoliosis) occurs in many cases and may become severe.

Heart muscle enlargement (cardiomyopathy) with or without heartbeat abnormality occurs in between half and two-thirds of FA patients, leading to shortness of breath after exertion, swelling in the lower limbs, and frequent complaints of cold feet.

There are some atypical forms of FA. For example, a portion of the Acadian population, who originated in northern France and now live in parts of Canada and Louisiana, have a very slowly progressing form of the disorder and only occasionally have heart problems, leading them to live longer than most patients with FA. Other forms include late-onset Friedreich ataxia (LOFA), in which symptoms begin after age 25, and Friedreich ataxia with retained reflexes (FARR). All three of these forms have been shown to result from changes in the same gene as the “classic” form. There have been a few patients with classic FA described in whose cases the frataxin gene on chromosome 9 has been shown not to be the cause. A form of ataxia caused by a gene change resulting in vitamin E deficiency, but having similar symptoms to FA, has been identified with changes in a different gene on chromosome 8.

Diagnosis

Diagnosis of FA involves a careful medical history and thorough neurological exam. Lab tests include electromyography, an electrical test of muscle, and a nerve conduction velocity test. An electrocardiogram may be performed to diagnose heart arrhythmia.

Direct DNA testing is available, allowing FA to be more easily distinguished from other types of ataxia. This testing is accomplished by counting the number of GAA repeats in the frataxin gene to see whether there is a significant expansion and by looking for other gene changes in patients who only show a GAA expansion in one copy of the frataxin gene. The same genetic test may be used to determine the presence of the genetic defect in the carrier state (i.e., one normal copy and one defective copy of the frataxin gene) in unaffected individuals, such as adult siblings, who would like to learn their chances of producing an affected child. During pregnancy, the DNA of a fetus can be tested using cells obtained from a procedure called chorionic villi sampling (CVS), in which cells from the placenta are studied, and amniocentesis, in which skin cells from the amniotic fluid surrounding the baby are tested.

Treatment and management

As of 2021, studies had been inconclusive concerning medical treatment of FA, but progress had been made in the management of symptoms caused by FA. Physical and occupational therapy are used to maintain range of motion in weakened muscles. Adaptive techniques and devices can be used to compensate for loss of coordination and strength. Some patients find that using weights on their arms can help to dampen the worst of their uncoordinated arm movements.

Heart problems and diabetes are treated with drugs specific to those conditions.

Prognosis

Clinical trials for FA, including a phase 2 trial of the experimental drug elamipretide, began in 2021. This drug helps to restore the ability of mitochondria to produce energy. It is being tested on people with FA and symptoms of vision and heart deterioration. Participation in U.S. clinical trials is voluntary and at no cost to the participant. All clinical trials receiving U.S. government funding, and some supported by private industry, are posted at <https://www.clinicaltrials.gov>. Foreign trials are listed at <https://www.orpha.net>.

The rate of progression of FA is highly variable. Most patients lose the ability to walk within 15 years of symptom onset, and 95% require a wheelchair for mobility by age 45. Reduction in lifespan from FA

QUESTIONS TO ASK YOUR DOCTOR

- How often should I be evaluated for progression?
- Aside from a neurologist, what doctors should I see regularly?
- Is there genetic screening to determine whether my future children will inherit this disorder?
- What is my life expectancy?
- Are there any activities I should avoid?
- How fast do you think my ataxia will progress?
- What are the ways I can increase my life expectancy (such as diet, nutrition, or exercise)?

complications, usually cardiac, is also quite variable. Average age at death, usually from heart problems, is in the mid-30s, but some may live into their mid-60s. The particular length of the triple repeat has not been correlated strongly enough with disease progression to allow prediction of the course of the disease on this basis.

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ORGANIZATIONS

Friedreich's Ataxia Research Alliance, 533 W. Uwchlan Avenue, Downingtown, PA 19335, (484) 879-6160, (484) 872-1402, info@cureFA.org, <https://cureFA.org>

Muscular Dystrophy Association, 161 N. Clark, Suite 3550, Chicago, IL 60601, (800) 572-1717, mda@mdausa.org, <https://www.mda.org>

National Ataxia Foundation, 600 Highway 169 South, Suite 1725, Minneapolis, MN 55426, (763) 553-0020, (763) 553-0167, naf@ataxia.org, <https://www.ataxia.org>

National Institute of Neurological Disorders and Stroke, P.O. Box 5801, Bethesda, MD 20824, (301) 496-5751 or (800) 352-9424, <https://www.ninds.nih.gov>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <https://rarediseases.org>

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Frontonasal dysplasia

Definition

Frontonasal dysplasia (FND), also called median cleft syndrome, is a rare genetic disorder that affects the prenatal development of the face and head. There are at least three different types of FND that have different signs and symptoms and are caused by mutations in different genes.

Description

The term *frontonasal dysplasia* was first used in 1970 to describe disorders characterized by at least two of the following features:

- widely spaced eyes (hypertelorism)
- a broad nose
- a cleft (slit) on one or both sides of the nose
- absence of the skin that forms the tip of the nose
- a central cleft affecting the nose, upper lip, and/or palate (roof of the mouth)
- incomplete formation of the front of the skull
- a "widow's peak" hairline—a hairline that extends farther than normal and comes to a point in the center of the forehead

FND may include:

- other facial malformations
- absence or malformation of the corpus callosum that connects the left and right brains
- intellectual disability

Additional characteristics distinguish the different types of FND:

KEY TERMS

ALX—Gene family encoding transcription factors that are required for normal prenatal development of the head and face; mutations in the *ALX1* gene cause frontonasal dysplasia (FND) type 3; mutations in *ALX3* cause FND1; mutations in *ALX4* cause FND2.

Autosomal dominant—A pattern of genetic inheritance in which only one abnormal gene is needed to display the trait or disorder.

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are needed to display the trait or disorder.

Hypertelorism—Abnormally wide spacing of the eyes.

Philtrum—The vertical groove on the median line of the upper lip.

Transcription factors—Proteins that regulate the activity (transcription) of specific genes.

- FND1 causes nose abnormalities, an elongated area between the nose and upper lip (the philtrum), and drooping upper eyelids (ptosis).
- FND2 can cause hair loss (alopecia) and an enlarged parietal foramen (the opening in the two bones making up the top and sides of the skull). Males with FND2 often have genital malformations.
- FND3 is associated with the most severe facial abnormalities, although severity varies widely. In general, FND3 is characterized by missing or very small eyes (anophthalmia or microphthalmia, respectively) and low-set backward-facing ears.

Genetic profile

FND is caused by mutations in different *ALX* genes.

- FND1 is caused by mutations in the *ALX3* gene, located on the short arm (p) of chromosome 1 at 1p13.3.
- FND2 is caused by mutations in the *ALX4* gene on chromosome 11 at 11p11.2.
- FND3 is caused by mutations in the *ALX1* gene located on the long arm (q) of chromosome 12 at 12q21.

ALX stands for “aristaless-like homeobox.” *ALX* genes produce proteins called transcription factors that regulate the activities (protein production) of other genes by binding to DNA. Specifically, these transcription factors control genes that produce proteins that are necessary for regulating cell growth, division, and movement

(migration). This ensures that cells grow and stop growing correctly and migrate to their proper positions during development. *ALX3* and *ALX4* proteins are important for the development of the nose and surrounding tissues. *ALX1* protein is important for development of the nose, mouth, and eyes. Mutations in these genes reduce or eliminate functioning of their respective proteins, which disrupts the organization of cells during the development of the head and face, especially the middle of the face. The facial clefts result from abnormal development of the nose, philtrum, and upper lip, which can also interfere with the formation of the skull and other facial features.

FND1 and FND3 are inherited in an autosomal recessive pattern. This means that two mutated *ALX* genes, one inherited from each parent, are required to develop the disorder. The parents, with one mutated gene each, typically have no signs or symptoms of FND, because they have a second normal *ALX* gene.

FND2 is inherited in an autosomal dominant pattern, so that the condition develops in a fetus that has only one mutated *ALX4* gene and one normal *ALX4* gene. The mutated gene may have been inherited from an FND-affected parent or may have arisen by spontaneous mutation in the egg, sperm, or early embryo, in the absence of a family history of FND. FND1 and FND3 can also be caused by sporadic mutations. Genetic testing is available for *ALX* gene mutations.

Demographics

FND is believed to be very rare, although more than 100 cases have been reported in the medical literature. It has not been associated with any particular ethnic or social group. Some reports indicate that FND is more common in males than in females and that it is associated with increased parental age, which may increase the risk of sporadic gene mutations in egg or sperm cells.

Signs and symptoms

In addition to the characteristics described, severe FND may include a vertical groove down the middle of the face, which, in the most extreme instances, may cause the nose to vertically separate into two parts (median cleft nose). Malformation of the bony structures (orbits) that hold the eyeballs can cause vision defects and even blindness.

A group of heart abnormalities known as the tetralogy of Fallot has been observed in a few cases of FND. This is a combination of four heart disorders: an abnormal narrowing of the valve that opens from the right ventricle of the heart into the pulmonary artery (pulmonary stenosis); a hole or perforation in the wall between the left and right ventricles of the heart that allows blood to flow

QUESTIONS TO ASK YOUR DOCTOR

- What type of frontonasal dysplasia does my child have?
- What surgeries does my child require?
- What is my child's prognosis?
- What is my risk of having another child with frontonasal dysplasia?
- Is preimplantation or prenatal genetic screening available for frontonasal dysplasia?

directly from the higher-pressure left ventricle to the lower-pressure right ventricle (ventricular septal defect); abnormal positioning of the aorta on the right rather than the left side of the heart (dextroposition of the aorta), which means that blood flows out of the right ventricle into the aorta so that deoxygenated blood rather than oxygenated blood is delivered to the body; and finally, an abnormally large right ventricle (hypertrophy of the right ventricle), which is generally associated with the three other anomalies, since each of these overburdens the right ventricle. This set of conditions leads to poor oxygenation of the blood, causing a “blue baby” at birth and requiring immediate surgery.

Skeletal deformities have been observed in some cases of FND. These include the presence of an extra toe arising from the great toe (hallucal polydactyly) and severe underdevelopment of the major bone of the shin (tibial aplasia).

Brain anomalies can include the absence of the corpus callosum connecting the left and right hemispheres of the brain and swelling or hernias in the brain (basal encephalocele). When intellectual disabilities occur, they appear to be associated with the degree of hypertelorism: the greater the distance between the eyes, the greater the likelihood of developmental delays.

Diagnosis

Frontonasal dysplasia is generally diagnosed at birth based on the observed facial abnormalities. The presence of two or more of the following symptoms is considered a positive diagnosis:

- a skin-covered gap in the bones of the forehead (anterior cranium bifidum occultum)
- hypertelorism
- median cleft lip
- median cleft nose

- any abnormal development of the center (median cleft) of the face

FND may be diagnosed prenatally by ultrasound observations of craniofacial deformations (holoprosencephaly). It can also be diagnosed prenatally by genetic testing if the relevant gene mutation(s) in the family have been identified.

Treatment and management

Cosmetic surgery can correct at least some of the facial defects associated with FND. Multiple surgeries may be required for severe cases. Surgeries include reformation of the eyelids (canthoplasty), reformation of the orbits (orbitoplasty), surgical positioning of the eyebrows, and plastic surgery of the nose (rhinoplasty).

In cases of congenital heart defects, corrective surgery is required shortly after birth.

Surgery can remove an extra toe and correct underdevelopment of the tibia (shin bone). The tibia supports five-sixths of the body weight when standing, with the smaller fibula supporting the remaining one-sixth. If surgery is not performed to correct shin-bone defects, the individual may never be able to stand or walk.

In the rare cases of FND-associated intellectual impairment, early and ongoing intervention is necessary.

Prognosis

Life expectancy depends on the severity of the FND and whether surgeries can improve problems such as breathing and eating difficulties caused by the facial clefts. However, most individuals with FND are of average intelligence and can expect a normal lifespan. In the rare cases of associated heart abnormalities, the infant may die shortly after birth if corrective surgery is not performed immediately.

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“Frontonasal Dysplasia.” NORD. <https://rarediseases.org/rare-diseases/frontonasal-dysplasia/> (accessed June 8, 2021).

ORGANIZATIONS

Children’s Craniofacial Association, 13140 Coit Rd., Suite 517, Dallas, TX 75240, (214) 570-9099 or (800) 535-3643, (214) 570-8811, contactCCA@ccakids.com, <http://www.ccakids.com>

FACES: The National Craniofacial Association, PO Box 11082, Chattanooga, TN 37401, (423) 266-1632 or (800) 332-2373, <http://www.faces-cranio.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06813-1968, (203) 744-0100 or (800) 999-6673, (203) 797-9590, <http://www.rarediseases.org>

Paul A. Johnson
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Frontonasal malformation see **Frontonasal dysplasia**

Frontotemporal dementia

Definition

Frontotemporal dementia (FTD) is one of a group of conditions that cause progressive degeneration of the anterior temporal lobe, the decision-making and behavior control center of the brain; and the frontal lobe, the language and emotion control center of the brain. Dementia is not a disease in itself but is a general term used to describe the loss of the ability to think, reason, and remember, all symptoms that may accompany a wide variety of conditions and diseases.

Description

Although less common than Alzheimer’s disease, the most common of the dementias, FTD is the third most common form of dementia.

Arnold Pick, a neuropsychiatrist, identified the first type of FTD in the early 1890s, when he noticed the dramatic shrinkage in the frontal and temporal brain regions during the autopsies of some people with a dementia. This shrinkage seriously disrupted the ability of these individuals to use language.

In later examinations of Pick’s tissue samples, the pioneer neuropathologist Alois Alzheimer, who was the first to identify Alzheimer’s disease, observed that the shrunken brain regions showed similar microscopic changes. Some nerve cells appeared swollen; others contained spherical abnormalities. Later, the swollen cells became known as Pick’s cells; the tiny spheres were called Pick’s bodies; and the disorder itself became known as Pick’s disease.

As scientists acquired more knowledge of brain pathology, they observed that in some cases of FTD degeneration, Pick’s cells or bodies were not present. During the 1970s and 1980s, new diagnostic imaging techniques revealed that frontotemporal degeneration comprised a wide variety of symptoms aside from language difficulties. Imaging studies also suggested that frontotemporal disease is more common than was originally believed, representing up to 20% of dementia cases.

A combination of all of these factors, including reduced emphasis on Pick’s abnormalities, varied symptoms, and newly recognized frequency, contributed to an expanding list of names for frontotemporal disorders. To help clarify the situation, researchers adopted the term *frontotemporal dementia* to encompass all the disorders resulting from gradual deterioration of the frontal and temporal regions of the brain. Sometimes, however, the terms Pick’s disease, FTD, and frontotemporal lobar degeneration (FTLD) are used interchangeably.

In general terms, damage to cells in the temporal lobe appears to produce language and emotional dysfunction. Patients with the most severe damage to the frontal lobe experience more severe problems with decision-making function and behavior. Initially, the damage may occur on just one side of the brain. In most cases, however, as the disease progresses, both sides of the brain are affected.

Frontotemporal dementia most commonly refers to a group of specific disorders. These include:

- **Pick’s disease:** A rare brain disease that is characterized by shrinkage of the tissues of the brain’s frontal and temporal lobes and the presence of small deposits (Pick’s bodies) in the nerve cells of the affected area. Pick’s bodies are not always present in FTD. The disease resembles Alzheimer’s disease in the personality changes and disorientation that may precede memory loss.
- **Corticobasal degeneration:** A progressive neurologic disorder that is characterized by nerve cell loss and shrinkage of multiple areas of the brain, including the cerebral cortex and basal ganglia. Symptoms like rigidity and loss of muscle coordination resemble those symptoms found in Parkinson’s disease.
- **Progressive aphasia:** A rare neurologic disorder that is characterized by progressively impaired language

abilities, although other mental functions and activities of daily living are preserved.

- **Semantic dementia:** Also known as fluent progressive aphasia, semantic dementia is a language disorder in which patients exhibit a progressive deterioration of the understanding and recognition of words, although impairment in other cognitive faculties is not present.
- **Frontotemporal dementia with Parkinsonism-17 (FTDP-17):** A type of progressively worsening dementia that involves the frontal and temporal areas of the brain, and is characterized by behavioral and cognitive changes, psychiatric symptoms, language difficulties, and Parkinsonian symptoms, such as tremor and muscle rigidity. This form of FTD is linked to the *MAPT* gene on chromosome 17.
- **Frontotemporal dementia with motor neuron disease (FTD-MND):** A disorder in which FTD coexists with MND and primarily affects the temporal lobe of the brain; also known as amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease) with dementia or ASL-FTD. ALS is a neuromuscular disease that progressively weakens and destroys motor neurons, the cells in the nervous system that send messages from the brain to the rest of the body.

Genetic profile

Frontotemporal dementia may be sporadic, occurring in one family member; familial, involving two or more family members; or hereditary. In most cases, about 60%, FTD is sporadic. When FTD is diagnosed in a person with no family history of FTD or dementia, the isolated or sporadic case appears to pose no increased risk to family members.

About 40% of FTD cases are believed to have a genetic component, such as a positive family history for FTD or a related neurodegenerative condition or dementia. Of those, about 10% have mutations in the *MAPT* gene, which is located on chromosome 17. The children of a person with a mutation in this gene have a 50% chance of inheriting that same disease-causing mutation. Researchers have found some linkage to chromosome 9 and some to chromosome 3, and other FTD genes are likely to be found in the future.

The *MAPT* gene is responsible for the instructions for making a protein called tau protein. Tau protein is found throughout the nervous system and in the brain. These proteins are integral in producing the internal framework of cells including neurons. Tau helps to build and secure structures within the cell called microtubules which help cells maintain their shape, move materials inside the cell membrane, and divide. Mutations in the *MAPT* gene cause the tau proteins to malfunction and begin to form abnormal clumps within cells. These

clumps cause cells to die. Researchers are not sure why, but when an individual has mutations in the *MAPT* gene, neurons in parts of the frontal and temporal lobe of the brain begin to die, causing the symptoms of FTDP-17.

FTDP-17 is one of several conditions known as the tauopathies because they all involve an abnormal clumping of tau proteins within the brain. FTDP-17 is inherited in an autosomal dominant pattern, meaning that only one copy of the mutated gene is necessary to cause the condition.

About 5%–10% of patients have a family history that suggests a hereditary condition with an autosomal dominant pattern of inheritance, meaning that there is a clear pattern of FTD-type diagnoses being passed from parent to child, with virtually every patient having an affected parent, and each child of an affected person having a 50% chance of inheriting the disorder. Only one of the subtypes, FTDP-17, is exclusively hereditary.

FTD has been linked to two additional known genetic mutations. Mutations in the *GRN* and *CHMP2B* genes are known to cause FTD. The *GRN* gene on chromosome 17 is responsible for making a protein called granulin or progranulin. Granulin is present in many tissues and is important in controlling growth and survival of cells. Granulin is active in the brain. Though it is still unclear how, granulin appears to be significant in the survival of nerve cells called neurons. Mutations in the *GRN* gene prevent granulin from forming in sufficient quantities. When there is not enough granulin in the brain, it is associated with a buildup of a protein called TAR DNA-binding protein (TDP-43). Researchers have discovered that when TDP-43 accumulates in the brain it forms clumps that inhibit neuron function and ultimately leads to cell death. The symptoms of FTD occur when the neurons in the frontal and temporal regions of the brain begin to die as the TDP-43 clumps accumulate in those regions. Researchers have not yet discovered why the neurons in these regions are susceptible to the abnormal TDP-43. FTD caused by this mutation is called *GRN*-related frontotemporal dementia.

The *CHMP2B* gene on chromosome 3 is responsible for helping make a protein called charged multivesicular body protein 2B. This protein works in the brain to remove proteins that need to be broken down. Mutations in the *CHMP2B* gene cause this protein to be formed abnormally so that it cannot transport and degrade proteins. This failure leads to the death of neurons and causes the symptoms of *CHMP2B*-related frontotemporal dementia.

Both *GRN* and *CHMP2B* FTD are inherited in an autosomal dominant pattern, meaning that only one copy of the mutated gene is necessary to cause the condition. In most cases of these types of FTD, an affected individual has at least one parent and one other family member with the same condition.

Researchers have also identified a type of FTD associated with ALS. Doctors first considered ALS a disease of the body not necessarily involving dementia; however, as more people with ALS were treated and studied, it became apparent that a percent of those patients were experiencing symptoms of dementia that are very similar to those of FTD.

Several genetic mutations have been found that correspond with combined symptoms of ALS and FTD, a condition known as ALS-FTD. Mutations in the following genes have been identified in known cases of ALS-FTD:

- **ANG**—The *ANG* gene on chromosome 14 is responsible for coding instructions for producing a protein called angiogenin, which helps new blood vessels grow from existing blood vessels. In individuals with ALS, the *ANG* gene is more likely to be mutated in multiple ways. Researchers theorize that these mutations reduce the activity of angiogenin and lead to the death of neurons. Patients with *ANG* mutations are more likely to have symptoms of ALS along with symptoms of FTD.
- **C9orf72**—The *C9orf72* gene on chromosome 9 is responsible for producing a little understood protein found within the brain. This protein is found in neurons both in the cytoplasm, the fluid inside the cell, and at the presynaptic terminals, or specialized cells at the tips of neurons. Mutations of this gene are known to cause ALS, and individuals with this mutation are more likely to have ALS-FTD.
- **DCTN1**—The *DCTN1* gene on chromosome 2 provides instructions for making a protein called dynactin-1. Two versions of this protein are found within neurons. These proteins join with other proteins to form a protein complex called the dynactin complex, which is important in the formation of microtubules that create a pathway for materials to move within a cell. Researchers have discovered several mutations in the *DCTN1* gene that are associated with an increased risk of developing ALS. Individuals with this type of ALS also have an increased risk of developing ALS-FTD.
- **FUS**—The *FUS* gene on chromosome 16 provides instructions for making a protein called fused in sarcoma (FUS). This protein is involved in the process of transcription, the first step in the series by which DNA transfers information to produce RNA. Specifically, the FUS protein is important in producing messenger RNA, which carries the instructions necessary for transcription to be completed. There are more than 50 mutations in the *FUS* gene that are known to cause ALS. In individuals with these mutations, some also develop ALS-FTD.
- **TARDBP**—The *TARDBP* gene on chromosome 1 provides instructions for making a protein called transactive response DNA binding protein 43 kDa (TDP-43), which is important in the process of transcription. TDP-43 has

been found in the nucleus of many different tissue cells. The *TARDBP* gene is especially active during fetal development and is important in the formation of neurons and internal organs. Much like mutations in the *FUS* gene, more than 50 different mutations in the *TARDBP* gene have been linked to ALS. Researchers believe that these mutations cause the TDP-43 protein to form clumps and that these clumps cause neurons and muscle tissue to die. Individuals with known mutations in the *TARDBP* gene are more likely to have ALS-FTD.

- Other genes that have been linked to ALS-FTD as of 2021 include the *CYLD* gene on chromosome 16; the *OPTN* gene on chromosome 10; the *SQSTM1* gene on chromosome 5; and the *TBKI* gene on chromosome 1.

Demographics

It is estimated that as many as seven million Americans may be affected with some form of dementia, and FTD may account for about 25% of those dementias. FTD occurs most frequently between the ages of 35 and 75, and was believed to affect men and women equally. Recent studies, however, have indicated that FTD appears to be more common in men and is a more common cause of early-onset dementia than previously recognized.

Signs and symptoms

FTD comprises a wide variety of symptoms that vary widely from person to person, depending on the degree of involvement of the frontal and temporal lobes and the side of the brain affected.

Although two major symptom patterns emerge in all forms of FTS, namely gradual and progressive changes in behavior and language, some symptoms are more closely associated with one subtype of FTD than another. In general, the range of symptoms associated with FTD includes behavioral, linguistic, cognitive, emotional, neurologic, and psychiatric.

A progressive deterioration in the ability to control or adjust behavior appropriately in different social contexts is the characteristic feature of all the behavioral changes. This results in embarrassing social situations that can be one of the most disturbing aspects of FTD. Patients with FTD often present two seemingly opposite behavioral profiles in the early and middle stages of the disease. Some people are hyperactive, restless, distracted, and uninhibited. Others are apathetic, lack spontaneity, and are emotionally blunted.

Behavioral symptoms include:

- Compulsive behaviors involving, for example, eating, drinking, or dressing

- Repetitive behaviors, such as turning the television on and off
- Deteriorating personal hygiene habits, such as bathing, grooming, and dressing
- Hyperactive behaviors, such as pacing, agitation, aggression
- Impulsive or inappropriate behaviors involving, for example, sexual acting-out
- Changes in sleep patterns, including prolonged sleepiness, especially in those with more apathetic behaviors

Linguistic symptoms include:

- Decreasing speech to the point of total silence in some patients conversation is not spontaneous but rather mechanical
- Weak-sounding, imprecise, or incoherent speech
- Difficulties remembering the rules of English grammar and syntax
- Repetition of a word or phrase uttered by another (echolalia)
- Repetition of a word or phrase uttered by the person themselves (palilalia)
- Loss of the ability to speak

Cognitive symptoms include:

- Distractibility and impatience
- Rigid and inflexible thinking and impaired judgment
- Difficulty with abstract reasoning
- Poor financial judgment

As opposed to those affected by Alzheimer's disease, patients with FTD tend to have normal results on intelligence tests until that point in the disease process at which apathy results in lower scores.

Emotional symptoms include:

- Apathy or indifference to people and events
- Lack of understanding of self and others
- Lack of empathy toward and understanding of others, including family members and close friends
- Frequent and abrupt mood changes

Neurologic symptoms include:

- Movement dysfunction, including decreased facial expression, slow movements, rigidity, difficulties with posture, and sometimes abnormal eye movements
- Muscle dysfunction, such as weakness, muscle jerking, or atrophy

Psychiatric symptoms include:

- Depression
- Manic behavior

- Paranoia
- Visual or auditory hallucinations

Diagnosis

Although medical knowledge of FTD is still evolving and a broad range of subtypes is involved, current technology is providing the first evidence of the pathologic changes that occur in specific areas of the brain that cause FTD's varied symptoms. For example, loss of function in an individual's temporal lobe produces language changes, and loss of function in the frontal lobe appears to lead to behavioral symptoms, including aggressive, antisocial, and other socially unacceptable behaviors.

Because of its symptoms, FTD is often initially misdiagnosed as a psychiatric problem, Alzheimer's disease, or Parkinson's disease. However, there are features that rule out other diagnoses and identify features that pinpoint FTD.

Medical history

The presentation of the disorder within families can vary. Some people may have FTD alone, and others may develop Parkinsonism or psychiatric symptoms. Because of this variability, a careful analysis of family medical and social history can help clarify whether an affected person has a sporadic or a hereditary form of the disorder.

It is important to interview another source, such as a spouse, partner, or adult child, regarding changes in the patient's cognitive performance or behavior that are having a negative impact on the patient's activities of daily living. This source is important in establishing information about past performance and behavior, as well as the progression of symptoms that the patient may not be able to provide reliably. The additional source may also provide information that can be used to test the patient's recent and long-term memory. Significant functional changes in memory and other cognitive domains that interfere with everyday activities (such as driving, functioning at work, and/or interactions with family and friends) signal a disease state and are not part of the typical aging process.

It is essential to determine the potential for medication-induced confusion or dementia by studying the patient's drug inventory and looking for compounds that may cause or exacerbate any loss of mental capacity.

Physical examination

A targeted physical examination should be performed in all patients with dementia. Signs of systemic disorders, such as vasculitis, systemic lupus erythematosus (SLE, a chronic inflammatory condition), tuberculosis, and hypothyroidism, suggest that further evaluation is necessary.

KEY TERMS

Computed tomography (CT)—Imaging procedure that uses x-rays and computers to create detailed pictures of areas inside the body.

Electroencephalogram (EEG)—A test that measures the electronic waves of the brain.

Dementia—A group of disorders and symptoms that impact memory, reasoning, social abilities, and intellectual functioning and that impair the ability to function normally in daily life.

Frontal lobe—Region of the brain located in the frontal and upper cortex, it is responsible for higher mental functions like critical thinking and decision making.

Magnetic resonance imaging (MRI)—A test that uses a magnet and radio waves to take pictures of organs and structures inside the body.

Positron emission tomography (PET)—A test that uses a special type of camera and a radioactive chemical called a tracer to look at organs in the body.

Single-photon computed tomography (SPECT)—Nuclear imaging that uses gamma rays to produce 3D images of inside the body.

Temporal lobe—Region of the brain located at the bottom middle part of cortex, right behind the temples; it is responsible for processing auditory information.

Physical problems, such as profound hearing or visual loss, may exacerbate FTD.

Laboratory studies

The American Academy of Neurology practice parameters suggest that routine evaluation of a patient with dementia should include: complete blood count (CBC); serum electrolytes, including calcium; glucose; blood urea nitrogen (BUN) and creatinine; liver function tests; thyroid tests; vitamin B₁₂ level; and syphilis serology.

Neurologic examination

Neurologic examination may reveal signs that vary according to which part of the brain is affected, either the temporal or the frontal lobe, with associated behavioral and language changes. Careful neurologic examination should include observation of gait and posture, cranial nerves, motor strength, sensation, and reflexes. In more advanced stages of FTD, neurologic examination often reveals motor dysfunction and reflex abnormalities.

Neuropsychological examination

This examination assesses, for example, language, behavior, abstraction, memory, executive, motor skills, and visual-spatial functioning. There are many tools available for cognitive testing. The goal of testing is to demonstrate a decline in intellectual function, to assess whether depression is a contributing factor, to make predictions about future functioning, and to plan care. The Mini-Mental State Examination (MMSE) and the Geriatric Depression Scale may be administered by primary caregivers and should be performed on all patients with dementia. More detailed evaluation, such as the Wechsler Adult Intelligence Scale (WAIS), the Blessed Information, Memory and Concentration Test (BIMC), visuospatial testing, and the Boston Diagnostic Aphasia Evaluation, also may be helpful in making a diagnosis.

Neuroimaging studies

These studies include magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), and single-photon computed tomography (SPECT). They help to determine the exact location and extent of atrophy in the brain as well as areas of decreased blood flow. Electroencephalogram (EEG), or brain scan, results are usually normal even in advanced stages of the disease.

Although differentiating FTD from dementias, such as Alzheimer's disease, has been difficult, with more sophisticated brain imaging, such as SPECT, some researchers have claimed that they can diagnose Alzheimer's disease with an accuracy rate of nearly 100%. Differentiating among the various subtypes of FTD, however, still remains a challenge. Sometimes definitive diagnosis of these conditions can be made only by brain autopsy after death.

Treatment and management

There is no cure for FTD, and in most cases, disease progression cannot be slowed. Although no medications have been proven effective specifically for FTD, many physicians look to the medications and treatment approaches used in similar disorders to develop a therapeutic approach. For example, some patients with FTD benefit from selective serotonin reuptake inhibitors (SSRIs), which are used in treating depression; and acetylcholinesterase inhibitors, which are used in treating Alzheimer's disease to help prolong the activity of neurotransmitters in the brain. Physicians may also use antioxidants, such as vitamin E or coenzyme Q10, which are known to slow the progression of damage to brain cells in general.

FTD is progressive and after a few years, a patient's ability to live and function independently are decreased, leaving them dependent on others for activities of daily

living. Care of patients with FTD focuses on maximizing quality of life, treating neuropsychiatric complications, ensuring patient safety, and supporting and educating caregivers. It is important for caregivers and families to consider long-term management issues and identify a team of experts who can help with difficult medical, financial, and emotional challenges. Also, it is important to have a physician who is knowledgeable about FTD and comprehensive approaches to treatment. In addition, speech therapists, occupational and physical therapists, neuropsychologists, nurses, and genetic counselors may be helpful.

Prognosis

Prognosis varies, but studies have shown that a person with FTD may live with the disease an average of 8 years, with a range of 3–17 years. A more slowly progressive form of FTD occurs in the small percentage of people with familial tau-positive disease. People with FTD-MND have the shortest life expectancy, both before and after diagnosis.

Resources

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ORGANIZATIONS

ALS Association, 1300 Wilson Boulevard, Suite 600, Arlington, VA 22209, (800) 782-4747, <http://www.alsa.org>

Association for Frontotemporal Degeneration, 2700 Horizon Drive, Suite 120, King of Prussia, PA 19406, (267) 514-7221 or (866) 507-7222, <http://www.theaftd.org>

FTD Support Forum, <http://ftdsupportforum.com>

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Fryns syndrome

Definition

Fryns syndrome is a multiple congenital anomaly syndrome usually resulting in neonatal death.

Description

Fryns syndrome is a genetic condition involving abnormalities in many organ systems that usually results in neonatal death. The condition was first reported in 1979 by J. P. Fryns a Belgian geneticist.

Typical anomalies include a characteristic facial appearance, including a broad nasal bridge (part of the nose between the eyes), small jaw, abnormal ears, cleft palate, abnormal fingers, underdevelopment of the lungs, and abnormalities of the urogenital system (kidneys and genitals). Diaphragmatic hernia (opening in the diaphragm muscle that can allow contents of the lower abdomen like the liver or intestine or stomach to move up into the chest cavity through the hole) can also be seen in some cases. Some researchers believe that there may be a distinct subset of patients without diaphragmatic hernia who are more mildly affected.

Genetic profile

Fryns syndrome is inherited in an autosomal recessive manner. This means that two defective gene copies must be inherited, one from each parent, for the disease to manifest itself. Persons with only one gene mutation are carriers for the disorder. A person who is a carrier for Fryns syndrome does not have any symptoms and does not know he/she is a carrier unless he/she has had a child with Fryns syndrome. Carrier testing is not available since the gene location is not known at this time. The likelihood that each member of a couple would be a carrier for a mutation in the same gene is higher in people who are related (consanguineous). When both parents are carriers for Fryns syndrome, there is a one in four chance (25%) in each pregnancy for a child to have the disease. There is a two in three chance that a healthy sibling of an affected child is a carrier.

There have been several different chromosome abnormalities reported with a Fryns syndrome-like appearance. Investigation for a candidate gene causing Fryns syndrome has not yet identified the causative gene.

Demographics

The number of affected individuals is reported as 0.7% out of every 10,000 births. There does not appear to be any ethnic difference in prevalence. There are more than 50 documented cases of Fryns syndrome in the literature.

QUESTIONS TO ASK YOUR DOCTOR

- At what stage of development is it possible to diagnose Fryns syndrome? On what factors is such a diagnosis based?
- What are the characteristic features of a child with Fryns syndrome?
- What do researchers know about the genetic basis of Fryns syndrome?
- What is the prognosis for a child born with Fryns syndrome?

Signs and symptoms

The most frequent anomalies have been described as diaphragmatic defects, underdeveloped lungs, cleft lip and palate (usually on both sides, called bilateral), heart defects, cysts in the kidneys, urinary tract abnormalities, and limb underdevelopment.

Most patients also have underdeveloped external genitals, abnormal internal reproductive structures, abnormalities in the digestive tract, and abnormalities in the structure of the brain. Fewer patients have eye abnormalities.

Other reported anomalies include fetal hydrops (fluid surrounding the fetus prenatally, usually fatal), prematurity, scoliosis (curvature of the spine), extra vertebrae or ribs, abnormal bone formation, and small chest cavity.

Diagnosis

Prenatal diagnosis has been possible in several fetuses by use of ultrasound to identify in one fetus fetal hydrops, diaphragmatic hernia, and dilation of the cerebral ventricles and in another with cystic hygroma and diaphragmatic hernia. These anomalies themselves can be isolated or as a part of another genetic syndrome; it is the specific combination of anomalies that would lead one to suspect Fryns syndrome. Definitive diagnosis is not possible until after birth or autopsy.

Treatment and management

Since Fryns syndrome is a genetic disease caused by mutations in specific genes, there is no cure at this time. Some of the anomalies may be amenable to surgery, such

as diaphragmatic hernia or cleft palate, but the entire prognosis for the baby must be considered.

Special education for intellectually disabled individuals is indicated if the child survives.

Prognosis

Unfortunately, the prognosis for babies with Fryns syndrome is poor, with usual neonatal death occurring due to the lung hyperplasia and respiratory distress or other anomalies. Approximately 14% of infants survive the neonatal period. Survivors typically do not have complex heart malformations and less frequently have diaphragmatic hernias, milder lung hypoplasia, and neurologic impairment (usually severe to profound intellectual disability with serious brain malformations).

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ORGANIZATIONS

Genetic Alliance, 26400 Woodfield Road #189, Damascus, MD 20872, (202) 966-5557, (202) 966-8553, info@geneticalliance.org, <http://www.geneticalliance.org>

Share Pregnancy and Infant Loss Support, 402 Jackson St., Saint Charles, MO 63301-3468, (800) 821-6819, info@nationalshare.org, <http://nationalshare.org>

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The GALE ENCycloPEDIA *of*
GENETIC DISORDERS

FIFTH EDITION

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BRIGHAM NARINS, EDITOR

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Galactosemia

Definition

Galactosemia is a type of inherited disease known as inborn errors of metabolism—in which the transformation of galactose (a simple sugar found in dairy products and human breast milk) to glucose (the form of sugar the body uses to produce energy) is blocked, allowing galactose to increase to toxic levels in the body. If galactosemia is untreated, high levels of galactose cause vomiting, diarrhea, lethargy, low blood sugar, brain damage, jaundice, liver enlargement, cataracts, susceptibility to infection, and death.

There are three main types of galactosemia:

- Classic galactosemia (galactosemia type I)—the most common and most severe type.
- Galactokinase deficiency (galactosemia type II)—less severe with fewer symptoms than classic galactosemia.
- Galactose epimerase deficiency (galactosemia type III)—the most rare form, this type of galactosemia has similar symptoms to the classic type; however, the symptoms may range from mild to severe.

Description

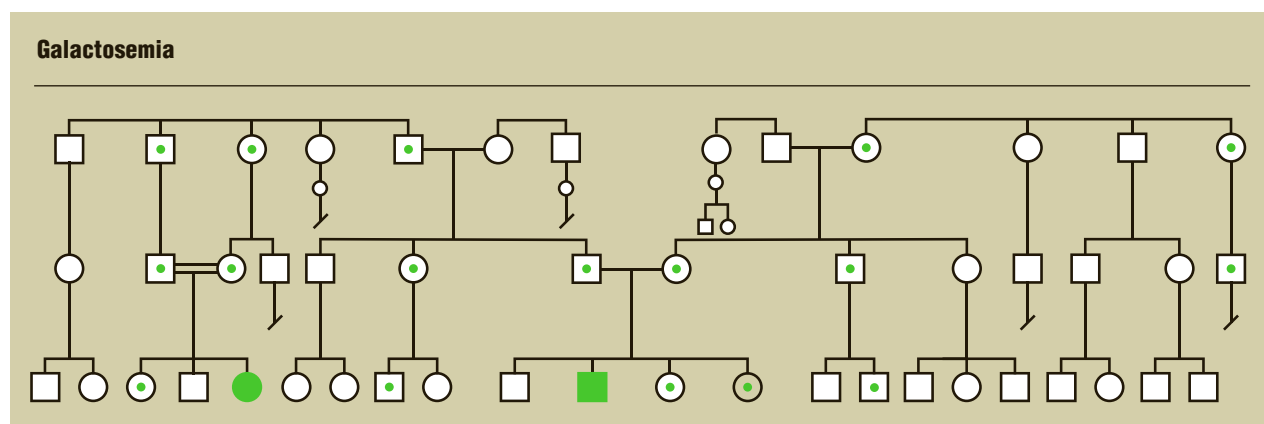
Galactosemia is a rare but potentially life-threatening disease that results from the inability to metabolize galactose. Lactose, the principle carbohydrate of human milk, commercial infant formulas, and other dairy products, is broken down in the human intestine into its component sugars: glucose and galactose. After absorption by the intestine, galactose is sequentially metabolized by three separate enzymes (galactokinase, galactose-1-phosphate uridylyltransferase, and galactose-4-epimerase) to convert it to glucose, a usable form of fuel for individual cells.

“Metabolism” refers to all chemical reactions that take place in living organisms. A metabolic pathway is a series of reactions in which the product of each step in

the series is the starting material for the next step. Enzymes are the chemicals that help the reactions occur. Their ability to function depends on their structure, and their structure is determined by the deoxyribonucleic acid (DNA) sequence of the genes that encode them. Inborn errors of metabolism are caused by mutations in these genes that do not allow the enzymes to function properly.

Classic galactosemia, the most common form of galactosemia, is caused by a deficiency of the second enzyme in the pathway, galactose-1-phosphate uridylyltransferase (GALT), and is typically associated with cataract formation, intellectual disability, and liver damage. Galactokinase deficiency (also known as GALK deficiency or galactosemia type II) is a rarer form of galactosemia caused by the absence of the enzyme galactokinase, which is responsible for the first step of the conversion of galactose to glucose. However, unlike the more serious form of classic galactosemia, galactokinase deficiency mainly manifests as injury to the eyes without damage to other organ systems. The third and final form of galactosemia, galactose epimerase deficiency (galactosemia type III), is the rarest of the group; few cases have been described, and the symptoms of this form of galactosemia are variable but usually mild. Serious consequences from galactosemia can be prevented by screening newborns at birth with a simple blood test.

Galactosemia may have been described in German medical publications as early as 1908; in 1917, F. Goepert noted symptoms of galactosemia in an infant and sibling, suggesting that the disorder could be inherited. In 1935, the American scientists H. H. Mason and M. F. Turner described a patient with a group of symptoms that could be prevented by removal of milk from the diet. In 1954, the individual steps in the metabolic pathway for the conversion of galactose to glucose were described by L. F. Leloir, who was later awarded a Nobel Prize in Chemistry for his efforts. Leloir’s work made it possible for scientists such as V. Schwatz and K. J. Isselbacher to demonstrate that defects in this metabolic pathway



Galactosemia: pedigree analysis chart (Gale)

were responsible for galactosemia and its associated symptoms.

Genetic profile

Galactosemia is caused by mutations in the *GALE*, *GALK1*, and *GALT* genes. These genes provide instructions for making the enzymes that process galactose obtained from the diet by breaking it down into glucose and other molecules that the body can store or use for energy. Mutations in the *GALT* gene on chromosome 9 at 9p13 are responsible for classic galactosemia (type I). Most mutations almost completely eliminate the activity of the enzyme produced from the *GALT* gene, resulting in the life-threatening galactosemia symptoms. Another *GALT* mutation, the Duarte variant, lowers but does not eliminate the activity of the enzyme, resulting in milder galactosemia.

Mutations in the *GALK1* gene on chromosome 17 at 17q24 are responsible for galactosemia type II, while mutations in the *GALE* gene on chromosome 1 at 1p36-p35 cause galactosemia type III. The enzymes made from the *GALK1* and *GALE* genes are also important in the breakdown of galactose. If not present, galactose and related compounds can build up to toxic levels in the body and damage tissues and organs.

Every cell in a person's body has two copies of each gene. Each of the types of galactosemia is inherited as a recessive trait, which means that galactosemia is only present in individuals with two mutated copies of one of the three genes. This also means that carriers, who only have one copy of a gene mutation, will not be aware that they are carrying a mutation unless they have had a genetic test, because it is masked by the normal gene on the second chromosome they also carry and the fact that they have no symptoms of the disease. For each step in the conversion of galactose to glucose, if only one of the

two copies of the gene controlling that step is normal (i.e., for carriers), enough functional enzyme is made so that the pathway is not blocked at that step. If a person has galactosemia, both copies of the gene coding for one of the required enzymes are defective and the pathway becomes blocked. If two carriers of the same defective gene have children, the chance of any of their children getting galactosemia (the chance of a child getting two copies of the defective gene) is 25% (one in four) for each pregnancy.

Demographics

In the United States, classic galactosemia occurs in 1 in 30,000 to 60,000 newborns. Galactosemia type II and type III are less common: type II is believed to affect fewer than 1 in 100,000 newborns and type III appears to be very rare. Worldwide, the prevalence of galactosemia is estimated at 6 per 100,000 live births.

Signs and symptoms

Galactosemia type I

Newborns with galactosemia type I appear normal at birth, but begin to develop symptoms after they are given milk for the first time. Symptoms include vomiting, diarrhea, lethargy (sluggishness or fatigue), low blood glucose, jaundice (a yellowing of the skin and eyes), enlarged liver, protein and amino acids in the urine, and susceptibility to infection, especially from gram-negative bacteria. Cataracts (a grayishwhite film on the eye lens) can appear within a few days after birth. People with galactosemia frequently have symptoms as they grow older even though they have been given a galactose-free diet. These symptoms include speech disorders, cataracts, ovarian atrophy and infertility in females, learning disabilities, and behavioral problems.

KEY TERMS

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light, resulting in blurry vision. Surgery may be performed to remove the cataract.

Enzymes—Proteins within the body that cause chemical reactions such as breaking food into a form that can be used as energy.

Galactose—One of the two simple sugars, together with glucose, that makes up the protein lactose found in milk. Galactose can be toxic in high levels.

Glucose—One of the two simple sugars, together with galactose, that makes up the protein lactose found in milk. Glucose is the form of sugar that is usable by the body to generate energy.

Inborn error of metabolism—Any of a number of rare genetic disorders that inhibit the body's ability to turn food into energy.

Lactose—A sugar made up of glucose and galactose. It is the primary sugar in milk.

Metabolic pathway—A sequence of chemical reactions that lead from some precursor to a product, in which the product of each step in the series is the starting material for the next step.

Metabolism—The total combination of all of the chemical processes that occur within cells and tissues of a living body.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Newborn screening—The act of testing all infants for a specific disease shortly after birth for the purpose of preventing disease progression through prompt medical treatment.

Galactosemia type II

Galactosemia type II is less harmful than galactosemia type I. Babies born with galactosemia type II will develop cataracts at an early age unless they are given a galactose-free diet. They do not generally have liver damage or neurologic disturbances.

Galactosemia III

There are two forms of galactosemia III, a severe form, which is exceedingly rare; and a benign form. The

benign form has no symptoms and requires no special diet. However, newborns with galactosemia III, including the benign form, have high levels of galactose-1-phosphate that show up on the initial screenings for elevated galactose and galactose-1-phosphate. This situation illustrates one aspect of the importance of follow-up enzyme function tests. Tests showing normal levels of GALT and GALK allow people affected by the benign form of galactosemia III to enjoy a normal diet.

The severe form has symptoms similar to those of galactosemia I, but with more severe neurological problems, including seizures.

Diagnosis

The newborn screening test for classic galactosemia is quick and straightforward; all states in the United States and most provinces in Canada require testing on all newborns. Blood from a baby who is two to three days old is usually screened for high levels of galactose and galactose-1-phosphate. If either of these compounds is elevated, further tests are performed to find out which enzymes (GALT, GALK, or GALE) are present or missing.

DNA testing may also be performed to confirm the diagnosis. Clinical testing is available for the eight common *GALT* galactosemia (G) mutations. For individuals with Duarte variant (D/G) galactosemia identified by biochemical testing of the individual and both parents, the Duarte mutations can be identified by targeted mutation analysis.

If there is a strong suspicion that a baby has galactosemia, galactose is removed from their diet right away. In this case, an initial screen for galactose or galactose-1-phosphate will be meaningless. In the absence of galactose in the diet, this test will be negative whether the baby has galactosemia or not. In this case, tests to measure enzyme levels must be given to find out if the suspected baby is indeed galactosemic.

In addition, galactosemic babies who are refusing milk or vomiting will not have elevated levels of galactose or galactose phosphate, and their condition will not be detected by the initial screen. Any baby with symptoms of galactosemia (for example, vomiting) should be given enzyme tests.

Treatment and management

Galactosemia type I and type II are treated by removing galactose from the diet. Since galactose is a breakdown product of lactose, the primary sugar constituent of milk, this means all milk and foods containing milk products must be totally eliminated. Other foods like

QUESTIONS TO ASK YOUR DOCTOR

- My child has just been diagnosed with galactosemia; do I or my spouse need to have genetic testing?
- What medical problems does my child face?
- What other medical specialists does my child need to see?
- What foods does my child need to avoid completely?
- Is there a cure for this disorder?

legumes, organ meats, and processed meats contain considerable galactose and must be avoided. Pills that use lactose as a filler must also be avoided. Soy-based and casein hydrolysate-based formulas are recommended for infants with galactosemia.

Treatment of the severe form of galactosemia III with a galactose-restricted diet has been tried, but this disorder is so rare that the long-term effects of this treatment are unknown.

Since most people are unaware that they are carriers of a gene mutation causing galactosemia, the disease is usually detected on a newborn screening test. For couples with a previous child with galactosemia, prenatal diagnosis is available to determine whether a pregnancy is similarly affected. Families who have a child diagnosed with galactosemia can have DNA testing, which would enable other relatives to determine their carrier status. Prospective parents can then use that information to conduct family planning or to prepare for a child with special circumstances. Children born with galactosemia should be put on a special diet right away to reduce the symptoms and complications of the disease.

Prognosis

Early detection in the newborn period is the key to controlling symptoms. Long-term effects in untreated babies include severe intellectual disability, cirrhosis of the liver, and death. About 75% of untreated babies die within the first two weeks of life. On the other hand, with treatment, a significant proportion of people with galactosemia type I can lead nearly normal lives, although speech defects, learning disabilities, and behavioral problems are common. In addition, cataracts due to galactosemia II can be completely prevented by a galactose-free diet.

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ORGANIZATIONS

- Galactosemia Foundation, 350 Northern Blvd, STE 324-1079, Albany, NY 12204-1000, (866) 900-7421, outreach@galactosemia.org, <http://www.galactosemia.org>

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Galactosialidosis

Definition

Galactosialidosis is a rare inherited metabolic disorder with multiple symptoms that can include skeletal abnormalities, intellectual disability, and progressive neurological degeneration.

Description

Galactosialidosis is a very rare genetic disorder with progressive signs and symptoms that are almost identical to those of neuraminidase deficiency alone, a disorder that is often called sialidosis. These symptoms can include skeletal and facial abnormalities, seizures, vision and hearing loss, cardiac and kidney problems, and intellectual disability. However, as with sialidosis, the severity of the symptoms of galactosialidosis varies greatly.

Galactosialidosis is a member of a large family of disorders called lysosomal storage disorders, each of which is caused by a deficiency in a specific lysosomal protein or

enzyme. Galactosialidosis is caused by the absence or impaired functioning of an enzyme called cathepsin A that affects the functioning of other enzymes and causes various substances to accumulate in lysosomes.

Galactosialidosis is also known as Goldberg syndrome, after M. F. Goldberg and colleagues who first described the disorder in 1971. The disorder is also sometimes called protective protein/cathepsin A (PPCA) deficiency, deficiency of lysosomal protective protein, neuraminidase deficiency with beta-galactosidase deficiency, or deficiency of cathepsin A.

Galactosialidosis is caused by a mutation, or change, in the gene encoding cathepsin A. Cathepsin A forms a very large multi-enzyme complex with three other enzymes: beta-galactosidase, N-acetylgalactosamine-6-sulfate sulfatase (GALNS), and alpha-N-acetylneuraminidase. The latter enzyme is commonly referred to as neuraminidase 1 or sialidase. Whereas sialidosis is caused by a mutation in the gene encoding neuraminidase, a mutation in the gene encoding cathepsin A can affect the activities of all of the enzymes in the complex. However, neuraminidase is the enzyme that is most dependent on cathepsin A. Without functional cathepsin A, there is little or no neuraminidase activity. Although beta-galactosidase activity is reduced, a significant amount of active enzyme remains. Therefore, the symptoms of galactosialidosis are more similar to those of sialidosis than to those of beta-galactosidase deficiency. Mutations in the gene encoding beta-galactosidase can result in disorders known as GM1-gangliosidosis (beta-galactosidosis) or Morquio B disease.

Cathepsin A also forms a complex on the cell surface with neuraminidase 1 and the elastin binding protein produced from the same gene as lysosomal beta-galactosidase. Elastin binding protein plays a role in the formation of elastic fibers in connective tissues.

Galactosialidosis is subdivided into three types, depending on the age of onset: severe, neonatal or early-infantile; milder, late-infantile; and juvenile/adult. The juvenile/adult form is the most common. There also is an atypical form of galactosialidosis. The type and severity of the disorder depends on the specific mutation(s) present in the genes encoding cathepsin A.

Lysosomal storage diseases

Neuraminidase, beta-galactosidase, cathepsin A, and GALNS are all enzymes that function inside lysosomes. Lysosomes are membrane-bound spherical compartments or vesicles within the cytosol (fluid part) of cells. Lysosomes contain more than 50 different enzymes that are responsible for digesting, or hydrolyzing, large molecules and cellular components. These include proteins, polysaccharides (long linear or branched chains of sugars),

and lipids (large, insoluble biomolecules that are usually built from fatty acids). The smaller breakdown products from the lysosome are recycled back to the cytosol.

Galactosialidosis is one of at least 41 genetically distinct lysosomal storage diseases. In these disorders, some of the macromolecules in the lysosome cannot be degraded. Instead, these large molecules or their partial-breakdown products accumulate, and the lysosomes swell to the point that cellular function is disrupted.

Neuraminidase deficiency

Neuraminidase removes sialic acid from the ends of oligosaccharides, which are relatively short chains of sugars. Sialic acid, also known as N-acetylneuraminic acid, is a type of sugar molecule that often is at an end of an oligosaccharide. These oligosaccharides with terminal sialic acid residues may be attached to proteins called glycoproteins.

Neuraminidase deficiency prevents the breakdown of oligosaccharides and glycoproteins that contain sialic acid, and leads to the accumulation and excretion of these substances. It also can lead to the production of abnormal proteins. Following protein synthesis, some lysosomal enzymes reach the lysosome in an inactive form and require further processing for activation. One such processing step is the neuraminidase-catalyzed removal of sialic acid residues from oligosaccharides on enzymes. Thus, under conditions of neuraminidase deficiency, other lysosomal enzymes may not behave properly.

Cathepsin A

Cathepsin A is required for the transport of neuraminidase to the lysosome. Once inside the lysosome, the enzymatic activity of cathepsin A may be involved in the activation of neuraminidase. Furthermore, cathepsin A mediates the association of multiple molecules of neuraminidase and beta-galactosidase, as well as GALNS. In the absence of cathepsin A, all three enzymes are rapidly degraded in the lysosome. Thus, cathepsin A protects and stabilizes these enzyme activities. In the absence of cathepsin A, substrates for these enzymes may accumulate to dangerous levels.

Gangliosides are very complex components of cell membranes. They are made up of a long-chain amino alcohol called sphingosine, a long-chain fatty acid, and a very complex oligosaccharide that contains sialic acid. Lysosomal beta-galactosidase is responsible for hydrolyzing gangliosides.

GALNS catalyzes the first step in the lysosomal breakdown of a special type of sugar called keratan sulfate. Both gangliosides and keratan sulfate may accumulate with galactosialidosis.

In addition to its protective functions, cathepsin A has at least three enzymatic activities of its own, including the ability to cleave (break apart or hydrolyze) other proteins. Some of the neurological abnormalities that develop with galactosialidosis may be due to the loss of this activity, particularly cathepsin A's ability to cleave endothelin-1. This peptide is overabundant and abnormally distributed in the neurons and glial cells of the brain and spinal cord of individuals with galactosialidosis.

Genetic profile

Galactosialidosis is an autosomal recessive disorder that can be caused by any one of a number of different mutations in the gene encoding cathepsin A. This gene is known as *CTSA*. It is sometimes called *PPGP*, for beta-galactosidase protective protein. The disorder is autosomal since the *CTSA* gene is located on chromosome 20, rather than on the X or Y sex chromosomes. The disorder is recessive because it only develops when both genes encoding cathepsin A, one inherited from each parent, are abnormal. However, the two defective genes do not need to carry the same mutations. If the two mutations are identical, the individual is a homozygote. If the two mutations are different, the affected individual is called a compound heterozygote.

CTSA mutations

The type of galactosialidosis and the severity of the symptoms depend on the specific mutations that are present. In general, the higher the level of cathepsin A activity in the lysosomes, the milder the characteristics of galactosialidosis, and the later the onset of disease.

With some mutations in the *CTSA* gene, very little of the cathepsin A precursor protein is produced, and there is no mature cathepsin A in the lysosome. With other mutations, the precursor protein may not be correctly processed into mature protein. Some individuals with severe early-infantile galactosialidosis carry mutations that prevent precursor cathepsin A from being targeted to the lysosome. The lysosomes of these individuals have no cathepsin A.

In contrast, individuals with the late-infantile form of galactosialidosis carry at least one mutant *CTSA* gene whose product can reach the lysosome. However, there may be only a small amount of cathepsin A in the lysosome, the cathepsin A may lack enzymatic activity, the cathepsin A chains may be unable to combine to form the normal two-chained form, or the cathepsin A may be degraded rapidly. Nevertheless, with these mutations, the symptoms of galactosialidosis are mild and progress very slowly with no intellectual disability.

Other identified mutations prevent the cathepsin A molecules from folding properly, or shorten the cathepsin A protein so that it cannot form a complex with the other enzymes.

Compound heterozygotes, with different mutations in their *CTSA* genes, usually have symptoms that are intermediate in severity between those of homozygotes. Occasionally, the symptoms of a compound heterozygote may be milder than those of either homozygote because the two mutant cathepsin A proteins can complement, or compensate, for each other's abnormalities. Genetic testing may be available for mutations in the *CTSA* gene.

Demographics

As an autosomal recessive disorder, galactosialidosis occurs with equal frequency among males and females. Since it requires two defective copies of the *CTSA* gene, one inherited from each parent, it is much more common in the offspring of couples who are related to each other (consanguineous), such as first or second cousins.

Galactosialidosis appears to occur with the highest frequency among Japanese. The juvenile/adult form is particularly common among Japanese, and specific mutations in the *CTSA* gene occur with a high frequency in this population.

Signs and symptoms

Although the features of galactosialidosis vary greatly, they are very similar to those of neuraminidase deficiency (sialidosis). These progressive symptoms include red spots in the eyes known as cherry-red macules. Eventually, the corneas may become cloudy, and cataracts and blindness may develop. Hearing loss is also common with galactosialidosis.

Myoclonus or sudden involuntary muscle contractions may become debilitating and may eventually develop into myoclonic seizures. Tremors and various other neurological conditions may develop. There may be a progressive loss of muscle coordination, called ataxia, and walking and standing can become increasingly difficult.

Small red skin lesions called angiokeratoma are signs of galactosialidosis. Swollen liver and spleen (hepatosplenomegaly) may develop. Cardiac disease can be one of the major consequences of the disorder.

Symptoms of the more severe forms of galactosialidosis include coarse or malformed facial features and a variety of skeletal malformations (dysostosis multiplex), including short stature. Intellectual disability also may be present. Galactosialidosis is one cause of nonimmune hydrops fetalis, the excessive accumulation of fluid in the fetus.

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are needed to display the trait or disease.

Beta-galactosidase—An enzyme that forms a complex with cathepsin A.

Dysostosis multiplex—A variety of bone and skeletal malformations.

Fibroblast—A cell that forms connective tissue fibers such as skin.

Ganglioside—A complex membrane lipid made up of a long-chain fatty acid, a long-chain amino alcohol, and an oligosaccharide containing sialic acid.

Glycoprotein—A protein with at least one carbohydrate group.

Heterozygote—Having two different versions of the same gene.

Homozygote—Having two identical copies of a gene or chromosome.

Lysosome—A membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

Myoclonus—Twitching or spasms of a muscle or an interrelated group of muscles.

Oligosaccharide—Several monosaccharide (sugar) groups joined by glycosidic bonds.

Polysaccharide—A linear or branched macromolecule composed of numerous monosaccharide (sugar) units linked by glycosidic bonds.

Recessive—Refers to a genetic trait that is expressed only when present on both members of a pair of genes, one inherited from each parent.

Sialic acid—N-acetylneuraminic acid, a sugar that is often at the end of an oligosaccharide on a glycoprotein.

Sialidosis—An inherited disorder also known as neuraminidase deficiency.

Vacuolation—The formation of multiple vesicles, or vacuoles, within the cytosol of cells.

multiplex. Magnetic resonance imaging (MRI) or computer tomography (CT) scans may be used to determine brain atrophy. An electroencephalogram (EEG) may indicate epileptic activity.

Neuraminidase activity

Typically, neuraminidase deficiency is diagnosed by measuring the activity of the enzyme in cultures of fibroblast cells (connective-tissue cells) that have been grown from cells obtained by a skin biopsy. Neuraminidase activity usually is measured by testing the ability of fibroblast cell preparations to hydrolyze, or cleave, a synthetic compound such as 4-methylumbelliferyl-D-N-acetylneuraminic acid. Hydrolysis by neuraminidase liberates 4-methylumbelliferone, which is a compound with fluorescence that can be measured accurately. The normal range of neuraminidase activity in fibroblasts is 95–653 picomoles per minute per milligram of protein. With galactosialidosis, neuraminidase activity in fibroblasts may be less than 4% of normal.

Beta-galactosidase activity

Beta-galactosidase activity in blood cells is measured in much the same way as neuraminidase activity in fibroblasts. Using the substrate 4-methylumbelliferyl-alpha-D-galactopyranoside, the fluorescence of 4-methylumbelliferone that is liberated through the action of beta-galactosidase is measured.

In severe forms of galactosialidosis, beta-galactosidase activity is less than 15% of normal, and neuraminidase activity is less than 1% of normal. The combination of low beta-galactosidase and low neuraminidase in fibroblasts, with normal levels of other lysosomal enzymes, is diagnostic for galactosialidosis.

Cathepsin A activity

The enzymatic activity of cathepsin A also can be measured in fibroblasts. In the early-infantile form of galactosialidosis, cathepsin A activity may be completely lacking. A small amount of cathepsin A activity (2%–5% of normal) usually is present in the lysosomes of individuals with other forms of galactosialidosis. The highest levels of cathepsin A activity are associated with the least severe and later-onset forms of the disorder. Carriers with a single mutated *CTSA* gene may have only half of the normal level of cathepsin A activity even though they are without symptoms of the disorder.

Histology

Galactosialidosis causes the lysosomes to fill with sialyloligosaccharides and sialylglycopeptides (partially degraded proteins with sialyloligosaccharides still

Diagnosis

Early-infantile onset

Some findings of galactosialidosis, including facial and skeletal abnormalities, may be apparent at birth. Skeletal x-rays may be used to diagnose dysostosis

QUESTIONS TO ASK YOUR DOCTOR

- Why do you believe my child has galactosialidosis?
- Is genetic testing available for galactosialidosis?
- What information will genetic testing provide?
- What is our risk of having another child with galactosialidosis?
- Is prenatal testing available for galactosialidosis?

attached). These swollen lysosomes may form inclusion bodies and give cells a vacuolated appearance that is diagnostic of lysosomal storage disease.

Neuraminidase deficiency may be diagnosed by histological or microscopic examination of a number of different types of cells that may show this cytosolic vacuolation. These cells include the Kupffer cells of the liver, lymphocytes (white blood cells that produce antibodies), bone marrow cells, epithelial skin cells, fibroblasts, and Schwann cells, which form the myelin sheaths of nerve fibers.

Urine tests

Neuraminidase deficiency may be diagnosed by screening urine for the presence of sialyloligosaccharides, using chromatography to separate the components of the urine on the basis of size and charge. In unaffected individuals, sialyloligosaccharides are cleaved by neuraminidase and therefore are present in the urine in only very low amounts. With neuraminidase deficiency, urine levels of sialyloligosaccharides may be three to five times higher than normal.

Sialylglycopeptides can be detected in the urine under conditions of neuraminidase deficiency. In galactosialidosis, keratan sulfate, which accumulates because of the low activity of GALNS, also can be identified in the urine.

Prenatal diagnosis

Galactosialidosis may be diagnosed prenatally. In at-risk fetuses, cultured fetal cells from the amniotic fluid (amniocytes), obtained by amniocentesis or cultured chorionic villi cells, obtained by chorionic villus sampling (CVS) in the early weeks of pregnancy, may be tested for neuraminidase and beta-galactosidase activities. Furthermore, the enzymatic activities of cathepsin A can be measured in amniocytes and chorionic villi. Cathepsin A activity is normally very high in these cells, and low activity is an indication of an affected fetus. However,

since carriers of a single mutated *CTSA* gene do not have symptoms of galactosialidosis, it may be difficult to recognize an at-risk fetus unless there is a family history of the disorder. Genetic testing for mutations in the *CTSA* gene is available from a number of labs in the United States, Canada, and Europe as of 2021.

Treatment and management

At present, there is no treatment for galactosialidosis. Rather, attempts are made to manage individual symptoms. Myoclonic seizures in particular, are very difficult to control.

Prognosis

The prognosis for individuals with this disorder varies greatly depending on the specific genetic mutation, which determines the age of onset and severity of the disease. Individuals with mild forms of galactosialidosis may have nearly normal life expectancies. However, the early-infantile form of galactosialidosis usually results in death shortly after birth.

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ORGANIZATIONS

- International Advocate for Glycoprotein Storage Diseases (ISM RD), 20880 Canyon View Dr., Saratoga, CA 95070, info@ismrd.org, <http://www.ismrd.org>

Margaret Alic, PhD

Gamete donor anonymity

Definition

Gamete donor anonymity refers to the practice of protecting the identities of people who donate male sperm, female oocytes, or embryos as third parties for assisted reproductive technologies (ART), most often in vitro fertilization (IVF). The term *donor* is still used, even though most gamete donors are compensated financially for their donations.

Gamete donor anonymity has become a vexed question in developed countries as of 2021 because of the conflicting perspectives and wishes of gamete donors, gamete recipients, and the offspring born through ART. Of the eight million children born worldwide since the introduction of IVF in 1978, at least two million of these children were born as the result of gamete and embryo donation.

Description

Gamete donor anonymity was standard practice from the earliest experiments with IVF up through the early twenty-first century, when a combination of technological and social changes made donor anonymity difficult to maintain. Although some countries have instituted legislative changes requiring open sperm or egg donation (also called known donation or identity disclosure donation), others continue to allow anonymous gamete donations even while encouraging disclosure among donors, recipients, and the resultant offspring.

History of sperm donation

Maintaining anonymity has always been simpler for sperm donors, because the ejaculation of semen is a natural process that occurs outside the male body, whereas oocyte retrieval involves a surgical procedure—the insertion of a needle through a woman's vagina to her ovaries to remove oocytes through aspiration. In addition, given the fact that some law codes held the biological father of a child responsible for financial support, both sperm donors and the physicians who assisted infertile male patients had both social and legal reasons to maintain donor anonymity.

The earliest-known successful case of a healthy full-term pregnancy resulting from donor insemination took place in Philadelphia in 1884. Dr. William Pancoast, a well-known local physician, was approached by the wife of a wealthy merchant who was concerned that she was sterile. Pancoast determined that it was the husband whose low sperm count—the result of a severe case of gonorrhea—was responsible for the wife's inability to



A medical technician prepares sperm samples for freezing. This process will allow the sperm to be unfrozen at some future point and used for artificial insemination. It is done for donated sperm and for sperm from men undergoing medical procedures that might lead to infertility. (Leeds Teaching Hospitals NHS Trust/Science Source)

conceive. Pancoast therefore called the wife back to his office for another “examination,” during which he gave her chloroform, inserted fresh semen obtained from one of the six medical students invited to observe the procedure, and packed the wife's cervix with gauze. Nine months later, the woman gave birth to a healthy baby boy. The full story did not come out until 1909, when one of the medical students present at the 1884 procedure wrote a letter to a medical journal describing what had taken place. He did inform the son, then a twenty-five-year-old businessman, of the circumstances of his conception before publishing the letter.

Prior to the 1980s, sperm donations were typically obtained privately by physicians from their friends or colleagues for use in either intracervical insemination (ICI), in which raw semen is inserted deep into the woman's vagina as close to the cervix as possible; or intrauterine

insemination (IUI), in which washed sperm are inserted directly into the uterus through a catheter. Anonymity was taken for granted by both donors and recipients. After IVF was introduced in 1978, growing interest in ART led to a shortage of donated sperm. In the 1980s, medical students and college undergraduates were recruited to donate sperm, paid for their donations, and promised anonymity; however, semen samples were rarely tested for sexually transmitted diseases (STIs). This policy changed in 1988 in response to the AIDS crisis, when the Centers for Disease Control and Prevention (CDC) required sperm donors to be tested for HIV antibodies at the time of donation, their semen to be frozen, and retested six months later before the gametes could be used.

Some countries have instituted limits on the number of offspring that a sperm donor's donations may produce. The reason for limitation is to lower the risk of accidental incest; that is, sexual activity or marriage between persons unaware of a close familial relationship between them. While limitations imposed by law on sperm donation are common worldwide, they are voluntary in the United States and Japan.

History of egg donation

Egg donation is a much more complicated process; it was not considered feasible until 1983, when the first successful oocyte donation took place in Australia. By 1987, 17 fertility centers in the United States offered oocyte donation, a number that increased to over 400 centers by 2005. As with sperm donors, oocyte donors had to be recruited when the demand for their gametes outran the supply. The first oocyte donors were typically women undergoing IVF who were willing to donate their extra oocytes, or women who were friends or relatives of women seeking an oocyte donor. The next group of donors included married women under age 35 who had had all the children they wanted. Physicians then began to recruit college students, on the grounds that oocytes from younger women have a better chance of producing a viable pregnancy, and because college women are presumably of above-average intelligence.

Remuneration for oocyte donation is much higher than for sperm donation because of the inconvenience and health risks involved. An oocyte donor must receive hormonal stimulation timed to coincide with the stimulation given to the recipient; she must then undergo an intrusive procedure in a hospital or fertility clinic in order to retrieve the mature oocytes. Health risks include infection; hyperstimulation of the ovaries; unintentional pregnancy; and reduced fertility in later life. Because of these physical risks and possible psychological complications from the procedure, oocyte donors are paid on

average between \$8,000 and \$10,000 per donation cycle as of 2021, while donors with demonstrated superior intelligence or athletic ability may be offered as much as \$50,000. By contrast, sperm donors are paid an average of \$125 per approved sample.

Technological changes

The contrast between the relative simplicity of sperm donation and the greater complexity of oocyte donation, as well as the different timelines of these two types of gamete donation, reflects the role of medical technology in making gamete donation increasingly widespread and thereby calling donor anonymity into question. There are three changes in particular that are relevant in this context: the rise of the Internet and social media; advances in DNA identification and analysis; and the popularity of direct-to-consumer genetic testing.

The Internet and social media made it possible for large numbers of people worldwide to share information and opinions with thousands and potentially millions of online viewers. This ease of communication led many participants to share personal and family secrets that would have been previously kept private, and some were encouraged to disclose more and more information about their lives. One common issue was the matter of adoption; younger Internet users, particularly the so-called Millennials and Generation Z, have little difficulty in turning to the Web to locate information about their biological parents if they know themselves to be adoptees.

The Internet has also made it possible for people to learn about advances in DNA detection and analysis, and apply that information to their own situation. Since 1985, when DNA was first used to solve a homicide case in the United Kingdom, forensic laboratories have been able to use smaller and smaller samples of DNA from body fluids and skin cells to identify criminals, and this same improvement in technology was put to use for the general public in the early direct-to-consumer DNA test kits.

The first DTC genetic tests were marketed within a few years after the completion of the Human Genome Project in 2003. These first tests were expensive, costing about \$1,000, but improvements in technology led to the price dropping to as low as \$59 by 2018. As the price of DTC testing fell, its popularity increased, as did its advertising in the mass media. The accumulation of data from DTC testing by such services as GEDmatch has made it increasingly easy for adoptees searching for their biological parents to track down their relatives. Some geneticists estimate that so many DTC tests have been completed in the United States that even people who have not taken such a test are likely to be related genetically to

someone who has—making gamete donor anonymity all but impossible.

Still another technological development has complicated gamete donor anonymity, namely facial recognition software. The Center for Human Reproduction (CHR) in New York City reported a case in 2018 in which a third party recognized one of the center's oocyte donors by comparing the donor's anonymous photograph on the center's website with the same photograph on the donor's social media account.

Social changes

Changes in technology have intersected with changes in social attitudes regarding family structure, sexism, children's rights, and patients' rights. One longstanding reason for gamete donor anonymity was to protect the traditional nuclear family, understood as a husband and wife and their legitimate offspring. This protection was based on three premises that are no longer generally accepted: the notion that doctors always know what is best for patients; that men have the right to decide what women are allowed to know; and that the wishes of adults for secrecy are privileged over the interests of children for disclosure. The Pancoast incident is a good historical example of this paternalism. The physician did not inform the husband of the artificial insemination until after the baby's birth; both men agreed to keep the wife in the dark about it; and the son was not informed until he was 25, and then only because one of the former medical students did so as a courtesy before his letter about the incident was published.

Another motivation for sperm donor anonymity in particular came from the eugenics movement of the 1920s and 1930s. Many eugenicists believed that genetically superior men had an obligation to the species to father as many children as possible, even in violation of conventional morality. One proponent of this view was Charles Lindbergh, the famous aviator. In the mid-1950s, he took advantage of frequent business trips to Europe to father seven children by three different women in Germany, even though he had already had six children by his American wife, Anne.

Social changes that have come about since the 1970s include greater acceptance of nontraditional households, including same-sex couples, single-parent households, and families consisting of three or more unmarried people (sometimes called polyamory). A majority of gamete donors in developed countries have no objection to donating sperm or oocytes to nontraditional families. However, the greater instability of these families and the high rate of divorce and remarriage among heterosexual couples could increase the likelihood that the offspring

may have questions about their genetic identity when they become adults. On the one hand, an ever larger proportion of adolescents and young adults have grown up in households with a shifting population of parents, grandparents, step-parents, and parents' sexual partners, and have adapted as well as they could to the older adults' actions. On the other hand, these same young people are often strongly motivated to search for their biological parents and/or half-siblings in order to resolve their own identity issues.

Legislation regarding donor anonymity

Countries differ in regard to the legality of gamete donor anonymity. Some countries, such as the United Kingdom, Australia, New Zealand, Austria, Germany, Switzerland, Sweden, Norway, and the Netherlands, require gamete donors to make their identifying information available to the resultant offspring when the children reach the age of 18; one result of this legislation has been a measurable drop in the number of men willing to donate sperm. Another result is an increase in fertility tourism—in this context, people traveling from a country where gamete donors are legally identifiable to other countries where donor anonymity is still allowed.

The United States is an outlier in regard to donor anonymity; there is no federal law requiring open identification of gamete donors as of 2021, and private sperm and oocyte donation is still practiced. Although such professional organizations as the American Society for Reproductive Medicine (ASRM) strongly encourage disclosure, they continue to respect the wishes of some gamete donors to remain anonymous.

A document published by the ethics committee of the ASRM in 2018 stated, “The . . . Committee finds that disclosure to offspring about the fact of donor conception and, if available, characteristics of the donor(s), may serve the offspring's best interests. The Committee also recognizes that the decision is a highly personal one about which the parties may have differing values.” The ASRM also recommends psychological counseling and informed consent about disclosure and information sharing for both gamete donors and recipients, as well as advising all parties to keep in mind that later changes in the law may affect any nondisclosure agreements made.

Regulation of sperm banks and fertility clinics in the United States

In the United States, sperm banks and clinics offering donated semen are required by law to register with the Food and Drug Administration (FDA), which can perform unannounced on-site inspections. The FDA is primarily concerned, however, with the risk of infectious disease

KEY TERMS

Accidental incest—Sexual activity or marriage between persons who are unaware of a close familial relationship between them.

Assisted reproductive technology (ART)—A collective term for a group of procedures done to address problems with fertility. ART includes such techniques as in vitro fertilization, cryopreservation of donated gametes or embryos, and pre-implantation genetic diagnosis.

Carrier—In genetics, a person who has a genetic mutation associated with a disease and is capable of passing it on. A carrier may or may not display the symptoms of the disease.

Ethics—The branch of philosophy dealing with questions of good and evil, and with moral duties and obligations in human society.

Eugenics—A set of beliefs and practices intended to improve the genetic quality of a country's human population, either by limiting the reproduction of people considered unfit or by encouraging the reproduction of healthier, more intelligent, and more attractive people.

Fertility fraud—A recently coined term for physicians' use of their own sperm in assisted reproductive techniques.

Fertility tourism—The practice of traveling to another jurisdiction or country for fertility treatments unavailable or illegal in one's own country.

Forensic—Pertaining to the use of science or medicine in the investigation and establishment of evidence in a court of law.

Gamete—A sex cell (sperm or ovum) containing the haploid number of chromosomes and capable of

fusing with a gamete of the opposite sex to form a zygote.

Haploid—Referring to cells that have only one chromosome of each type, and therefore have only one complete set of genes.

In vitro fertilization (IVF)—A form of assisted reproduction technology in which a human ovum (egg) is combined with sperm outside the body in a laboratory container ("in vitro" means "in glass").

Informed consent—The process of obtaining permission from a person before conducting a health care procedure on a person, enrolling a person in a clinical trial, or disclosing that person's private information.

Oocyte (pronounced OH-uh-site)—A diploid cell in females from which an egg or ovum develops by meiosis.

Pre-implantation genetic testing (PGT)—A screening test performed on embryos created by IVF to analyze the genetics of each embryo prior to transfer into the intended mother's uterus.

Surrogacy—The practice in which a woman, called a surrogate mother, carries a pregnancy to term for another person or persons who cannot have children, who will become the legal parent(s) of the child after birth. Surrogacy may or may not involve a legal contract.

Third-party reproduction—Any instance of human reproduction in which DNA or gestation is provided by a third-party donor other than the parent(s) who will rear the resulting child. It is also called donor-assisted reproduction.

transmitted through semen; it does not deal with screening and testing for genetic disorders. The FDA regulates oocyte as well as sperm donation under the general heading of human tissue and tissue products. Some states, including New York and California, regulate sperm banks, but most do not.

Sperm banks and fertility clinics offering oocyte donation may register with the American Association of Tissue Banks (AATB), an organization established in 1977. Registration with the AATB is voluntary as of 2021, however; it is not required by either federal or state law.

The CDC collects data about ART from over 440 fertility clinics in the United States as of 2021. Its system

is called the National Assisted Reproductive Technology Surveillance System or NASS. NASS is, however, intended to measure the success and outcomes of assisted reproductive technologies carried out in these clinics. While patient data include demographic characteristics and medical histories, DNA profiles are not included, and the CDC does not have an official position on gamete donor anonymity.

Fertility fraud cases

One direct result of the boom in DTC genetic testing has been the uncovering of what is termed fertility fraud—that is, physicians' use of their own semen to inseminate

QUESTIONS TO ASK YOUR DOCTOR

- What is your opinion of gamete donor anonymity?
- Have any of your patients used the results of DTC genetic testing to look for their biological parents or previously unknown relatives?
- Have any of your patients been affected by fertility fraud?

patients who thought they were receiving either their husbands' sperm or that of an anonymous donor. Beginning around 2014, both recipients of donated sperm and their now-grown offspring discovered through DTC testing that the donated sperm had been provided by the recipients' doctors. As of 2021, cases of fertility fraud have led to lawsuits not only in the United States (in Indiana, California, Texas, Virginia, Idaho, and Vermont) but also in Canada and the Netherlands. One Indianapolis physician is known to have fathered over 50 children, while the Canadian physician whose medical license was revoked in 2014 fathered at least 16 children.

According to legal professionals, however, it is difficult to define the precise crime that these doctors committed at the time that sperm donation was considered confidential. When a Virginia physician was taken to court in 1992 for using his own sperm to impregnate his patients, prosecutors discovered there was no law on the books prohibiting doctors from administering their own sperm to unwitting patients; they had to prosecute the doctor on 52 counts of perjury and fraud. A new law passed in Indiana in 2019 makes fertility fraud a felony and allows families affected by such fraud before 2019 to bring a civil suit in court. Texas passed similar legislation criminalizing fertility fraud in 2019, and Florida and Colorado followed in 2020.

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ORGANIZATIONS

American Association of Tissue Banks (AATB), 8200 Greensboro Drive, Suite 404, McLean, VA 22102, (703) 229-1020, aatb@aatb.org, <https://www.aatb.org>

American College of Obstetricians and Gynecologists (ACOG), 409 12th Street SW, Washington, DC 20024-2188, (800) 673-8444, (202) 638-5577, <https://www.acog.org/>

American Society for Reproductive Medicine (ASRM), J. Benjamin Younger Office of Public Affairs, 726 7th Street, SE, Washington, D.C. 20003, (202) 863-4985, asrm@asrm.org, <https://www.asrm.org/>

National Society of Genetic Counselors (NSGC), 330 North Wabash Avenue, Suite 2000, Chicago, IL 60611, (312) 321-6834, nsgc@nsgc.org, <https://www.nsgc.org>

Society for Assisted Reproductive Technology (SART), 1209 Montgomery Highway, Birmingham, AL 35216-2809, (205) 978-5000, (205) 978-5018, sart@asrm.org, <https://www.sart.org/>

U.S. Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, Atlanta, GA 30333, (800) CDC-INFO (232-4636), <http://www.cdc.gov/cdc-info/requestform.html>, <http://www.cdc.gov>

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) 463-6332, <https://www.fda.gov/>

Rebecca J. Frey, PhD

Gangliosidosis-GM1 see **GM1-gangliosidosis**

Gardner syndrome see **Familial adenomatous polyposis**

Gastric cancer

Definition

Gastric cancer (also known as stomach cancer) is a disease in which the cells forming the inner lining of the stomach become abnormal and start to divide uncontrollably, forming a mass or a tumor.

Description

The stomach is a J-shaped organ that lies in the abdomen, on the left side. The esophagus (or the food pipe) carries the food from the mouth to the stomach. The stomach produces many digestive juices and acids that mix with the food and aid in the process of digestion. The stomach is divided into five sections. The first three are together referred to as the proximal stomach and produce acids and digestive juices, such as pepsin. The fourth section of the stomach is where the food is mixed with the gastric juices. The fifth section of the stomach

acts as a valve and controls the emptying of the stomach contents into the small intestine. The fourth and the fifth sections together are referred to as the distal stomach. Cancer can develop in any of the five sections of the stomach. The symptoms and the outcomes of the disease may vary depending on the location of the cancer.

In many cases, the cause of the gastric cancer is unknown. Several environmental factors have been linked to gastric cancer. Consuming large amounts of smoked, salted, or pickled foods has been linked to increased gastric cancer risk. Nitrates and nitrites, chemicals found in some foods such as cured meats may be linked to gastric cancer as well.

Infection by the *Helicobacter pylori* (*H. pylori*) bacterium has been found more often in people with gastric cancer. *H. pylori* can cause irritation of the stomach lining (chronic atrophic gastritis), which may lead to precancerous changes of the stomach cells.

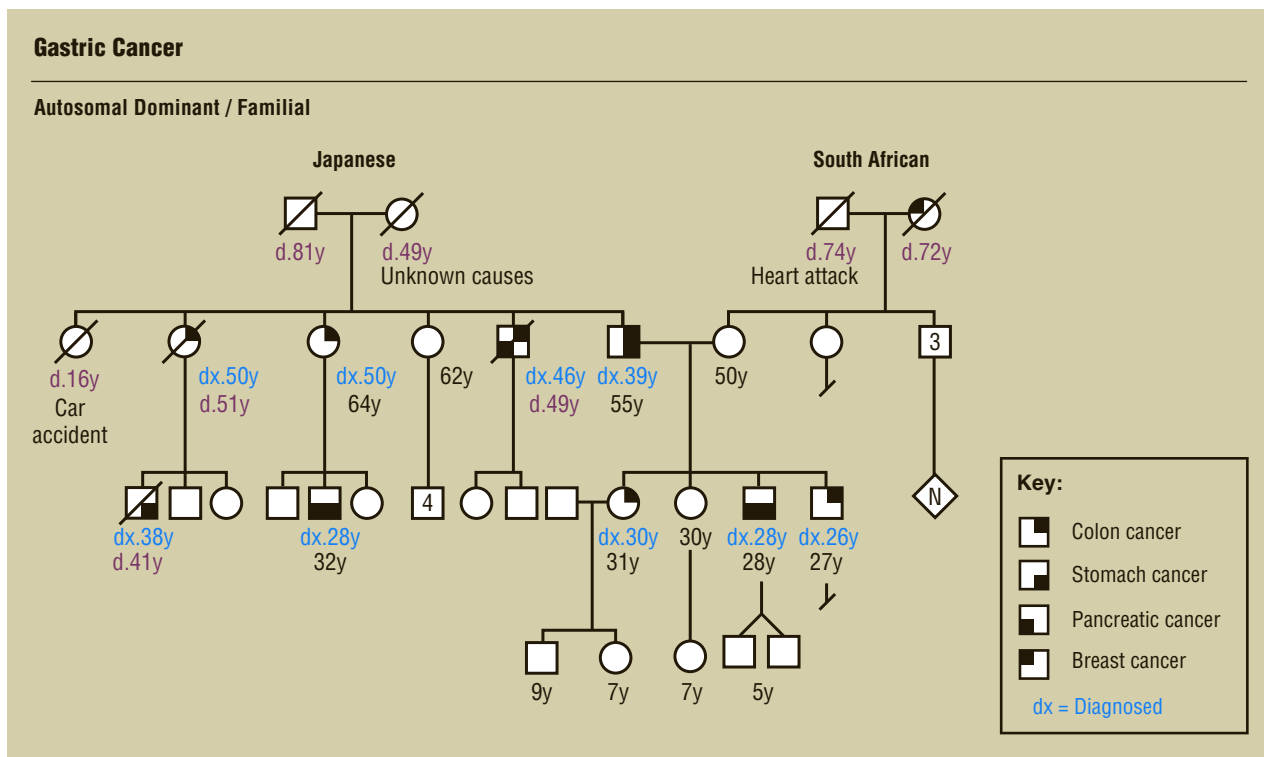
People who have had previous stomach surgery for ulcers or other conditions may have a higher likelihood of developing gastric cancers, although this is not certain. Another risk factor is developing polyps, benign growths in the lining of the stomach. Although polyps are not cancerous, some may have the potential to turn cancerous.

People with blood relatives who have been diagnosed with gastric cancer have an increased risk of developing the disease. In addition, people who have inherited disorders such as hereditary diffuse gastric cancer (HDGC), familial adenomatous polyposis (FAP), and Lynch syndrome have an increased risk for gastric cancer. For unknown reasons, gastric cancers occur more frequently in people with the blood group A.

Genetic profile

Although environmental or health factors may explain frequent occurrences of gastric cancer in families, it is known that inherited risk factors also exist. Some studies show close relatives having an increased risk of gastric cancer two to three times that of the general population. The primary gene currently associated with gastric cancer is the *CDH1* gene, and other possible gene mutations include mutations from the *MAP3K6* gene.

Familial cancer syndromes are hereditary conditions in which specific types of cancer, and perhaps other features, are consistently occurring in affected individuals. HDGC, FAP, and hereditary nonpolyposis colon cancer (HNPCC) are familial cancer syndromes that increase the risk of colon cancer. HNPCC is a hereditary colon cancer with an autosomal dominant type of inheritance. It has a possible underlying mutation in one or more of



Gastric cancer: pedigree analysis chart (Gale)

the following genes: *MSH2*, *MLH1*, *MSH6*, *PMS1*, and/or *PMS2*.

FAP is due to changes in the *APC* gene, although a reported 25%–30% of cases are *de novo* mutations, which means they are not related to family history. Individuals with FAP typically have more than 100 polyps (mushroom-like growths) in the digestive system, as well as other effects. Polyps are noncancerous growths that have the potential to become cancerous if not removed. At least one study estimated that the risk of gastric cancer was seven times greater for individuals with FAP than for the general population.

The number of polyps present is an important distinction between FAP and HNPCC. Polyps do not form at such a high rate in HNPCC, but individuals with this condition are still at increased risk of colon, gastric, and other cancers. At least five genes are known to cause HNPCC, but alterations in the *hMSH2* or *hMLH1* genes have been found in the majority of HNPCC families.

Other inherited conditions such as Peutz-Jeghers, Cowden, Li-Fraumeni, and other syndromes have been associated with gastric cancer. All of these syndromes have distinct features beyond gastric cancer that aid in identifying the specific syndrome. The inheritance pattern for most of these syndromes is dominant, meaning that

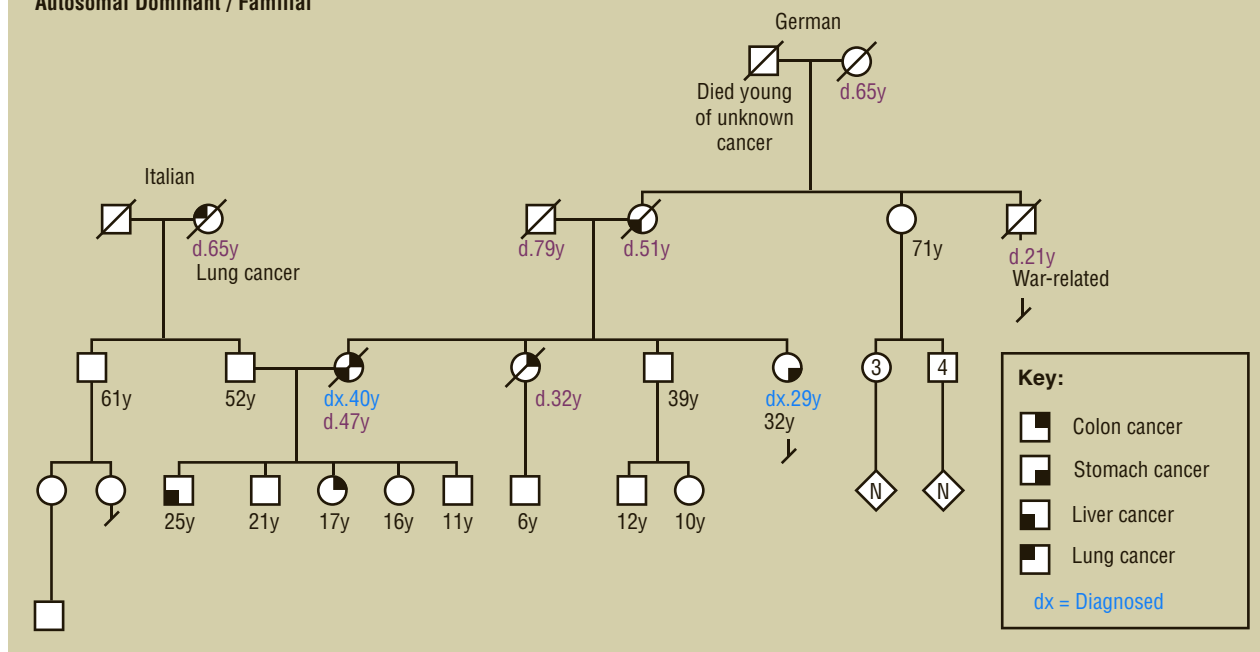
only one copy of the gene needs to be inherited for the syndrome to be present.

Current standards for defining hereditary gastric cancer not due to known genetic conditions are often applied. In areas with low rates of gastric cancer, hereditary gastric cancer has been defined according to the International Gastric Cancer Linkage Consortium as (1) families with two or more cases of gastric cancer in first- or second-degree relatives (siblings, parents, children, grandparents, nieces/nephews, or aunts/uncles) with at least one case diagnosed before age 50; or (2) three or more cases at any age. In countries with higher rates of gastric cancer, such as Japan, the suggested criteria are (1) at least three affected first-degree relatives (sibling, children, or parents) with one being the first-degree relative of the other two; (2) at least two affected generations (without a break); and (3) at least one cancer occurrence before age 50.

Inherited changes in the *E-Cadherin/CDH1* gene first were reported in three families of native New Zealander (Maori) descent with gastric cancer and later were found in families of other ancestry. The *E-Cadherin/CDH1* gene, which plays a role in cell to cell connection, is located on chromosome 16 at 16q22. The percentage of hereditary gastric cancer that is due to *E-Cadherin/CDH1* gene alterations is uncertain. In

Gastric Cancer

Autosomal Dominant / Familial



Gastric cancer: pedigree analysis chart (Gale)

summary, most gastric cancer is due to environmental or other non-genetic causes. A small portion of cancer of the stomach, about 8%, is due to inherited factors, one of which is *E-Cadherin/CDH1* gene alterations.

Demographics

Gastric cancer is the fourth most common cancer throughout the world, with an estimated 900,000 cases per year. It is one of the leading causes of cancer deaths in many areas of the world, most notably Japan and Korea, but the number of new gastric cancer cases is decreasing in some areas, especially in developed countries. As of 2015, death due to gastric cancer had been reported in over 723,000 individuals, and of that an estimated 1%–3% was due to a hereditary predisposition. In the United States, the use of refrigerated foods and increased consumption of fresh fruits and vegetables instead of preserved foods may be a reason for the decline in gastric cancer. Early screening, especially in those with a family history, may also be a reason behind a recent decline.

Signs and symptoms

Gastric cancer can be difficult to detect at early stages since symptoms are uncommon and frequently unspecific. The following can be symptoms of gastric

cancer: poor appetite or weight loss; fullness even after a small meal; abdominal pain; heartburn; belching; indigestion or nausea; vomiting, with or without blood; welling or problems with the abdomen; anemia; or blood on stool (feces) examination. Signs and symptoms of gastric cancer typically do not occur until later stages, making the prognosis poor due to a late diagnosis.

Diagnosis

In addition to a physical examination and fecal occult blood testing (checking for blood in the stool), special procedures are done to evaluate the digestive system including the esophagus, stomach, and upper intestine. Procedures used to diagnose gastric cancer include barium upper gastrointestinal (GI) x-rays, upper endoscopy, and endoscopic ultrasound. Genetic testing can also be used to determine an individual's predisposition to gastric cancer.

Upper GI x-rays

The first step in evaluation for gastric cancer may be x-ray studies of the esophagus, stomach, and upper intestine. This type of study requires drinking a solution with barium to coat the stomach and other structures for easier viewing. Air is sometimes pumped into the stomach to help identify early tumors.

KEY TERMS

Adenocarcinoma—A type of cancer that originates in glandular tissue, has glandular characteristics, or both.

Barium—A chemical put into a solution and swallowed to help with outlining the gastrointestinal system during an x-ray study.

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Cancer—A disease caused by uncontrolled growth of the body's cells.

Chemotherapy—Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of the cancerous cells or by killing the cancer cells.

Chronic atrophic gastritis—Irritation and breakdown of the stomach wall over a period of time.

Dominant inheritance—A type of genetic inheritance pattern that results in one form of a gene being dominant over other forms. Therefore, the dominant allele can express itself and cause disease even if only one copy is present.

Duodenum—Portion of the small intestine nearest the stomach; the first of three parts of the small intestine.

E-Cadherin/CDH1—A gene involved in cell-to-cell connection. Alterations in this gene have been found in several families with increased rates of gastric cancer.

Endoscope—A slender, tubular optical instrument used as a viewing system for examining an inner part of the body. With an attached instrument, the endoscope can be used for biopsy or surgery.

Esophagus—The part of the digestive tract that connects the mouth and stomach; the food pipe.

Familial adenomatous polyposis (FAP)—Inherited syndrome causing large numbers of polyps and increased risk of colon cancer and other cancers.

Familial gastric cancer—Gastric cancer that occurs at a higher rate in some families.

Fecal occult blood test—Study of stool (feces) to identify loss of blood in the gastrointestinal system.

Gastric—Associated with the stomach.

Gastrointestinal (GI) system—Body system involved in digestion, the breaking down and use of food.

Gene—A building block of inheritance that contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Genetic counselor—A health professional with advanced training in genetics and psychology who educates people about genetic conditions and testing.

Helicobacter pylori (H. pylori)—Bacterium that infects humans and may be associated with an increased risk of gastric cancer.

Hereditary non-polyposis colon cancer (HNPCC)—A genetic syndrome causing increased cancer risks, most notably colon cancer. Also called Lynch syndrome.

Li-Fraumeni syndrome—Inherited syndrome known to cause increased risk of different cancers, most notably sarcomas.

Lymph node—A bean-sized mass of tissue that is part of the immune system and is found in different areas of the body.

Nitrates/nitrites—Chemical compounds found in certain foods and water that, when consumed, may increase the risk of gastric cancer.

Pernicious anemia—A blood condition with decreased numbers of red blood cells related to poor vitamin B12 absorption.

Peutz-Jeghers syndrome (PJS)—Inherited syndrome causing polyps of the digestive tract and spots on the mouth as well as increased risk of cancer.

Polyp—A mass of tissue bulging out from the normal surface of a mucous membrane.

Radiation—High-energy rays used in cancer treatment to kill or shrink cancer cells.

Staging—A method of describing the degree and location of cancer.

Stomach—A muscular hollow organ that secretes gastric acid and digestive enzymes, and continues the process of digestion begun with chewing.

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.

X-ray—An image of the body made by the passing of radiation through the body.

Upper endoscopy

Endoscopy allows a diagnosis in about 95% of cases. In upper endoscopy, a small tube called an endoscope is placed down the throat so that the esophagus, stomach, and upper small intestine can be viewed. If a suspicious area is seen, a small sample of tissue, a biopsy, is taken. The tissue from these samples can be examined for evidence of cancer.

Endoscopic ultrasound

Endoscopic ultrasound allows several layers to be seen, so it is useful in determining where cancer may have spread. With this test, an endoscope is placed into the stomach and sound waves are emitted. A machine analyzes the sound waves to detect differences in the tissues in order to identify tumors.

Genetic testing

If a certain genetic syndrome such as HDGC, FAP, or HNPCC is suspected, genetic testing may be available either through a clinical laboratory or through a research study. Testing for *E-cadherin/CDH1* gene alterations is mainly available through research studies. Once an *E-cadherin/CDH1* gene change is identified through research, the results can be confirmed through a certified laboratory.

When a gene change is identified, genetic testing may be available for other family members. For most genetic tests, it is helpful to test the affected individual first, since he or she is most likely to have a gene change. Genetic testing is usually recommended for consenting adults; however, for syndromes in which gastric cancer is a common feature, testing of children may be reasonable for possible prevention of health problems.

The detection rate and usefulness of genetic testing depends on the genetic syndrome. If genetic testing is under consideration, a detailed discussion with a knowledgeable physician, genetic counselor, or other practitioner is helpful in understanding the advantages and disadvantages of the genetic test. It is also important to realize that testing positive for the *E-cadherin/CDH1* gene does not necessarily mean that the individual will be affected with cancer. However, he or she may have an increased risk compared to an individual without the gene.

Treatment and management

Regular mass screening for gastric cancer has not been found useful in areas such as the United States, where gastric cancer is less common. When gastric cancer is diagnosed in the United States, it is usually discovered at later and less curable stages. However, individuals

with an increased risk of gastric cancer, including those with a known genetic syndrome or with a family history of the disease, may consider regular screening before the development of cancer. If a known hereditary cancer syndrome is suspected, screening should follow the generally accepted guidelines for these conditions.

The current standard of care for the treatment and management of gastric cancer utilizes upper endoscopy and biopsy in families with hereditary gastric cancer, including screening every 6 to 12 months for individuals with known *E-cadherin* gene alterations, if no other treatment has been done. Some individuals with a known hereditary gastric cancer risk have surgery to remove the stomach prior to development of any gastric cancer, but the effectiveness of this prevention strategy is uncertain. Several other less drastic prevention measures have been considered, including changes in diet, use of vitamins, and antibiotic treatment of *H. pylori*. The American Cancer Society recommends limiting use of alcohol and tobacco. Genetic testing for *CDH1* in immediate family members is also a widely used screening method when hereditary gastric cancer has been diagnosed.

Treatment of gastric cancer in nearly all cases involves some surgery. The amount of the stomach or surrounding organs that is removed depends on the size and location of the cancer. Sometimes surgery is performed to try to remove all of the cancer in hopes of a cure, while other times surgery is done to relieve symptoms. Possible side effects of stomach surgery include leaking, bleeding, changes in diet, vitamin deficiencies, and other complications.

Chemotherapy involves administering anticancer drugs either intravenously (through a vein in the arm) or orally (in the form of pills). This can either be used as the primary mode of treatment or after surgery to destroy any cancerous cells that may have migrated to distant sites. Side effects (usually temporary) of chemotherapy may include low blood counts, hair loss, vomiting, and other symptoms.

Radiation therapy is often used after surgery to destroy the cancer cells that may not have been completely removed during surgery. Generally, to treat gastric cancer external beam radiation therapy is used. In this procedure, high-energy rays from a machine that is outside of the body are concentrated on the area of the tumor. In the advanced stages of gastric cancer, radiation therapy is used to ease symptoms such as pain and bleeding.

Prognosis

Staging is a method of describing cancer development. There are five stages in gastric cancer, with stage 0 being the earliest cancer that has not spread while stage

QUESTIONS TO ASK YOUR DOCTOR

- What stage of cancer am I in and what is my prognosis?
- Should my siblings and children be screened for cancer earlier in life now that I have been diagnosed?
- What are my treatment options?

IV includes cancer that has spread to other organs. Expected survival rate can be roughly estimated based on the stage of cancer at the time of diagnosis.

The prognosis for patients with early-stage cancer depends on the location of the cancer. When cancer is in the proximal part of the stomach, only 10%–15% of people survive five years or more, even if they have been diagnosed with early-stage cancer. For cancer that is in the distal part of the stomach, if it is detected at an early stage, the outlook is somewhat better. About 50% of people survive for at least five years or more after initial diagnosis. However, only 20% of the patients are diagnosed at an early stage. Chance of survival depends on many factors, and it is difficult to predict survival for a particular individual.

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- "What Is Stomach Cancer?" American Cancer Society. <https://www.cancer.org/cancer/stomach-cancer/about/what-is-stomach-cancer.html> (accessed July 8, 2021).

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- American Cancer Society, 250 Williams St. NW, Atlanta, Georgia 30303, (800) 227-2345, <http://www.cancer.org>

National Cancer Institute, BG 9609 MSC 9760, 9609 Medical Center Dr., Bethesda, MD 20892-9760, (800) 422-6237, <http://www.cancer.gov>

No Stomach for Cancer, PO Box 46070, Madison, WI 53744, (608) 692-5141, info@nostomachforcancer.org, <http://www.nostomachforcancer.org>

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Gastroschisis

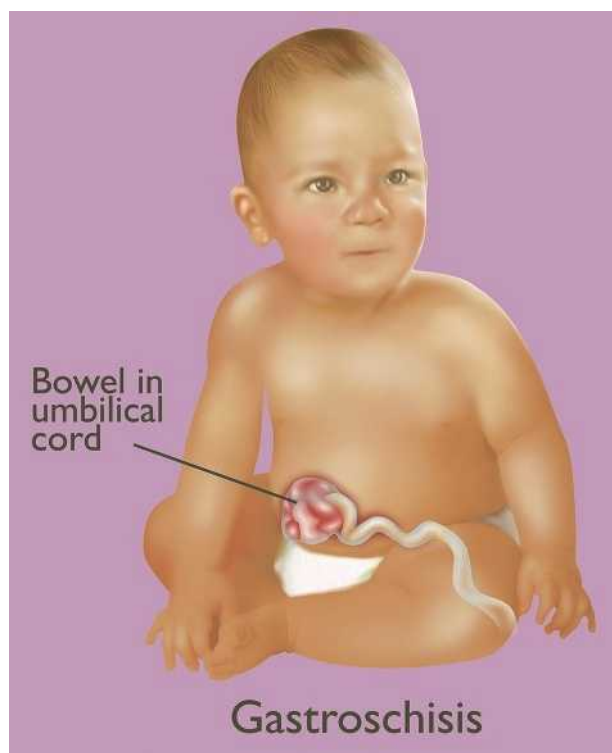
Definition

Gastroschisis, which literally means "split abdomen," is a hernia (open fissure) in the muscle and skin of the abdominal wall that allows the contents of the abdominal cavity to be exposed to the outside of the body. The opening is usually 2–5 in. (5–12.7 cm) long and located in the median plane of the abdomen to the right of the umbilical cord.

Gastroschisis appears during the fetal period and causes the fetal intestines to be exposed to the amniotic fluid with no covering sac. Because amniotic fluid contains the urine of the fetus, this exposure may irritate the fetal intestines, causing swelling and shortening during development. As fetal development progresses, the opening becomes smaller relative to the size of the intestines. Consequently, the bowel may either become strangulated or malrotated. After the infant is born, the intestines are placed back inside the abdominal cavity and the opening is closed surgically. The intestines may still pose long-term functional problems because of the previous irritation and formation of adhesions.

Description

Gastroschisis is caused by a defect in the normal fetal developmental pattern. In fetal development, the midgut (intestines) loops out of the abdominal cavity in a normal process known as physiological umbilical herniation. This process begins in the sixth week of fetal development because there is not enough room in the abdominal cavity for the growing liver, kidneys, and intestines. By the tenth week of fetal development, the liver and kidneys have decreased in size and the abdominal cavity has grown. In a normal fetus, the intestines return to the abdominal cavity at this time, and the abdominal wall forms around them. In a fetus with gastroschisis, the return of the intestine to the abdominal cavity fails to occur. The pancreas, stomach, liver, spleen, bladder, uterus, ovaries, or fallopian tubes are rarely also herniated. The cause of the failure of the intestines to return



An illustration of a baby with gastroschisis, a defect in the abdominal wall that allows the contents of the digestive system to protrude. (Gwen Shockey/Science Source)

to the abdominal cavity is unknown. The attachment of the umbilical cord is normal.

Genetic profile

The cause of gastroschisis is unknown; no definite genetic association has been determined. Chromosomal abnormalities are rarely associated with gastroschisis, and familial occurrence is exceptionally rare. Most genetic centers do not recommend the testing of infants with isolated gastroschisis. The familial cases that have been reported include occurrence in twins. Gastroschisis is not usually seen in association with other types of birth defects. Deformations of the fetal urinary tract can develop because of gastroschisis. These do not represent separate malformations, and genetic testing is not indicated.

A genetically associated issue that may arise is the misdiagnosis of gastroschisis for the distinct condition known as omphalocele. This misdiagnosis occurs in 5% of patients with omphalocele, and has serious implications because omphalocele is often associated with chromosomal abnormalities and additional non-gastrointestinal malformations.

Demographics

Gastroschisis is not a common birth defect. It occurs in approximately 2–6 infants per 10,000 live births in the United States and internationally. Most cases of gastroschisis are sporadic with no familial association. Abnormalities of the intestines as a direct consequence of gastroschisis are seen in 5% of patients. Gastroschisis occurs slightly more often in males than in females. Young maternal age, maternal drug usage, and origination from a socially or economically disadvantaged background all increase the risk of gastroschisis. Very low maternal weight is associated with three times increased risk for gastroschisis. High maternal intake of nitrosamines found in preserved meat and beer doubles the risk of gastroschisis. High maternal weight reduces risk. A low maternal intake of chemicals called carotenoids found in many fruit and vegetables or glutathione from animal protein causes three to four times increased risk for gastroschisis. Carotenoids and glutathione are antioxidants that have a protective effect on the fetus and decrease oxygen stress or oxygen deprivation. Any factor that reduces blood flow to the fetus, thereby causing oxygen stress, can be a factor in the development of gastroschisis. Maternal intake of aspirin or ibuprofen (Advil) causes four to five times increased risk for gastroschisis. Both medications are inhibitors of the cyclooxygenase enzyme and influence blood flow to the fetus. Acetaminophen (Tylenol) has no demonstrated association with gastroschisis. Decongestants, especially pseudoephedrine and phenylpropanolamine, more than double the risk because they cause constriction of blood vessels and decrease blood flow to the fetus. Illness and fever have no association with the development of gastroschisis.

Signs and symptoms

A mother carrying a fetus with gastroschisis will not experience any unusual signs or symptoms in early pregnancy. Gastroschisis may be suspected when maternal serum screening, which is typically performed at 15–20 weeks of gestation, reveals an elevated alpha-fetoprotein level (AFP). Gastroschisis is an open defect in the fetal abdominal wall that allows the leakage of AFP from the fetal tissues into the amniotic fluid. The increased amount of amniotic fluid AFP is absorbed into the maternal circulation and can be easily measured in a maternal serum screening test. An elevated AFP level detected in maternal serum is not indicative of gastroschisis specifically, but this does alert the obstetrician that a detailed ultrasound of the fetus is indicated. An elevated maternal serum AFP level is present in approximately 75%–80% of cases of gastroschisis. Gastroschisis may also be incidentally detected in the second trimester during routine ultrasonography.

KEY TERMS

Amniocentesis—A transabdominal puncture of the amniotic sac to remove amniotic fluid for chemical analysis.

Computerized axial tomography (CAT) scan—A noninvasive technique to show computerized images of a structure in the body.

Exomphalos—An umbilical protrusion or hernia; it is also called omphalocele.

Ultrasonogram—The image produced by the use of inaudible sound of high frequency called ultrasound to photograph a tissue, organ, or infant.

Diagnosis

Ultrasonogram is the primary method of diagnosis for gastroschisis because it is noninvasive, rapid, and allows for real-time fetal monitoring. Gastroschisis is often diagnosed before 20 weeks of gestation by an ultrasonogram that may show some or all of the following: loops of fetal intestines floating exposed to amniotic fluid with or without other organs, signs of intestinal obstruction, or a defect in the middle of the abdominal wall to the right of a normal umbilical cord.

With a transvaginal sonogram, the diagnosis has been made as early as 12 weeks of gestation. The diagnosis may be made difficult by flexed fetal limbs. The detection rate in the United States is approximately 75% with the use of ultrasonogram. Frequent ultrasonograms may be necessary to monitor potential injury to the fetal intestines as the pregnancy progresses. A blood clot around the umbilicus as a result of a traumatic amniocentesis or premature detachment of the placenta may mimic gastroschisis on an ultrasonogram.

Once the infant is born and has received corrective surgery, radiographs and bowel contrast studies may be necessary to diagnose intestinal complications. While these procedures are noninvasive, they expose the infant to a certain level of radiation. A computed axial tomography (CAT) scan is not considered a medically suitable method by which to diagnose gastroschisis. Magnetic resonance imaging (MRI) is not usually used for diagnosis due to high expense and limited availability.

Treatment and management

In cases of gastroschisis, the infant is usually delivered in a hospital with a neonatal intensive care unit. If the infant's other organs are mature enough, the child is often delivered at 36 weeks, often using a cesarean

section. At birth, infants with gastroschisis die without immediate corrective surgery and intensive hospital care. The infant is given intravenous fluids, and the intact intestinal contents are temporarily placed in a surgical plastic clinging film attached to the infant's stomach. The plastic film helps to prevent infection, heat loss, and dehydration.

If the fissure and intestinal spillage is small to medium, the intestines are reinserted into the abdominal cavity and the fissure is surgically closed within 12–24 hours after birth. If the fissure is large or complicated, then the procedure may occur in stages over several days. A silastic bag (silicone plastic called a silo) is used to gradually return the intestines to the abdominal cavity at each stage. Finally the silo is removed and the skin is surgically closed.

Approximately 48% of infants with gastroschisis are small for gestational age. During the recovery period, the infants receive nutrition and fluids intravenously. Once the intestines are able to receive food, infants may begin breast- or bottle-feeding. Normal feedings usually begin by the fourth week from delivery date. However, some infants with gastroschisis have associated complications that require months of intravenous feeding. Infants are discharged from the hospital once they are attaining sufficient weight gain and are followed closely over several months.

Prognosis

The overall prognosis for an infant with gastroschisis without extensive complications is very good. Most deaths occur as a result of premature delivery, infection, and bowel necrosis. The clinical outcome is not correlated with the size of the hernia as estimated using ultrasonography or with the known time of exposure to amniotic fluid. Although the survival rate is high, the postoperative hospitalization is often lengthy with complications. If the intestines sustained damage from exposure to amniotic fluid or from twisting, then the prognosis is of poorer quality. Complications that negatively influence prognosis include intestinal damage, prematurity, fetal growth restriction, and shortening of the gut secondary to irritation. Gastroschisis diagnosed prenatally may resolve in utero, causing the death of portions of the intestines. This may result in a condition known as chronic short gut syndrome with a poor prognosis, including problems with diarrhea, slow weight gain, vitamin or mineral deficiencies, and increased mortality. Spontaneous resolution of gastroschisis and closure of the abdominal hernia have been reported. Gastroschisis may also cause deformations of the fetal urinary tract, resulting in a poor prognosis.

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"Gastroschisis." MedlinePlus. September 19, 2019. <https://medlineplus.gov/ency/article/000992.htm> (accessed June 8, 2021).

ORGANIZATIONS

Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476/(202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

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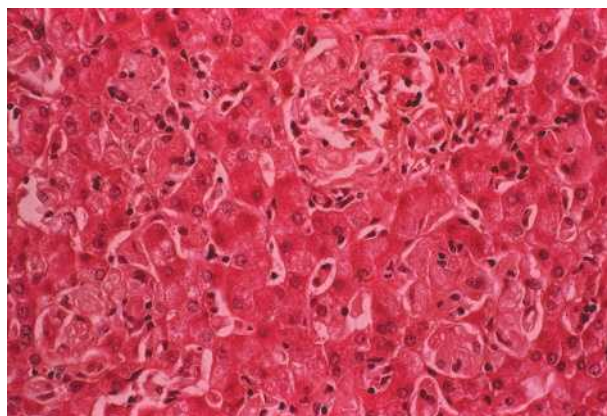
Gaucher disease

Definition

Gaucher (pronounced go-SHAY) disease is a rare genetic metabolic disorder that results in accumulation of fatty molecules called cerebrosides. It can have serious effects on many body organs, including the liver, spleen, bones, and central nervous system.

Description

Gaucher disease was first described by the French physician Philippe Gaucher in 1882. It is the most common of a class of over 50 diseases called lysosomal storage diseases, each of which is characterized by the accumulation of a different chemical substance, depending on the exact disease. Gaucher disease is characterized by a wide array of symptoms, and the severity of the disease ranges from undetectable to lethal.



Light micrograph of a human liver with Gaucher disease, a genetic disorder (autosomal recessive) that results in the deficiency of the enzyme glucocerebrosidase, which in turn results in the accumulation of the fat (lipid) glucocerebroside. (CNRI/Science Source)

Three forms of the disease are recognized: Types 1, 2, and 3. Type 1 is by far the most common and shows the mildest symptoms. It is non-neuronopathic, meaning that the central nervous system (brain and spinal cord) is not affected. The onset of Type I can occur at any age in childhood or adult life, with the average age of onset at about age 21. Some affected individuals have no symptoms throughout adult life.

Type 2, known as acute neuronopathic Gaucher disease, is present at birth or in early infancy. It accounts for fewer than 1% of patients with Gaucher disease. Type 2 attacks the nervous system, causing serious and progressive brain damage, and is often fatal within the first three months of life.

Type 3, known as chronic neuronopathic Gaucher disease, generally becomes apparent during childhood. It has some of the features of both the adult and infantile forms. This affects fewer than 5% of individuals with Gaucher disease.

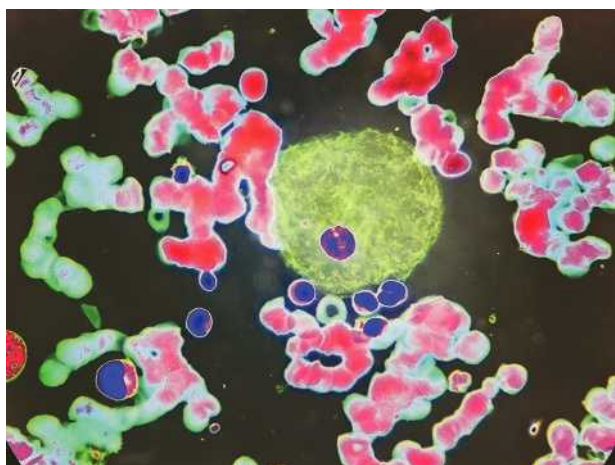
Gaucher disease is caused by the absence or near absence of activity of an enzyme called glucocerebrosidase (GC). The normal action of GC is to break down a common molecule called glucocerebroside. If not broken down, glucocerebroside accumulates in certain cells to levels that can cause damage. Especially affected are the spleen, liver, and bone. The cellular structures in which glucocerebroside accumulates are called lysosomes. The common link among these organs is that they house a large number of cells called macrophages. A macrophage is part of the immune system. It is a large cell that surrounds and consumes a foreign substance (such as bacteria) in the body.

Genetic profile

Gaucher disease is caused by mutations in the *GBA* gene on the long arm of chromosome 1, which provides the coding necessary to produce a protein called beta-glucocerebrosidase. This protein is responsible for creating an enzyme that breaks down a fatty substance called glucocerebroside into a useable glucose (sugar) and a simple fat molecule called ceramide. Mutations in the *GBA* gene prevent the breakdown of glucocerebroside and cause it to build up inside cells. Once the glucocerebroside reaches toxic levels, tissues and organs are damaged, leading to the symptoms of Gaucher disease.

Gaucher disease is inherited in an autosomal recessive pattern, which means that each parent of an individual with the disease must have one copy of the mutated gene and pass this copy on to their child. The parents typically do not show signs or symptoms of the disease. Persons with only one gene mutation are carriers for the disorder. A person who is a carrier for Gaucher disease does not have any symptoms and does not know he or she is a carrier unless he or she has had specific testing. When both parents are carriers for Gaucher disease, there is a one in four chance (25%) in each pregnancy for a child to have Gaucher disease. There is a 50% chance that a healthy child of two parents who are carriers will be a carrier of the disease.

Genetic counseling is advised for individuals with Gaucher disease, and for their relatives, to accurately assess risk and discuss testing options. For couples who have previously had a child with Gaucher disease, or in situations where both parents are carriers for known Gaucher mutations, prenatal genetic testing is available to determine whether a fetus is affected. Families in which a person has been diagnosed with Gaucher disease can have DNA testing, which enables other



Light micrograph showing Gaucher's cell and peripheral blood. (Garry DeLong/Science Source)

KEY TERMS

Cerebrosides—Fatty carbohydrates that occur in the brain and nervous system.

Enzymatic replacement therapy—A treatment method used to replace missing enzymes. It is possible to synthesize enzymes and then inject them intravenously into patients.

Glucocerebroside—A cerebroside that contains glucose in the molecule.

relatives to determine their carrier status. Prospective parents can then use that information to conduct family planning or to prepare for a child who may have special needs.

Demographics

The three forms of Gaucher disease differ in their population genetics. Type I is most common in persons of Eastern European (Ashkenazi) Jewish descent. Among that population, the disease occurs at about a rate of about one in 450 live births, and about one in 10 to 15 persons is a carrier, making it the most common genetic disease affecting Jewish people. There are about 6,000 people with Gaucher disease in the United States. The other two types occur equally in all ethnic groups. Type 2 occurs at a rate of one in 100,000 live births, while type 3 is estimated to occur in one in 50,000 live births.

Signs and symptoms

The results of Gaucher disease are widespread in the body and include excessive growth of the liver and spleen (hepatosplenomegaly), weakening of bones, and, in acute cases, severe nervous system damage. Many patients experience bone crises, which are episodes of extreme pain in their bones because of reduced blood flow.

A wide array of other problems occur with Gaucher disease, such as anemia (lower than normal amounts of red blood cells). Just how these other symptoms are caused is not known, nor is it known why some patients have very mild disease, and others have much more significant problems. Even identical twins with the disease can have differing symptoms.

Diagnosis

Diagnosis of Gaucher disease can be confirmed by microscopic, enzymatic, and molecular tests. Biopsy

QUESTIONS TO ASK YOUR DOCTOR

- How do the three types of Gaucher disease differ from each other?
- How does the fact that the disorder is especially common among some groups affect genetic testing and genetic counseling for members of those groups?
- What is the prognosis for a child diagnosed with each of the three types of Gaucher disease?
- Are there groups or organizations from which I can obtain additional information about Gaucher disease?

(surgical removal of tissue from a problem area) of tissue is helpful for microscopic diagnosis. When biopsy tissue is examined under the microscope, cells of an individual with Gaucher disease appear swollen and show characteristic features of the cytoplasm and nucleus. Enzyme tests show deficiency (30% of normal levels) of the enzyme GC. A molecular analysis of DNA samples looking at four of the more common mutations shows defects in the gene for GC in 95% of Ashkenazi Jewish individuals and in 75% of non-Jewish people.

As of 2021, an algorithm was being tested to predict type 1 Gaucher disease in individuals in the high-risk population who show signs of enlarged spleen (splenomegaly) and/or a low blood platelet count (thrombocytopenia). The algorithm uses three measurements from a blood sample: platelet count, ferritin, and transferrin saturation. Platelets are elements of the blood involved in blood clotting. Ferritin is a blood protein that stores iron, and transferrin saturation is a measure of the amount of iron in the blood. Diagnosis can also be performed prenatally (before birth) if the parents' mutations are known by using amniocentesis or chorionic villus sampling. Diagnosis as to which of the three types of Gaucher disease an individual has is based primarily on the symptoms.

Treatment and management

Until the 1990s, only supportive therapy could be offered. Analgesics are used to control pain. Orthopedic treatment is used for bone fractures. Several treatments for anemia have been used, including vitamin and iron supplements, blood transfusions, and bone marrow transplants.

Current medical treatment for Gaucher disease includes the following:

- **Enzyme replacement therapy (ERT):** ERT has been shown to be effective for patients with type 1 Gaucher disease. Imiglucerase (Cerezyme), velaglucerase alfa (VPRIV), and taliglucerase alfa (Elelyso) are all medications approved by the Food and Drug Administration (FDA) for ERT. One of these may be injected once a week, once every three weeks, or once every other week, depending on the symptoms and option chosen. This treatment has proven especially effective in reversing the impact on organ systems; however, the associated bone disease may be slow to respond. ERT has not been shown to improve the neurologic symptoms of Gaucher disease type 2 and type 3.
- **Glucosylceramide synthase inhibitors:** The glucosylceramide synthase inhibitors miglustat (Zavesca) and eliglustat (Cerdelga) have been shown effective in treating patients with type 1 Gaucher disease who do not respond to ERT. Some individuals who have had this treatment have seen improvement in symptoms involving the spleen and liver. They have also shown improvement in platelet and hemoglobin levels.
- **Surgery:** In the past, partial or total removal of the spleen was a treatment option, but with the success of ERT, this treatment is rarely used today. However, surgery may be necessary to treat the skeletal symptoms of Gaucher disease.

Researchers continue to look for drugs to improve the treatment of Gaucher disease. Clinical trials are underway. All clinical trials receiving U.S. government funding, and some supported by private industry, are posted at <https://www.clinicaltrials.gov>. Foreign trials are listed at <https://www.orpha.net>.

Prognosis

A patient's expected lifespan varies greatly with the type of Gaucher disease. Infants with type 2 disease have a lifespan of a few months to as much as four years. Patients with types 1 and 3 of the disease have highly variable outcomes, with some patients dying in childhood and others living full lives. Little is known about the reasons for this variability.

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Children’s Gaucher Research Fund, 8110 Warren Court, Granite Bay, CA 95746, (916) 797-3700, (916) 737-3707, <https://www.childrensgaucher.org>

Genetic Alliance, 26400 Woodfield Road #189, Damascus, MD 20872, (202) 966-5557, (202) 966-8553, info@geneticalliance.org, <https://www.geneticalliance.org>

National Gaucher Foundation, 5410 Edson Lane #220, Rockville, MD 20851, (800) 504-3189, <https://www.gaucherdisease.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <https://rarediseases.org>

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Gene

Definition

A gene is the fundamental physical and functional unit of heredity. It is an individual element of an organism’s genome and determines a trait or characteristic by regulating biochemical structure or metabolic process.

Description

Genes are segments of nucleic acid consisting of a specific sequence and number of the chemical units of nucleic acids, nucleotides. In most organisms, the nucleic acid is deoxyribonucleic acid (DNA), although in retroviruses, the genetic material is composed of ribonucleic acid (RNA). Some genes in a cell are active more or less all the time, which means that they are continuously transcribed and provide a constant supply of their protein product. These are the “housekeeping” genes that are always needed for basic cellular reactions. Others may be rendered active or inactive depending on the needs and functions of the organism under particular conditions. The signal that masks or unmasks a gene can come from outside the cell—for example, from a steroid hormone or a nutrient—or it can come from within the cell itself as a result of the activity of other genes. In both

cases, regulatory substances can bind to the specific DNA sequences of the target genes to control the synthesis of transcripts.

In a paper published in 1865, Gregor Mendel (1823–1884) advanced a theory of inheritance dependent on material elements that segregate independently from each other in sex cells. Before Mendel’s findings, inherited traits were thought to be passed on through a blending of the mother and father’s characteristics, much like a blending of two liquids. The term “gene” was coined later by the Danish botanist Wilhelm Johannsen (1857–1927) to replace the variety of terms used up until then to describe hereditary factors. His definition of the gene led him to distinguish between genotype (an organism’s genetic makeup) and phenotype (an organism’s appearance). Before the chemical and physical nature of genes were discovered, they were defined on the basis of phenotypic expression, and algebraic symbols were used to record their distribution and segregation. Because sexually reproducing eukaryotic organisms possess two copies of an inherited factor (or gene), one acquired from each parent, the genotype of an individual for a particular trait is expressed by a pair of letters or symbols. Each of the alternative forms of a gene are also known as alleles. Dominant and recessive alleles are denoted by the use of higher and lower case letters. It can be predicted mathematically, for example, that a single allele pair will always segregate to give a genotype ratio 1AA:2Aa:1aa, and the phenotype ratio 2A:1aa (where A represents both AA and Aa since these cannot be distinguished phenotypically if dominance is complete).

The molecular structure and activity of genes can be modified by mutations, and the smallest mutational unit is now known to be a single pair of nucleotides, also known as a muton. To indicate that a gene is functionally normal, it is assigned a plus (+) sign, whereas a damaged or mutated gene is indicated by a minus (–) sign. A wild type *Escherichia coli* bacterium able to synthesize its own arginine would thus be symbolized as *arg*+, and strains that have lost this ability by mutation of one of the genes for arginine utilization would be *arg*–. Such strains, known as arginine auxotrophs, would not be able to grow without a supplement of arginine. At this level of definition, the plus or minus actually refers to an operon rather than a single gene, and finer genetic analysis can be used to reveal the exact location of the mutated gene.

The use of mutations in studying genes is well illustrated in a traditional genetic test called the cis-trans test, which also gave the gene the alternative name “cistron.” This is a complementation test that can be used to determine whether two different mutations (m1 and m2) occur in the same functional unit, i.e., within the same gene or cistron. It demonstrates how genes can be defined

phenomenologically and has been performed successfully in microorganisms such as yeasts.

It works on the principle that pairs of homologous chromosomes containing similar genes can complement their action. Two types of heterozygotes of the test organism are prepared. Heterozygotes are organisms with different alleles in the two homologous chromosomes, each of which was inherited from one parent. One heterozygote contains the mutations under investigation within the same chromosome, that is in the *cis*-configuration, which is symbolically designated ++/m1m2 (m1 and m2 are the two mutations under investigation, and the symbol “+” indicates the same position on the homologous chromosome in the unmutated, wild type state). The second mutant is constructed to contain the mutations in such a way that one appears on each of the homologous chromosomes. This is called the *trans*-configuration and is designated, for example, by m2+/+m1.

If two recessive mutations are present in the same *cis*-tron, the heterozygous *trans*-configuration displays the mutant phenotype, whereas the *cis*-configuration displays the normal, wild type phenotype. This is because in the *cis*-configuration, there is one completely functional unmutated *cistron* (++) within the system, which masks the two mutations on the other chromosome and allows for the expression of the wild type phenotype. If one or both mutations are dominant, and the *cis*- and *trans*-heterozygotes are phenotypically different, then both mutations must be present in the same *cistron*. Conversely, if the *cis*- and *trans*-heterozygotes are phenotypically identical, this is taken as evidence that the mutations are present in different *cistrons*.

In 1910, the American geneticist Thomas Hunt Morgan (1866–1945) began to uncover the relationship between genes and chromosomes. He discovered that genes were located on chromosomes and that they were arranged linearly and associated in linkage groups, with all the genes on one chromosome being linked. For example, the genes on the X and Y chromosomes are said to be sex-linked because the X and Y chromosomes determine the sex of the organisms (in humans X determines femaleness and Y determines maleness). Nonhomologous chromosomes possess different linkage groups whereas homologous chromosomes have identical linkage groups in identical sequences. The distance between two genes of the same linkage group is the sum of the distances between all the intervening genes. A schematic representation of the linear arrangement of linked genes, with their relative distances of separation, is known as a genetic map. In the construction of such maps, the frequency of recombination during crossing over is used as an index of the distance between two linked genes.

Advances in molecular genetics have allowed analysis of the structure and biochemistry of genes in greater

detail. They are no longer the nebulous units described by Mendel purely in terms of their visible expression (phenotypic expression). It is now possible to understand their molecular structure and function in considerable detail.

The biological role of genes is to carry, encode, or control information on the composition of proteins. The proteins, together with their timing of expression and amount of production, are possibly the most important determinants of the structure and physiology of organisms. Each structural gene is responsible for one specific protein or part of a protein, and codes for a single polypeptide chain via messenger RNA (mRNA). Some genes code specifically for transfer RNA (tRNA) or ribosomal RNA (rRNA) and some are merely sequences that are recognized by regulatory proteins. The latter are termed regulator genes. In higher organisms, or eukaryotes, genes are organized in such a way that at one end there is a region to which various regulatory proteins can bind, for example, RNA polymerase during transcription, and at the opposite end there are sequences encoding the termination of transcription. In between lies the protein encoding sequence. In the genes of many eukaryotes this sequence may be interrupted by intervening non-coding sequence segments called introns, which can range in number from one to many. Transcription of eukaryotic DNA produces pre-mRNA containing complementary sequences of both introns and the information carrying sections of the gene called exons. The pre-mRNA then undergoes post-transcriptional modification or processing in which the introns are excised and exons are spliced together, leaving the complete coding transcript of connected exons ready to code directly for the protein.

When the central dogma of genetics was first established, a “one gene—one enzyme” hypothesis was proposed, but today it is more accurate to restate this as a one-to-one correspondence between a gene and the polypeptide for which it codes. This is because a number of proteins are now known to be constituted of multiple polypeptide subunits coded by different genes.

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Genetic Disease Foundation, Mount Sinai School of Medicine,
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Gene editing

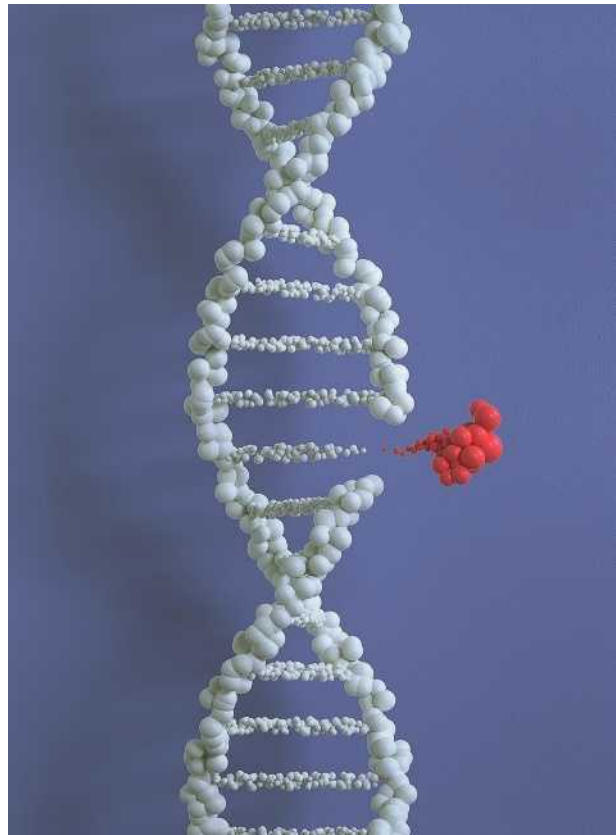
Gene editing (also called genome editing) refers to technologies that scientists can use to change an organism's DNA. Through a group of techniques, scientists can add, remove, or modify genetic material at specific locations in the genome. It is one aspect of gene therapy, which is replacement of faulty genes or an addition of genes to help cure or manage a disease.

Description

Gene-editing work began by editing genomes of organisms such as yeast and bacteria, and animals such as mice and zebrafish. Several approaches to gene editing have been attempted, many of which have proved lengthy and expensive to complete. With gene editing, there is the possibility of making changes to an individual's DNA, and therefore possibly to the DNA of future generations. Most of the technologies work like scissors to cut the DNA at a predetermined specific spot. Scientists then can remove, add, or replace genetic material where the cut was made.

Rapid advancements

The first gene editing technologies appeared in the late 1900s. Early strategies were based on nuclease systems to eliminate disease-causing genes or to repair damaged or mutated ones. Others have targeted DNA-binding proteins or meganucleases (nucleases with long DNA-bind recognition sites). Homologous recombination, an early genome-editing method that exchanged genetic information between two homologous DNA strands, was inefficient in most cell types, with a low probability that the technique would edit successfully. Zinc-finger nuclease editing improved specificity somewhat but was a difficult method to design and construct. Transcription-activator-like effector nucleases are a class of proteins used in genome editing that have offered similar effectiveness to zinc-finger nuclease editing but with a simpler design and construct.



Gene editing, in essence. (Shutterstock/Blue Andy)

CRISPR-Cas9

One approach to gene editing that has generated much interest since its 2009 development is called clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated protein 9 (Cas9). Based on RNA targeting, the technology is a simpler, faster, and less expensive way to edit genes, while also being more accurate than past methods. Scientists adapted CRISPR-Cas9 technology from a genome-editing system that occurs naturally in bacteria. When bacteriophages (viruses that attack bacteria) invade, bacteria capture tiny pieces of DNA from them and create DNA segments, which help the bacteria remember the virus. These bacteria are then able to respond to future attacks by recognizing the segments and releasing the DNA-cutting protein Cas9, which snips the genetic code of the invader.

Genome-editing methods

CRISPR technology has improved on past genome-editing methods. Within months of the new method's release, six independent reports discussed use of the system for programmable gene editing in vivo. Ex vivo gene editing removes cells from a patient, corrects them, and

KEY TERMS

Gamete—One of an organism's reproductive cells. Each contains a single (haploid) set of chromosomes.

Homologous—Similar in relation, position, value, or structure.

Nuclease—An enzyme that promotes hydrolysis of nucleic acids.

then places the corrected cells back into the patient via autologous transplantation. With in vivo editing, the patient receives injected vectors containing therapeutic elements.

Applications

Scientists have begun to develop gene therapies involving gene editing. Most research as of 2021 has focused on understanding diseases by using cells and animal models.

Laboratory

In laboratories, researchers can use genome editing to study diseases affecting humans. They edit the genes of animals such as mice, because many of the genes are similar across species (mice and humans share about 85 percent of their genes). By editing a single gene or several, researchers can observe the effects of the changes on the mouse's health to apply findings to understanding the pathology of human disease and to develop effective treatments.

Treating disease

Targeting of cells to treat diseases such as cancer has been an improvement in therapy. However, past gene therapy delivery has relied on viruses to introduce a functional transgene, since viruses have a natural ability to enter cells. Their capacity is limited, however. With nuclease-based genome editing, scientists can make targeted disruption (inactivation) of a coding sequence, substitute nucleotides successfully, target insertion of a transgene, or target alterations to non-protein coding genetic elements. In addition, the methods lead to creation of large deletions at chosen locations in the genome.

Germline gene editing

Many diseases, such as diabetes and cystic fibrosis, have a strong genetic basis. Germline gene editing involves reproductive cells. Editing of gametes or early embryos would propagate the resultant changes through

future cells of the organism. They then might be inherited by future generations, which could address hereditary diseases passed on from one generation to the next. Use of CRISPR-Cas9 can generate nuclease-induced double-stranded breaks in DNA (DSBs). These then can be repaired through homology-directed repair (HDR) or nonhomologous end-joining (NHEJ). Using CRISPR-Cas9 through NHEJ or high-fidelity HDR pathways can target genomic modifications, allowing introduction of small insertions and deletions.

Somatic gene editing

Gene editing of somatic cells (all cells other than reproductive ones) also can treat some hereditary diseases but only affect the genes of the treated individual, not passing of the disease to future generations. Applications of somatic gene editing have been at various stages of clinical development and include:

- HDR editing ex vivo to edit a non-disease-causing variant of sickle cell disease.
- In vivo HDR to express clotting factor from a strong promoter of hemophilia B.
- NHEJ editing of T-cells ex vivo to engineer resistance to HIV.
- Cancer immunotherapy in T-cells ex vivo with HDR or NHEJ to engineer more potent cancer-specific T-cells for genome editing.
- NHEJ editing in vivo to delete disease-causing expanded triplet repeat involved in Huntington's disease.

In May 2021, an example of gene-editing experiments was announced that could help restore vision to people who have a rare condition known as Leber congenital amaurosis. It was a first for editing genes in vivo, using CRISPR instruction methods delivered via viruses.

Ultimately, scientists hope that CRISPR-Cas9 methods can help remove malignant mutations from cancer patients and replace them with normal DNA sequences. As of 2020, initial success had been observed in working with leukemia and colon cancer models to promote cancer therapies. Gene editing could address infectious diseases as well. Studies also have revealed potential for treatment or prevention of some cardiovascular, metabolic, and neurodegenerative diseases through gene editing.

Ethics and acceptance

Although still in its infancy, gene editing shows breakthrough promise in disease prevention and treatment. Still, technical and ethical challenges remain. For example, as precise as CRISPR is, sometimes genome-editing tools target the wrong spot, and the errors could have consequences in patients. Therefore, assessing

QUESTIONS TO ASK YOUR DOCTOR

- Could the change you make to my genetic material pass down to my children and their children?
- What are the long-term effects of gene editing?
- Is there any way to prevent passing my disease on to my children?

safety and improving techniques are essential parts of future applications. Much of the laboratory work involving animals shows promise and advancement, but scientists also must determine whether the findings apply safely and effectively to treating disease in humans.

The ethics of gene editing are complex, affecting decisions made at laboratory and treatment points. Patient safety is foremost, as is informed consent. As a relatively new approach to medicine, gene-editing standards and regulation are still in development.

Germline gene editing in particular raises a number of ethical issues. On the one hand, safe and effective editing of germline genes could offer hope for families with inherited mutations leading to serious diseases and conditions by eliminating these mutations from their gene pool. In addition, enhancing traits such as resistance to infectious diseases could improve public health. Much debate about risks versus benefits is likely to continue, and the scientific community is approaching the technology with caution. Although editing these genes could address many inherited diseases, use of the technology to enhance human traits is unethical, and general agreement weighs against editing the genomes of germline cells as of 2021. Use of germline gene editing is largely considered premature until studied further, and its use is illegal in many countries.

Researchers continue to harness the rapid and effective results from CRISPR-Cas9 methods to learn how to modify, insert, or delete genetic material at precise locations. Eventually, the choices that scientists confront and the ethical decisions that scientists and policymakers must make will become more apparent.

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Human Genome Editing Initiative, 500 Fifth Street NW, Washington, D.C. 20001, (202) 334-2000, <https://www.nationalacademies.org/our-work/human-gene-editing-initiative>

National Center for Biotechnology Information, 8600 Rockville Pike, Bethesda, MD 20894, info@ncbi.nlm.nih.gov, <https://www.ncbi.nlm.nih.gov/>

National Human Genome Research Institute, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-9011, <https://www.genome.gov/>

Teresa G. Odle, BA, ELS

Gene fusion

Definition

Gene fusion is an alteration of genetic material from one or more events that exchange genetic information. These events typically occur in a developing embryo when genetic information is being replicated. A fusion of a gene may cause a wide variety of changes depending on the type and amount of genetic material lost or altered.

Description

Gene fusion is an abnormal event that occurs between genes on one or more chromosomes where genetic data are altered. This may occur due to a translocation event between chromosomes, an inversion event on one chromosome, or an interstitial deletion on one chromosome. Gene fusion can carry many implications depending on the alteration of the chromosomes and the rearrangement of the genetic data. Genetic data may be completely lost, partially lost, or—in most cases of cancer due to gene fusions—the expression of genetic data may be abnormally regulated, resulting in overexpression or underexpression of genes.

Recent research has determined that fusion of genes is associated with many forms of cancer. An understanding of the fusion has led to a more efficient and more effective treatment approach for these cancers.

Genetic profile

The first observance of gene fusion occurred in 1960 with the discovery of the Philadelphia chromosome associated with chronic myelogenous leukemia. Researchers found an alteration in chromosomes 9 and 22 due to a translocation event. This event transferred genetic material from chromosome 22 to chromosome 9, causing a shortening of 22 and an elongation of 9. The genetic data were fused on each chromosome, resulting in a *BCR-ABL* fusion gene. Since this first discovery, more research has been done on gene fusion events and the implications they have on the human body, specifically in regard to cancer. There are three mechanisms by which gene fusion may occur: translocation, interstitial deletion, or chromosomal inversion.

Translocation of genes may occur between chromosomes and have no negative implications. This will occur if the event is balanced and no genetic material is lost. The event is considered unbalanced if genetic material is lost and leads to an alteration in the expression of genes and proteins. An unbalanced translocation event on or between autosomal chromosomes is associated with disorders such as Down syndrome, leukemia, and other

KEY TERMS

Interstitial deletion—The deletion of a piece of one chromosome.

Inversion—A type of chromosomal defect in which a broken segment of a chromosome attaches to the same chromosome but in reverse position.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosome material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

forms of cancer. An unbalanced translocation event on or between sex chromosomes is associated with XX male syndrome due to the translocation of the *SRY* gene from the Y chromosome to the X chromosome, resulting in the expression of the *SRY* gene on the X chromosome.

Interstitial deletion of genetic information occurs when a portion of a chromosome is abnormally spliced, and the material on each side of the spliced site is fused together. This results in an abnormally shortened chromosome with missing genes. The phenotype of this event will be observed depending on the genetic material that is missing and any new or altered expression that may or may not occur.

Chromosomal inversion occurs within a single chromosome. Genetic material is spliced, the material is inverted (flipped), and then the material is reconnected to the same chromosome. If this inversion involves the centromere, it is referred to as pericentric inversion. If it does not involve the centromere, it is referred to as paracentric inversion. Much like the other two fusion events, the result of any chromosomal inversion will be determined by the genetic material altered.

Demographics

The presence of a gene fusion in different types of cancer varies. Research has shown that about 50% of prostate cancers are due to a gene fusion of *TMPRSS2-ERG*; and roughly 95% of all acute promyelocytic leukemia cases are due to a gene fusion event of *PML-RAR*.

Signs and symptoms

Gene fusion events may lead to a variety of disorders or none at all. An event that removes critical genetic

QUESTIONS TO ASK YOUR DOCTOR

- What is the result of my gene fusion?
- What genes have been altered and how does that show in my clinical case?
- What are my treatment options?
- What are the chances my children or siblings will have a gene fusion event?

material from a developing fetus may cause termination of the fetus. An event that causes a balanced fusion may have no implications and therefore no signs, symptoms, and/or pathology. Recent research has shown that multiple types of cancers are due to gene fusions on autosomal chromosomes. These cancers include breast cancer (such as *BCAS3-BCAS4* gene fusion), lung cancer, colon cancer, prostate cancer (such as *TMPRSS2-ERG* gene fusion), ovarian cancer, and multiple types of leukemia (*BCR-ABL* fusion gene in chronic myelogenous leukemia [CML]). Some of these cancers result from an upregulation of tyrosine kinase as coded by the fusion gene. Tyrosine kinase functions as an “on/off” switch for many cellular functions. When the tyrosine kinase is overactive on the “on” position, an overgrowth of cells occurs, leading to tumors and therefore cancer.

Diagnosis

Genetic testing can be performed to determine whether a gene fusion has occurred. This may include Sanger sequencing, PCR testing, fluorescence in situ hybridization (FISH), and/or whole-transcriptome sequencing (WTS). These testing methods have been successful in children with acute myeloid leukemia (AML) and in adults with prostate cancer. The hybrid sequencing approach has been useful in detecting gene fusion and the location of that fusion in patients with breast cancer. Gene fusions are very important biomarkers for cancer because they are always abnormal when present.

Treatment and management

Treatment and management of a gene fusion is based upon the genes involved and the clinical manifestations of the resulting fusion. CML, breast cancer, and prostate cancer due to a gene fusion event have recently been treated with tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib, all of which have had some success. Tyrosine kinase inhibitors work to decrease the activity of tyrosine kinase by competing with the activation site on

the enzyme. If the inhibitor binds to the activation site on the enzyme, the enzyme will not perform its coded function. Other tyrosine kinase inhibitors include sunitinib, gefitinib, and erlotinib for lung and pancreatic cancers.

Prognosis

The prognosis of a gene fusion event is fully dependent on the amount and type of genetic material lost or altered. The presence of the fusion gene *TMPRSS2-ERG* in prostate cancer, for example, has a poor prognosis due to the clinical manifestations and the lack of treatment options. Drug resistance to tyrosine kinase inhibitors may also be a factor in the prognosis of cancers and other pathologies related to gene fusion events.

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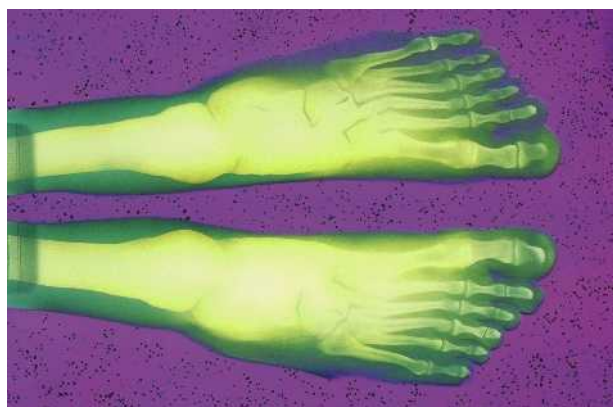
- American Cancer Society, 250 Williams St. NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org>

Taryn Terry, DC

Gene mutations

Definition

In a strict sense, mutations are changes in genes not caused by genetic recombination. A change in the base sequence of DNA, for example, represents a mutational change. Spontaneous mutations are mutations that occur at a given frequency without the need for an inducing agent of change (mutagenic agent). The term “mutation”



An x-ray of feet with six toes each, a condition known as polydactyly. It results from a genetic mutation. (Chris Bjornberg/Science Source)

is also used in a less technical sense to describe changes in the human genome (that is, evolution) that result from a broad spectrum of processes that act to increase or decrease genetic variation within a population.

Description

By definition, a gene is a hereditary unit that carries information used to construct proteins via the processes of transcription and translation. The human gene pool is the set of all genes carried within the human population. Genetic changes, including mutations, can be beneficial, neutral, or deleterious. In general, mutations, along with recombination and gene flow, act to increase genetic variation (i.e., the number of types of genes or alleles) within the human species.

The term “mutation” was originally used by the Dutch botanist Hugo De Vries (1848–1935) to describe rapid changes in phenotype from one generation to the next. Subsequently, scientists used the term “mutation” to describe long-term, multi-generational, and heritable physical changes to genes.

Mutations generally occur via chromosomal mutations, point mutations, frame shifts, and breakdowns in DNA repair mechanisms. Chromosomal mutations include translocations, inversions, deletions, and chromosome non-disjunction. Essentially there are five types of genetic rearrangements: deletions, duplications, inversions, translocations, and transposition.

Mutational deletions physically remove portions of genes (e.g., a portion of the DNA comprising the gene). Deletional mutations range from the single base point mutations to mutations that can span many functional genes. Chemical and radioactive agents account for the majority of induced point mutations. Scientists currently maintain that most cancers and other degenerative

diseases result from acquired genetic mutations due to environmental exposure, and not as an outcome of inherited traits. Chemicals capable of inducing genetic mutation (i.e., chemical mutagenesis or genotoxic compounds) include a wide variety of natural and man-made products.

Point mutations may be nonsense mutations leading to the early termination of protein synthesis; missense mutations (a mutation that results in a substitution of one amino acid for another in a protein); or silent mutations that cause no detectable change. Accordingly, the effects of point mutational changes range from 100% lethality (all individuals die, usually early in fetal development) to no observable (phenotypic) change.

Duplications result in multiple copies of genes, and can occur as a result of unequal crossover or chromosome breaks. In addition, because some alteration of DNA is inevitable in the replication process, any mutation that hinders the DNA repair mechanism increases the chance that a mutation will go uncorrected. Duplications also manifest a range of deleterious effects.

Inversions (changes in the orientation of gene bearing chromosomal regions) may cause deleterious effects if the inversion breaks through a gene critical to a particular protein or enzyme.

Translocations occur when a portion of one chromosome becomes linked to a non-homologous chromosome (a chromosome outside its normal pairing), or when portions of non-homologous chromosomes make a reciprocal exchange. Once again, the effect of such genetic change is a result of whether such translocations physically or functionally alter vital genes.

Recombination involves the reassortment of genes through new chromosome combinations. Recombination occurs via an exchange of DNA between homologous chromosomes (crossing over) during meiosis. Recombination also includes linkage disequilibrium. With linkage disequilibrium, variations of the same gene (alleles) occur in different combinations in the gametes (sexual reproductive cells) than should occur according to the rules of probability.

Gene flow occurs when individuals change their local genetic group by moving from one place to another. These migrations allow the introduction of new variations of the same gene (alleles) when they mate and produce offspring with members of their new group. In effect, gene flow acts to increase the gene pool in the new group. Because genes are usually carried by many members of a large population that has undergone random mating for several generations, random migrations of individuals away from the population or group usually do not significantly decrease the gene pool of the group left behind.

In contrast to mechanisms that operate to increase genetic variation, there are fewer mechanisms that operate to decrease genetic variation. Mechanisms that decrease genetic variation include genetic drift and natural selection.

Genetic drift results from the changes in the numbers of different forms of a gene (allelic frequency) that result from sexual reproduction. Genetic drift can occur as a result of random mating (random genetic drift) or be profoundly affected by geographical barriers, catastrophic events (e.g., natural disasters or wars that significantly affect the reproductive availability of selected members of a population), and other sociopolitical factors.

Natural selection is based upon the differences in the viability and reproductive success of different genotypes with a population (differential reproductive success). Natural selection can only act on those differences in genotype that appear as visible (phenotypic) differences that affect the ability to attract a mate and produce viable offspring that are in turn able to live, mate, and continue the species. The term “evolutionary fitness” describes the success of an entity in reproducing (i.e., contributing alleles to the next generation).

There are three basic types of natural selection. With directional selection, an extreme phenotype is favored (high or low body fat). Stabilizing selection occurs when an intermediate phenotype is fittest (for example, body fat content is neither too high nor too low), and for this reason, it is often referred to a normalizing selection. Disruptive selection occurs when two extreme phenotypes are more fit than an intermediate phenotype. In studying changes in the human genome, the operation of natural evolutionary mechanisms is complicated by geographic, ethnic, religious, and social groups and customs. Accordingly, the effects of various evolution mechanisms on human populations are not as easy to predict. Increasingly sophisticated statistical studies are carried out by population geneticists to characterize changes in the human genome.

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ORGANIZATIONS

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Gene panel testing

Definition

Gene panel testing is a laboratory technique for detecting mutations or variations in the DNA sequences of specific genes. Gene panels usually test simultaneously for different variations in multiple genes.

Purpose

There are many different gene panels used for a variety of purposes. Gene panel testing offers numerous advantages over conventional DNA sequencing of individual genes:

- Many different genes can be tested simultaneously.
- Many different mutations or variations (heterogeneity) in a single gene can be tested for simultaneously.
- Larger genes can be readily analyzed.

Diagnostic gene panel testing can definitively diagnose a genetic disorder and identify the specific gene mutation responsible for the disorder. It can also rule out a genetic disorder as the cause of symptoms. This knowledge can inform decisions about treatment and management. For example, gene panel testing can clarify a diagnosis of inherited heart disease, identify the cause of familial heart disease, and predict which family members are at risk for developing the disease. At-risk family members can then have periodic screenings and make lifestyle changes that may reduce their risk of heart disease.

Newborn screening for genetic disorders facilitates early treatment and management if a disorder is detected. For example, all newborns are tested for congenital hypothyroidism and phenylketonuria (a genetic disorder that if left untreated causes intellectual disability). In most

states, newborns are also tested for other genetic disorders.

Predictive or presymptomatic gene panel testing can detect gene mutations that increase the likelihood of developing a disease later in life. If a family member has a genetic disorder, predictive testing may indicate whether other family members will eventually develop a disorder such as hereditary hemochromatosis (iron overload in the body). For example, perhaps 5%–10% of the population is at higher risk for developing cancer because of specific inherited mutations. Such people tend to develop multiple cancers at an unusually young age. As of 2021, more than 50 hereditary cancer syndromes had been identified, including hereditary colorectal, breast, and uterine cancers; diffuse gastric cancer; Li-Fraumeni syndrome; and childhood Fanconi anemia. Multigene panel testing can detect inherited mutations in various genes that are associated with these cancers. Gene panel testing can also identify genetic variations that may increase susceptibility to a variety of disorders, including Alzheimer's disease. These types of gene panel testing may help people make decisions about their future medical care.

Reproductive gene panel testing can determine whether an embryo or fetus has a genetic disorder. Preimplantation gene panel testing is performed in conjunction with assisted reproductive technologies such as in vitro fertilization. A few cells are removed from the embryo and tested prior to implantation in the mother's uterus, thereby reducing the risk of a child with a genetic disorder. Prenatal gene panel testing may be offered to parents who are at increased risk of having a child with a genetic disorder. Negative results can reduce parental anxiety. Positive results provide parents with options, such as terminating the pregnancy or preparing for delivering and caring for a child with a disorder. For example, early detection of cystic fibrosis (CF) enables parents to plan for early monitoring and specialized care and treatment that can minimize complications and improve the child's prognosis and quality of life.

Cancers are caused by various multiple gene mutations in one or a few cells that enable them to grow uncontrollably. Specific cancer-causing mutations may respond to targeted cancer drug treatments. Gene panel testing of a tumor biopsy specimen can help identify the cancer type or subtype and select the most effective treatment. Cancer gene panel testing is also used to monitor responses to treatment and predict prognoses.

Description

Many different gene panels are used in clinical and research laboratories, and some are marketed directly to

consumers. Different panels test for mutations or variants in a single gene, a few different genes, or a large number of genes simultaneously. In addition to testing for genetic disorders, predisposition to diseases, and cancer-causing mutations, some gene panels are designed to determine familial relationships and ancestry. As new genes and mutations that cause or contribute to various diseases are discovered, they are added to existing gene panels.

Gene panel testing is performed on DNA (or sometimes RNA) that has been extracted from a variety of specimen types:

- blood
- urine
- saliva
- cells scraped from the inner cheek (a buccal swab)
- bone or other body tissues
- hair
- fetal cells obtained by chorionic villus sampling (CVS) or amniocentesis
- fetal cell-free DNA in maternal blood
- cancerous tumor cells from a biopsy

In the laboratory, the cells are isolated and broken, and the DNA is extracted. DNA sequences of suspected disease-causing or disease-susceptibility genes are compared with the DNA sequences of standard "normal" genes. The DNA is prepared for testing in different ways, depending on the gene panel technology. Enzymes can cut DNA into small pieces containing the gene(s) of interest. DNA of interest may be amplified to produce many copies and sequenced to determine the order of nucleotides (building blocks of DNA). Some gene panels are chips with DNA "probes" that "hybridize" to specific genetic variations in the samples. Others are chromosome microarrays for detecting chromosomal abnormalities. High-throughput next-generation ("next-gen") DNA sequencing has facilitated parallel sequencing of multiple genes simultaneously. Multigene panel ("multiplex") testing was introduced in the United States in 2013. It analyzes dozens of genes simultaneously at a cost that is comparable to analyzing a single gene. It accomplishes this by sequencing millions of short pieces of DNA, which are then compiled into genes using bioinformatic techniques. Prior to the advent of next-gen sequencing, gene panel testing for disease-causing mutations usually analyzed only genes that were known to be most commonly involved in a disorder. As of 2021, next-gen sequencing panels were available for cardiovascular and neurologic diseases, mitochondrial disorders, reproductive testing, and cancer genes.

Diagnostic panels

Panels for genetic or hereditary conditions generally test for specific mutations in one or a few genes that are inherited in standard Mendelian fashion. They are used for diagnosis, for defining the underlying mutation causing the disorder, or for risk assessment in individuals without symptoms. Panels usually include the most common mutations known to cause a specific disorder. For example, a panel for pathologic mutations causing hypertrophic cardiomyopathy will not include mutations associated with other cardiovascular disorders. Some panels contain mutations associated with multiple related conditions; for example, a pan-cardiomyopathy panel may include pathologic mutations for both hypertrophic cardiomyopathy and other types of cardiomyopathy. Some panels test for mutations associated with multiple diseases that result in similar clinical syndromes. Such panels can provide a specific diagnosis among several potential underlying diseases with similar symptoms, such as intellectual disability.

The newest gene panels may far exceed these descriptions. For example, the Targeted Gene Sequencing and Custom Analysis (TaGSCAN) test can identify about 95% of known gene mutations that trigger more than 750 diseases in children. The screening panel covers 514 genes associated with severe hereditary disorders, many of which are difficult-to-diagnose neurodevelopmental, immune system, and metabolic disorders and intellectual disabilities. A computer program selects the genes to be analyzed based on symptoms and family history.

Reproductive panels

Reproductive panels test for gene mutations associated with inherited genetic disorders. Preconception testing is most often performed for autosomal recessive mutations in potential parents who are at risk because of a family history. Preconception screening is sometimes performed for potential parents with no known risk factors. Prenatal testing via CVS or amniocentesis for mutations associated with a single disorder is generally used when there is a family history of a disorder. When there is no family history of an inherited disorder, prenatal screening or microarray panels usually include common mutations associated with multiple disorders. Fetal DNA obtained from maternal blood is used to screen for chromosomal aneuploidies (too many or too few chromosomes).

One of the most commonly used gene panels tests for mutations in the *CFTR* gene that cause CF. CF is an autosomal recessive disorder, so children with CF have inherited two mutated *CFTR* genes—one from each parent. The parents are carriers, each with one copy of a mutated *CFTR* gene but no symptoms of disease; however, each

of their children has a 25% risk of inheriting both mutated genes and having CF. As of 2021, more than 1,500 mutations had been identified in the *CFTR* gene, but only a few of these are common. The standard CF gene panel includes 23 of the most common mutations (occurring in more than 0.1% of the general U.S. population). Expanded panels may include 100 or more mutations to detect rare CF-causing mutations that are common to specific ethnic groups. CF gene panel testing is used as a carrier screen in the general population and high-risk subsets of the population, as well as to confirm CF diagnoses. The American College of Obstetricians and Gynecologists recommends that CF carrier screening be made available to all women of reproductive age. Fathers are not tested unless the mother tests positive for a *CFTR* mutation. If both parents are known carriers with identified *CFTR* mutations, preimplantation screening or prenatal diagnosis may be performed.

Cancer panels

Since the 2013 U.S. Supreme Court decision that invalidated patents on human genes, commercially available cancer gene panels have proliferated, and there are many more options for gene panel testing of tumor mutations. Cancer gene panels employ next-generation sequencing technologies to simultaneously test for inherited (germline) and somatic (acquired) mutations in multiple genes to assess cancer risk in people without symptoms who have a family history or other clinical indications. Panels with multiple somatic (acquired) mutations that are associated with various types of cancer are used to test tissue samples from patients' tumors to help select drugs that target specific mutations. Cancer panels vary in size from just the two inherited breast cancer susceptibility genes—*BRCA1* and *BRCA2*—to more than 50 different genes. Cancer gene panels have greatly improved the efficiency and decreased the cost of cancer genetic testing.

Precautions

Gene panel testing should be approached with caution:

- It is not available for all genes and genetic conditions, and cannot identify all inherited disorders and birth defects.
- The panels are not standardized; different commercial gene panels for the same condition may test different genes.
- Positive results from gene panel testing for susceptibility genes—and even for some causative genes—do not mean that an individual will necessarily develop the disease.

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Carrier testing—Testing performed to determine whether someone possesses one changed copy and one unchanged copy of a particular gene.

Chorionic villus sampling (CVS)—A procedure involving removal of a small placenta sample during pregnancy to obtain fetal chromosome results.

Cystic fibrosis (CF)—A respiratory disease characterized by chronic lung disease, pancreatic insufficiency, and an average age of survival of 20 years. Cystic fibrosis is caused by mutations in a gene on chromosome 7 that encodes a transmembrane receptor.

Germline mutation—A heritable change in the DNA of a germ cell (a cell destined to become an egg or in the sperm). When passed from one generation to the next, a germline mutation is incorporated in every cell of the body.

Microarray—A supporting material (usually glass or plastic) to which DNA fragments of known sequence are attached for the identification and sequencing of DNA samples.

Somatic mutations—*De novo* mutations that are acquired throughout life and affect only some cells in the body.

- A positive gene panel diagnostic test, such as for CF, confirms the diagnosis but does not predict how serious the disease will be, since even patients with identical gene mutations can have very different outcomes.
- The clinical significance of mutations and genetic variations detected by expanded gene panels is often unclear, and the number of detected variants increases as next-generation sequencing examines a larger portion of a person's genome.
- Gene panel tests can be marketed to consumers and clinicians without proof that detected gene variants are associated with disease risk.

- Misinterpretation of uncertain results by clinicians can lead to unnecessary and potentially harmful interventions and treatments.
- New sequencing technologies have a higher error rate than conventional direct DNA sequencing; thus they may be less accurate and increase the rate of false-positive results.
- Gene panel testing should be performed by a laboratory licensed for high-complexity testing. The accuracy of next-generation-sequencing gene panel testing should be comparable to that of conventional direct DNA sequencing.
- Although negative results can relieve anxiety, positive results can lead to a wide range of emotional responses, including anger, guilt, grief, fear, and depression.
- Gene panel testing is expensive and may not be covered by insurance.
- Many conditions for which gene panel testing is available are neither preventable nor treatable.
- Although predictive results from gene panel testing cannot be used to discriminate against people for employment or health insurance, in some circumstances, the results may be used to deny life insurance or long-term-care or disability insurance.

Gene panel testing for cancer susceptibility has only recently become clinically available, and there are no set guidelines for who should be offered testing. Furthermore, the results of cancer gene panel testing are becoming increasingly complex. The significance of gene variants is often unknown, and even clearly harmful mutations may be of uncertain clinical significance. The risk of uncertain results increases with the number of genes and mutations included in a panel. For example, most of the more than 100 genes included in some breast cancer gene panels have no known association with breast cancer—variants in only nine genes other than *BRCA1* and *BRCA2* have been linked to breast cancer. Furthermore, a 2015 study reported that up to half of cancer patients may not receive the most appropriate treatment if gene panel testing is performed only on their cancer tissue; rather, gene variants detected in tumor tissue must be compared to genes in the patient's normal tissue to confirm that they are involved in the cancer. The study reported that these false-positive results affect about 50% of cancer patients who have gene panel testing.

Preparation

The decision to undergo gene panel testing is a personal choice. Patients should consult with an experienced healthcare provider or genetic counselor who can discuss the benefits and pitfalls of testing. Patients should consider beforehand how they might react to positive and negative test results. Since gene panel testing often

QUESTIONS TO ASK YOUR DOCTOR

- Under what circumstances do you recommend gene panel testing?
- What type of gene panel testing do you recommend?
- Do you work with a specific genetic testing laboratory?
- Can you recommend a genetic counselor?
- Will my insurance pay for gene panel testing?

includes multiple family members, it can affect family relationships; for example, some family members may not want to be tested or may not want to share their genetic status.

Gene panel testing requires obtaining blood, urine, tissue, or other material from the patient. Fetal testing may require CVS or amniocentesis. Cancer panel testing may require a tumor biopsy.

Aftercare

Patients should consult a genetic counselor or specialist who can accurately interpret the results of gene panel testing and discuss future options, if necessary.

Results

Depending on the panel, results are available in a few weeks or months.

- Positive results mean that the laboratory is reasonably confident that it has identified a gene mutation that confirms a diagnosis, can guide treatment, or is associated with risk for a genetic disorder. The latter result may indicate steps that might help prevent the condition from developing. In some cases, a positive result indicates that other family members may want to be tested.
- Negative results only mean that a known disease-causing mutation was not found in the genes tested. A genetic cause or susceptibility may not have been detected because of the technology used; because the responsible gene was not analyzed; or because a rare mutation was not identified by the panel.
- Inconclusive results indicate that a mutation or variation was found, but its significance is unknown. This type of result is often referred to as a variant of unknown significance (VUS). However, it is possible that new

information concerning a VUS will become available in the future.

- If a gene panel test is negative or inconclusive, but the patient has symptoms, additional testing may be warranted.

Healthcare team roles

Laboratory professionals who perform and interpret gene panel tests are specially trained physicians and scientists. A geneticist or genetic counselor, as well as a specialist in the disease or disorder, should be involved in a patient's decision to have gene panel testing and in the interpretation of results.

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Gene pool

Definition

The term "gene pool" refers to the total sum of genetic information present in a population at any given time. A gene pool can be assigned to any set group or population. This is true for plants, animals, and humans alike. Each gene pool contains all of the inherited information for all of the traits of the members of the population.

Genetic information

Genetic information in the form of deoxyribonucleic acid (DNA) is passed down from generation to generation. DNA tells a person's body how to work and how to grow. It provides instructions that assign features to each individual, such as giving one person brown hair and another person blonde hair, and one person brown eyes and another person green eyes.

DNA is much like a linear string, with individual segments along the string known as genes. Genes provide the specific directions for the body. Each gene is a segment of DNA, and sequencing of the four base molecules of DNA create the gene. Variations in the sequence account for variations in genes. A gene is a unit of hereditary information with alternate versions known as alleles; each particular gene is found on the same chromosome in each individual. The long, linear strings of DNA are arranged into smaller packages known as chromosomes. In general, there are 46 chromosomes in each cell of a person's body. The 46 chromosomes can be matched into 23 pairs. One of each pair is inherited from the mother's egg and one of each pair is inherited from the father's sperm. Most animals, including humans, contain two copies of each chromosome and likewise two copies of each gene. Each individual receives one allele from each parent because they receive one of each of the 23 chromosomes from each parent.

Although each person has 46 chromosomes, the DNA that makes up those chromosomes is slightly different from individual to individual. It is this variation within specific genes that gives the diversity observed throughout populations around the world.

Alleles

Different versions of the same gene are referred to as alleles. Blood types are examples of alleles. In humans there are several different blood types, including A, B, O, and AB. These arise by various combinations of the three blood-type alleles: the A-allele, the B-allele, and the O-allele. The specific blood type a person has depends on the exact blood type alleles they inherited from their parents. For example, a person may inherit two O-alleles, in which case they would have type O blood, or they may inherit an A- and a B-allele, in which case they would have type AB blood, and so on.

Population genetics

Population genetics is the study of genetic variation within a population. This includes the subtle changes in DNA sequences and the frequencies of these different forms. Changes within the DNA sequences may arise through several pathways. Mechanisms commonly

studied by population geneticists include mutation, natural selection, and genetic drift.

Mutations are changes within the DNA sequence that alter the original directions encoded within DNA. Mutations may result from damage to DNA, or a mistake in the replication of DNA resulting in a sequence change. The majority of mutations arise by chance, although some may be caused by environmental factors, such as toxins that penetrate the cells of the body and attack the DNA. Natural selection is the difference in mortality (death rates) and fertility (birth rates) between different genetic types. The interplay of the expressed phenotype and the environment influences natural selection. If the phenotype is favorable, the individual survives and perpetuates his or her genetic profile in the gene pool. Genetic drift is a process by which the frequencies of specific alleles change, by chance, within a population.

Each gene pool accounts for all of the alleles for all of the traits of the members of a population. Within a population, different alleles will occur at different frequencies. For instance, approximately 44% of the population has type O blood, 42% of the population has type A blood, 10% of the population has type B blood, and 4% of the population has type AB blood. The percentages of each blood type are directly related to the frequency of each blood type allele. The more frequent the A-allele, the more frequent type A blood would be seen in the population.

The gene frequency of an allele is equal to the number of times the allele occurs compared to the total number of alleles for that trait.

Gene frequency equals the number of a specific type of allele, or the total number of alleles in the gene pool.

DNA changes and genetic disorders

Genetic disorders are caused by changes in the DNA sequence. In general, there is a non-disease-causing allele and a disease-causing allele. Some genetic disorders arise by sporadic mutations in the DNA sequence. Others are inherited from one or both of the parents.

There are several different inheritance patterns associated with genetic disorders. Autosomal dominant and autosomal recessive are two of the most common. Chromosomes come in pairs, one from the egg and one from the sperm. Autosomal dominant disorders require that a person inherit only one disease-causing allele in order to be affected. Even though the corresponding gene on the other chromosome in the pair may be the non-disease-causing allele, having one disease-causing allele is enough to cause the disorder to be present. Autosomal recessive disorders require that a person inherit two disease-causing alleles, one on each chromosome of the

pair, for the individual to be affected. If a person inherits only one disease-causing allele of a recessive disorder they are called a carrier. Carriers are not affected by disease; however, they carry the possibility of passing that disease on to a future child.

Hardy-Weinberg equilibrium

The frequency of disease-causing and non-disease-causing alleles along with the frequency of affected individuals, carriers, and unaffected individuals are related within a mathematical equation known as the Hardy-Weinberg equation.

The equation itself is written as $p^2 + 2pq + q^2 = 1$. For autosomal recessive disorders, p^2 represents the people within the population that have two non-disease-causing alleles (unaffected), $2pq$ represents the people within the population with one disease-causing allele and one non-disease-causing allele (carriers), and q^2 represents the people within the population that have two disease-causing alleles (affected). Because the Hardy-Weinberg equation deals with allele frequencies, the equation $p + q = 1$ may also be used. In this case, p represents the frequency of the non-disease-causing allele within the population, and q represents the frequency of the disease-causing allele within the population.

The Hardy-Weinberg equation is based on the work of Drs. Hardy and Weinberg. Independently, they suggested that there should exist an equilibrium, or balance, between different allele frequencies. They devised a list of conditions that must be true for this balance, known as the Hardy-Weinberg equilibrium, to occur. These include the following:

- No evolutionary forces are acting upon the population.
- The population is “infinitely” large (meaning it is so large that it may be assumed to be infinitely large).
- Individuals have two copies of each gene.
- There is random mating between individuals within the group.
- The frequencies of the alleles are the same in both males and females.
- Generations are non-overlapping.

The Hardy-Weinberg equation has several applications, including use by population geneticists to study the characteristics of certain populations and use by genetic counselors to calculate recurrence risks for individual families affected by genetic disease.

The future

There are several projects underway in an effort to further understand the gene pool, population genetics,

and the human genome. The Human Genome Diversity Project (HGDP) is an international project that seeks to understand the diversity and unity of the entire human species.

The Human Genome Project, a separate venture from HGDP, made the news in 2000 when scientists announced they had elucidated a working draft of the human genome sequence.

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Gene regulatory networks

Gene regulation refers to the mechanisms in place that induce or repress a gene's expression. Gene regulatory networks (GRNs) provide information about the interactions between regulators and potential targets they affect. Mathematical and computational models can help explain gene-to-gene interactions or protein-to-protein interactions.

Description

As scientists have learned more about the human genome, it has become clear that 98.5% of the genome does not appear to code for protein production. Through gathering of high-throughput expression data, researchers could infer the existence and potential of GRNs. Epigenetics addresses the types of changes that occur in gene expression through alterations to chromosomes rather than in the DNA sequence.

GRN computational modeling includes tasks such as:

- Key signal transducers, transcription factors and target genes proven as involved in activation of a targeted cellular program (typically from previous studies).
- Arrangement of known information in a network in which nodes (N) represent molecules, and the edges of the set (E) refer to relationships among molecules.
- Expression of the activation level of each N object in a discrete set of values.
- Defining of nodes as functions of the affecting edges to determine the state at each time instant of N changes.

Gene regulation

A complex process controls gene expression. Gene regulation mechanisms act to induce or repress a gene's expression. These can include structural and chemical changes to genetic material; binding of proteins to specific DNA elements to regulate transcription; or mechanisms that modulate the translation of mRNA. Certain promoters and introns affect regulation of genes. Promoters turn the transcription process on or off. Synthesizing of necessary proteins at the appropriate time guides proper function of cells, and all cells regulate transcription and translation of the cell DNA into proteins. The process at which a gene is turned on to produce RNA and protein is called gene expression. Even outside of genes, plenty of regulatory elements can modify the genes' functions. The regulators can be located far (thousands of millions of bases) away from the genes they affect. Promoters are the genes and genetic elements that regulate genes and are arranged in a linear fashion on chromosomes.



Illustration representing the gene regulatory network (GRN) of the bacterium *Escherichia coli*. The GRN is a network of nucleic acids, transcription factors, and proteins that interact to control gene expression within a cell. It allows a bacterium to respond to its environment, for example by switching on genes to process a new food source. (Equinox Graphics/Science Source)

KEY TERMS

Epigenetics—The study of how behaviors and environmental factors can lead to changes in how genes work. The changes are reversible and do not alter the DNA sequence.

Genotype—An organism's collection of genes, or the chemical composition of its DNA, which gives rise to a phenotype.

Introns—Non-coding sections of genes that are transcribed to precursors of mRNA but are edited out as mRNA matures.

mRNA—The single-stranded RNA molecule that delivers genetic instructions from the nucleus of a cell to the ribosomes, where proteins are made.

Phenotype—The observable traits of an individual, such as height, eye color, and blood type. Genotype contributes to phenotype, along with environmental factors.

Epigenetic mechanisms can regulate gene expression by modifying the chemicals of DNA bases and changing the chromosomal superstructure that packages DNA without directly altering the DNA sequence. Non-coding RNA sequences that play roles in regulating gene expression can be induced by environmental factors. There could be more than 100,000 RNA-only genes that contribute to gene regulation. In fact, researchers discovered in the first decade of the twenty-first century that the human genome contains far fewer genes than expected, and that genes are outnumbered at nearly 100 to 1 by elements that regulate genes.

Gene expression levels of bacteria are likely determined by RNA polymerase that recognizes promoter sequences to initiate transcription. Local genetic context contributes to phenotypic diversity in GRNs, and a single gene can be linked to gene expression patterns in its immediate chromosomal neighborhood.

Uncertainty

GRNs are mostly inferred based on data and are part of a highly complex biological system. Identifying important GRNs relies on study conditions, type and amount of data, experimental design, and the size of the network. Although methods might differ, the resulting inferred GRNs tend to vary little and represent similar biological information. Ensemble approaches rely on heavy computation.

QUESTIONS TO ASK YOUR DOCTOR

- If I did not inherit this disease, how did my genes cause it to develop?
- How can a gene regulatory network help diagnose or treat my condition?
- How do gene regulatory networks lead to better drugs to treat diseases?

Determining the accuracy or quality of an inferred GRN relies on including known interactions and assessing the statistical measures used. For a GRN to be complete in its ability to explain development, it should include the expression of relevant sets of cell type-specific proteins.

Usefulness

Along with other gene networks (transcriptional, protein interaction, and metabolic), GRNs interact with an individual's genotype and environmental factors to determine a phenotype. Each observable phenotype is associated with a GRN specific to that type. The more that can be learned about GRNs, the more molecular interactions can be understood. At the same time, GRNs likely are highly phenotype-specific, and they potentially represent a variety of physical biochemical interactions among genes and gene products related to a phenotype. In fact, GRNs are closer to a phenotype than are genetic or epigenetic markers.

Inferring GRNs is not the end result in their application to managing or preventing disease. Rather, the networks can help solve complex biological and biomedical interactions and problems. Current and potential applications include:

- Serving as maps or blueprints of molecular interactions.
- Capturing valuable biological information about causal interactions between gene products.
- Guiding experimental designs in genomics, including perturbations and interventions.
- Acting as biomarkers for diagnosis, prediction or screening, and prognosis.
- Increasing knowledge about interaction changes across different disease processes by comparing GRNs known to affect specific diseases. This can improve biological and biomedical understanding of phenotypes.

- Improving personalized medicine and drug design by creating connectivity maps based on molecular interaction networks.

Examples

Streptococcus pneumoniae contributes to high morbidity and mortality, yet it is part of the commensal nasopharyngeal flora. Use of synthetically generated GRNs helped to study what causes *S. pneumoniae* to transition from healthy flora to disease-causing pathogens. In a 2020 study, investigators were able to build complex GRNs such as genetic toggle switches into the pneumococcal genome for in vivo study of how gene expression regulation affects the pathogenicity.

Another 2020 study sought to explain how some vertebrate species can regenerate retinal cells after injury. Past research had identified genes that promote retinal regeneration, but not the details of the core GRNs that controlled the reprogramming of the cells. The authors found that treatments targeting GRNs that repress neurogenic competence could lead to the regeneration of retinal cells. With further study, these findings could help in the design of therapies targeted to restoring retinal neurons lost to degenerative disease.

Future

GRNs are poised to serve as critical aspects of the networks that explain gene actions and regulation. As more is learned about GRNs and their effects on disease processes, they are becoming the practical embodiment of systems biology approaches to gene expression. Gathering of more and deeper information through large and comprehensive databases will support understanding and application of holistic model interactions between molecules.

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- National Center for Biotechnology Information., 8600 Rockville Pike, Bethesda, MD 20894, info@ncbi.nlm.nih.gov, <https://www.ncbi.nlm.nih.gov/>
- National Human Genome Research Institute, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-9011, <https://www.genome.gov/>
- National Society of Genetic Counselors (NSGC), 330 N. Wabash Avenue, Suite 2000, Chicago, IL 60611, (312) 321-6834, (312) 673-6972, nsgc@nsgc.org, <http://www.nsgc.org>

Teresa G. Odle, BA, ELS

Gene therapy

Gene therapy involves treating a disease by adding, removing, or changing the genetic material in the cells of a patient. The transferred genetic material is typically DNA or RNA. Gene therapy seeks to correct abnormal genes which are not functioning properly. DNA is genetic material that contains the genes that have the instructions for the production of proteins. Proteins are responsible for the structure and all the functions of our body and cells. RNA is the genetic material that carries out the instructions for the production of proteins coded in the DNA.

Gene therapy was initially designed to treat inherited diseases, like cystic fibrosis. It is now being investigated as treatment for cancers, autoimmune-diseases like arthritis, and infectious diseases. Gene therapy can be somatic or germline. Somatic gene therapy involves adding, removing, or changing the genetic material in tissue or cells, which results in the production of a naturally



A technician uses a pipette to manipulate small quantities of liquid while doing gene therapy. (Phanie/Photo Researchers, Inc.)

occurring protein that is lacking or not functioning correctly. Germline gene therapy adds, removes, or changes the genetic material in reproductive cells, or embryos, to correct genetic defects that could be passed on to future generations.

Although gene therapy in humans has advanced rapidly, many questions surround its use. For example, some scientists are concerned that the therapeutic genes themselves may cause disease. Others fear that germline gene therapy may be used to control human development in ways not connected with disease, like intelligence or appearance.

The biological basis of gene therapy

Gene therapy has grown out of the science of genetics or how heredity works. Scientists know that life begins in a cell, the basic building block of all multicellular organisms. Humans, for instance, are made up of trillions of cells, each performing a specific function. Within the cell's nucleus (the center part of a cell that regulates its chemical functions) are pairs of chromosomes. These threadlike structures are made up of a single molecule of DNA (deoxyribonucleic acid), which carries the blueprint of life in the form of codes, or genes, that determine inherited characteristics.

A DNA molecule looks like a spiral ladder. The rungs of this ladder are called base pairs. They are made up of nitrogen molecules and arranged in specific sequences. Millions of these base pairs, or sequences, can make up a single gene, specifically defined as a segment of the chromosome and DNA that contains certain hereditary information. The gene or combination of genes formed by these base pairs ultimately direct an organism's growth and characteristics through the production of certain chemicals, primarily proteins, which carry out

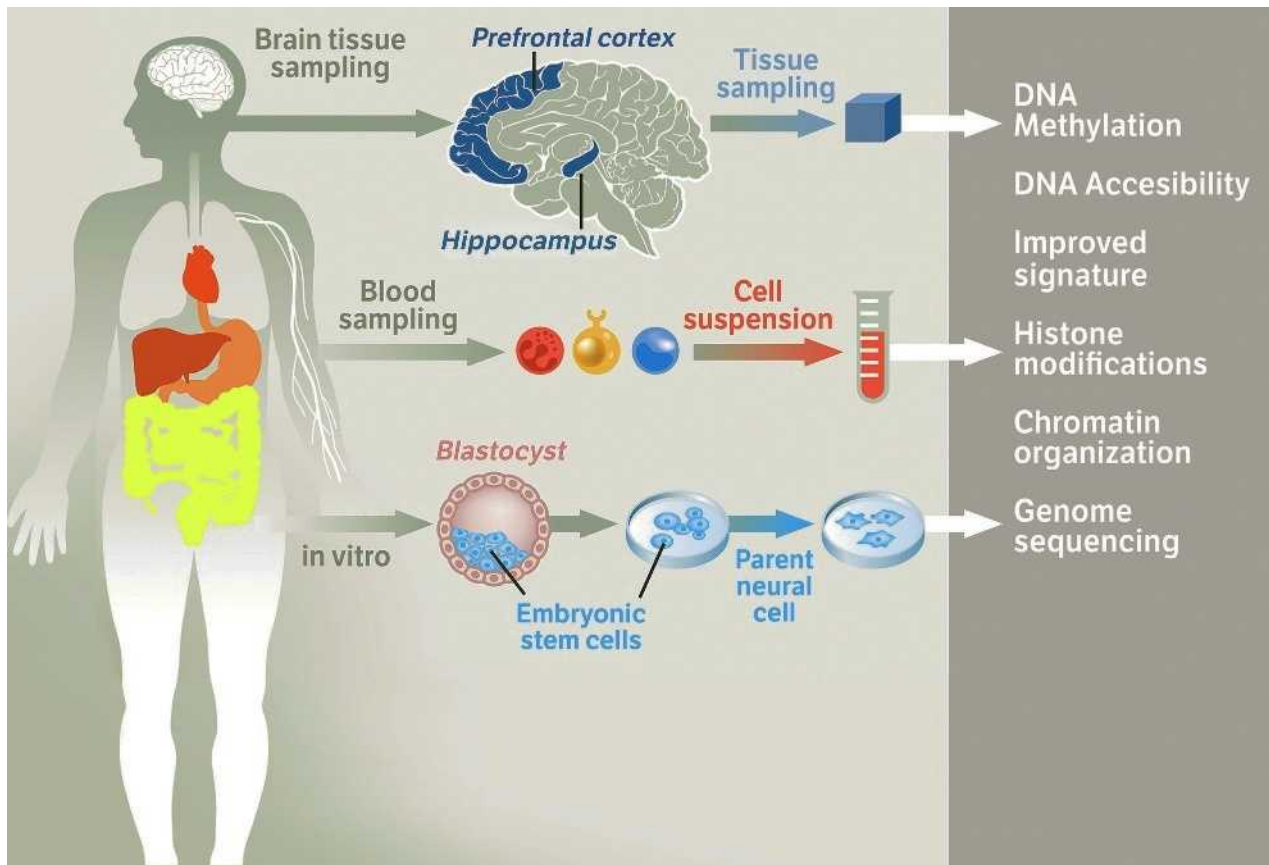


Diagram showing methods used to obtain samples for gene therapies. From top: brain tissue sampling, blood sampling, and in vitro culturing of embryonic stem cells. The brain tissue samples are from the prefrontal cortex and the hippocampus. The blood sample (three types of blood cells shown) is being processed in a cell suspension. The embryonic stem cells, from the blastocyst stage of embryo development, have been cultured in a Petri dish and used to make nerve cells. The methods include DNA methylation, histone modifications, and genome sequencing. (Jose Antonio Penas/Science Source)

most of the body's chemical functions and biological reactions.

Scientists have long known that pathogenic variants (mutations) in genes present within cells can cause inherited diseases like cystic fibrosis, sickle-cell anemia, and hemophilia. Similarly, errors in the total number of chromosomes can cause conditions such as Down syndrome or Turner syndrome. As the study of genetics advanced, however, scientists learned that an altered genetic sequence can also make people more susceptible to diseases, such as atherosclerosis, cancer, and even schizophrenia. These diseases have a genetic component but are also influenced by environmental factors (such as diet and lifestyle). The objective of gene therapy is to treat diseases by introducing functional genes into the body to alter the cells involved in the disease process by either replacing missing genes or providing copies of functioning genes to replace nonfunctioning ones. The inserted genes can be naturally occurring genes that produce the

desired effect, or they may be genetically engineered (or altered) genes.

Scientists have known how to manipulate a gene's structure in the laboratory since the early 1970s through a process called gene splicing. The process involves removing a fragment of DNA containing the specific genetic sequence desired, then inserting it into the DNA of another gene. The resultant product is called recombinant DNA, and the process is called genetic engineering.

Gene therapy approaches

There are different approaches to gene therapy. Viral and nonviral vectors were the first approaches used. More recently, different CRISPR/Cas techniques have been used.

Viral vectors

Gene therapy traditionally uses what is called a vector to transport the genetic material to the cell's nucleus. In

essence, vectors are molecular delivery trucks. Among the first and most popular vectors developed were viruses, because they invade cells as part of the natural infection process. Viruses can be excellent vectors because they colonize certain cell types and tissues in specific organs. As a result, vectors are chosen according to their attraction to certain cells and areas of the body.

One of the first vectors used was a retrovirus. Because these viruses are easily cloned (artificially reproduced) in the laboratory, scientists have studied them extensively and learned a great deal about their biological action. They have also learned how to remove the genetic information that governs viral replication, thus reducing the chances of infection.

Retroviruses work best in actively dividing cells, but cells in the body are relatively stable and do not divide often. As a result, these cells are used primarily for *ex vivo* (outside the body) manipulation. First, the cells are removed from the patient's body, and the virus or vector carrying the gene is inserted into them. Next, the cells are placed into a nutrient culture, where they grow and replicate. Once enough cells are gathered, they are returned to the body, usually by injection into the bloodstream. Theoretically, as long as these cells survive, they will provide the desired therapy.

Another class of viruses called adenoviruses may also prove to be good gene vectors. These viruses can effectively infect non-dividing cells in the body, where the desired gene product is then expressed naturally. In addition to being a more efficient approach to gene transportation, these viruses, which cause respiratory infections, are more easily purified and made stable than retroviruses, thus resulting in less chance of an unwanted viral infection. However, these viruses live for several days in the body, and some concern surrounds the possibility that the patient will infect others with the viruses through sneezing or coughing. Other viral vectors include influenza viruses, the Sindbis virus, and a herpes virus that infects nerve cells.

Nonviral vectors

Scientists have also researched nonviral vectors. These vectors rely on the natural biological process in which cells gather (uptake) macromolecules. One approach is to use liposomes, globules of fat produced by the body and taken up by cells. Scientists are also investigating the introduction of raw recombinant DNA by injecting it into the bloodstream or placing it on microscopic beads of gold shot into the skin with a "gene-gun." Another possible vector under development is based on dendrimer molecules, which are constructed in the laboratory by combining smaller molecules. They have

been used in manufacturing styrofoam, polyethylene cartons, and plexiglass. In the laboratory, dendrimers have been shown to be able to transport genetic material into human cells. They can also be designed to form an affinity for particular cell membranes by attaching to certain sugars and protein groups.

CRISPR/Cas

CRISPR/Cas is a tool derived from the immune system of bacteria that can be used in gene therapy. It can be used to change an organism's DNA by making a cut in the DNA at a specific location and tricking the body's DNA repair mechanism to make the desired change. A significant amount of research is being done to use CRISPR/Cas to treat genetic diseases such as sickle cell disease and cystic fibrosis. One promising gene therapy approach using CRISPR/Cas is called co-opting regulation bypass repair (CRBR). The CRBR technique inserts a shortened version of the normal gene with a terminator sequence at the end before the mutated version of the gene. The terminator sequence prevents the following mutated gene from being used. The advantage of this technique is that it can be used to repair any type of mutation in the gene and can be used in all types of adult tissues.

Gene therapy using CRISPR/Cas is currently only being used on humans in clinical trials. CRISPR/Cas can be used to treat genetic conditions outside of the body (*ex vivo*) and inside of the body (*in vivo*). For example, CRISPR/Cas was used to treat sickle cell disease *ex vivo*. Sickle cell disease is a genetic disease that causes abnormal red blood cells that can't properly carry oxygen throughout the body. A woman with sickle cell disease was successfully treated by removing cells from her bone marrow, using CRISPR/Cas to edit the DNA of these cells and infusing these repaired cells back into her body. Another clinical trial is testing CRISPR/Cas *in vivo* to treat a genetic cause of blindness called Leber's congenital amaurosis. The CRISPR/Cas components are injected directly into the eye to repair the DNA variation causing the blindness.

History

In the early 1970s, scientists proposed "gene surgery" for treating inherited diseases caused by faulty genes. The idea was to take out the disease-causing gene and surgically implant a gene that functioned properly. Although sound in theory, scientists, then and now, lack the biological knowledge or technical expertise needed to perform such a precise surgery in the human body.

In 1983, a group of scientists from Baylor College of Medicine in Houston, Texas, proposed that gene therapy could one day be a viable approach for treating

Lesch-Nyhan disease, a rare neurological disorder. The scientists conducted experiments in which an enzyme-producing gene (a specific type of protein) for correcting the disease was injected into a group of cells for replication. The scientists theorized that the cells could then be injected into people with Lesch-Nyhan disease, thus correcting the genetic defect that caused the disease.

As the science of genetics advanced throughout the 1980s, gene therapy gained an established foothold in the minds of medical scientists as a promising approach to treatments for specific diseases. One of the major reasons for the growth of gene therapy was scientists' increasing ability to identify the specific genetic malfunctions that caused inherited diseases. Interest grew as further studies of DNA and chromosomes (where genes reside) showed that specific genetic abnormalities in one or more genes occurred in successive generations of certain family members who had diseases including intestinal cancer, manic-depressive disorder, Alzheimer's disease, heart disease, diabetes, and many more. Although the genes may not be the only cause of the disease in all cases, they may make certain individuals more susceptible to developing the disease because of environmental influences, like smoking, pollution, and stress. In fact, some scientists theorize that all diseases may have a genetic component.

On September 14, 1990, a four-year-old girl with a genetic disorder that prevented her body from producing a crucial enzyme became the first person to undergo gene therapy in the United States. Because her body could not produce adenosine deaminase (ADA), she had a weakened immune system, making her extremely susceptible to severe, life-threatening infections. W. French Anderson and colleagues at the National Institutes of Health's Clinical Center in Bethesda, Maryland, took white blood cells (which are crucial to proper immune system functioning) from the girl, inserted ADA-producing genes into them, and then transfused the cells back into her body. Although the young girl continued to show an increased ability to produce ADA, debate arose as to whether the improvement resulted from the gene therapy or from an additional drug treatment she received.

Nevertheless, a new era of gene therapy began as more and more scientists sought to conduct clinical trial (testing in humans) research in this area. In that same year, gene therapy was tested on patients with melanoma (skin cancer). The goal was to help them produce antibodies (disease-fighting substances in the immune system) to battle the cancer.

These experiments have spawned an ever-growing number of attempts at gene therapies designed to perform a variety of functions in the body. For example, a gene

therapy for cystic fibrosis aims to supply a gene that alters cells, enabling them to produce a specific protein to battle the disease. Another approach was used for brain cancer patients, in which the inserted gene was designed to make the cancer cells more likely to respond to drug treatment. Gene therapy for patients who have artery blockage, which can lead to strokes, induces the growth of new blood vessels near clogged arteries, thus promoting improved blood circulation.

Currently, there are a host of new gene therapy agents in clinical trials. In the United States, both nucleic acid-based (*in vivo*) treatments and cell-based (*ex vivo*) treatments are being investigated. Nucleic acid-based gene therapy uses vectors (like viruses) to deliver modified genes to target cells. Cell-based gene therapy techniques remove cells from the patient in order to genetically alter them and then reintroduce them into the patient's body. Currently, gene therapies for the following diseases are being developed: cystic fibrosis (using adenoviral vector), HIV infection (cell-based), malignant melanoma (cell-based), Duchenne muscular dystrophy (cell-based), hemophilia B (cell-based), kidney cancer (cell-based), Gaucher disease (retroviral vector), breast cancer (retroviral vector), and lung cancer (retroviral vector). When a cell or individual is treated using gene therapy, and successful incorporation of engineered genes has occurred, the cell or individual is said to be transgenic.

The medical establishment's contribution to transgenic research has been supported by increased government funding. In 1991, the U.S. government provided \$58 million for gene therapy research, with increases in funding of \$15–40 million dollars per year over the following four years. With fierce competition over the promise of societal benefit in addition to huge profits, large pharmaceutical corporations have moved to the forefront of transgenic research. In an effort to be first in developing new therapies, and armed with billions of dollars of research funds, such corporations are making impressive strides toward making gene therapy a viable reality in the treatment of once-elusive diseases.

Diseases targeted by gene therapy

The potential scope of gene therapy is enormous. More than 4,200 diseases have been identified as resulting directly from abnormal genes, along with countless others that may be partially influenced by a person's genetic makeup. Initial research has concentrated on developing gene therapies for diseases whose genetic origins have been established, and for other diseases that can be cured or ameliorated by substances that genes produce.

The following are examples of potential gene therapies. People who have cystic fibrosis lack a gene needed to produce a salt-regulating protein. This protein regulates the flow of chloride into epithelial cells (the cells that line the inner mucous membranes and outer skin layers), which cover the air passages of the nose and lungs. Without this regulation, patients with cystic fibrosis build up a thick mucus that makes them prone to lung infections. A gene therapy technique to correct this abnormality might employ an adenovirus to transfer a normal copy of what scientists call the cystic fibrosis transmembrane conductance regulator, or *CFTR* gene. The gene is introduced into the patient by spraying it into the nose or lungs.

Familial hypercholesterolemia (FH) is also an inherited disease, resulting in the inability to process cholesterol properly, which leads to high levels of artery-clogging fat in the bloodstream. Patients with FH often have heart attacks and strokes because of blocked arteries. A gene therapy approach used to battle FH is much more intricate than most gene therapies because it involves partial surgical removal of patients' livers (*ex vivo* transgene therapy). Corrected copies of a gene that serves to reduce cholesterol buildup are inserted into the liver sections, which are then transplanted back into the patients.

Gene therapy has also been tested on patients with AIDS. The disease is caused by the human immunodeficiency virus (HIV), which weakens the body's immune system to the point that patients are unable to fight off diseases like pneumonia and cancer. In one approach, genes that produce specific HIV proteins have been altered to stimulate immune system functioning without causing the negative effects that a complete HIV unit has on the immune system. These genes are then injected in the patient's bloodstream. Another approach to treating AIDS is to insert via white blood cells genes that have been genetically engineered to produce a receptor that would attract HIV and reduce its chances of replicating.

Several cancers also have the potential to be treated with gene therapy. A therapy tested for melanoma, or skin cancer, involves introducing a gene with an anticancer protein called tumor necrosis factor (TNF) into test tube samples of the patient's own cancer cells, which are then reintroduced into the patient. In brain cancer, the approach is to insert a specific gene that increases the cancer cells' susceptibility to a common drug used in fighting the disease.

Gaucher disease is an inherited disease caused by a mutant gene that inhibits the production of an enzyme called beta-glucocerebrosidase. Patients with Gaucher disease have enlarged livers and spleens, and eventually

their bones deteriorate. Clinical gene therapy trials focus on inserting the gene for producing this enzyme.

Gene therapy is also being considered as an approach to solving a problem associated with a surgical procedure known as balloon angioplasty. In that procedure, a stent (in this case, a type of tubular scaffolding) is used to open the clogged artery. However, in response to the trauma of the stent insertion, the body initiates a natural healing process that produces too many cells in the artery and results in restenosis, or reclosing of the artery. The gene therapy approach to preventing this unwanted side effect is to cover the outside of the stents with a soluble gel that contains vectors for genes that reduce this overactive healing response.

The Human Genome Project

Although great strides have been made in gene therapy in a relatively short time, its potential usefulness has been limited by lack of scientific data concerning the multitude of functions that genes control in the human body. For instance, it is now known that the vast majority of genetic material does not store information for the creation of proteins; rather, it is involved in the control and regulation of gene expression and is therefore much more difficult to interpret. Even so, each individual cell in the body carries 20,000 genes coding for proteins. For gene therapy to advance to its full potential, scientists must discover the biological role of each of these individual genes and where the base pairs that make them up are located on DNA.

To address this issue, the National Institutes of Health initiated the Human Genome Project (HGP) in 1990. Completed in April 2003 and led by James D. Watson (one of the co-discoverers of the chemical makeup of DNA), the HGP provided the map for reading the human genome (a combination of the words *gene* and *chromosomes*). A genome map would clearly identify the location of all genes as well as the more than three billion base pairs that make them up. With a precise knowledge of gene locations and functions, scientists may one day be able to conquer or control diseases that have plagued humanity for centuries.

Scientists participating in the Human Genome Project identified an average of one new gene a day. Their goal was to determine the exact location of all of the genes on human DNA and the exact sequence of the base pairs that make them up. Some of the genes identified through this project include a gene that predisposes people to obesity, one associated with programmed cell death (apoptosis), a gene that guides HIV viral reproduction, and the genes of inherited disorders such as Huntington's disease, Lou Gehrig's disease, and some colon and breast

cancers. In February 2001, scientists published a rough draft of the complete human genome. With fewer than the anticipated number of genes found, around 30,000, the consequences of this announcement were enormous. When the human genome is completed, there will be more information available for gene therapy research and implementation.

The future of gene therapy

Gene therapy seems elegantly simple in its concept: supply the human body with a gene that can correct a biological malfunction that causes a disease. However, there are many obstacles and some distinct questions concerning the viability of gene therapy. For example, viral vectors must be carefully controlled lest they infect the patient with a viral disease. Some vectors, like retroviruses, can also enter cells functioning properly and interfere with the natural biological processes, possibly leading to other diseases. Other viral vectors, like the adenoviruses, are often recognized and destroyed by the immune system, so their therapeutic effects are short-lived. Maintaining gene expression so that it performs its role properly after vector delivery is difficult. As a result, some therapies need to be repeated often to provide long-lasting benefits.

One of the most pressing issues is gene regulation. Genes work in concert to regulate their functioning. In other words, several genes may play a part in turning other genes on and off. For example, certain genes work together to stimulate cell division and growth, but if these are not regulated, the inserted genes could cause tumor formation and cancer. Another difficulty is in learning how to make the gene go into action only when needed. For the best and safest therapeutic effort, a specific gene should turn on, for example, when certain levels of a protein or enzyme are low and must be replaced. But the gene should also remain dormant when not needed, to ensure that it does not oversupply a substance and disturb the body's delicate chemical makeup.

One approach to gene regulation is to attach other genes that detect certain biological activities and then react as a type of automatic off-and-on switch that regulates the activity of the other genes according to biological cues. Although still in the rudimentary stages, researchers are making headway in inhibiting some gene functioning by using a synthetic DNA to block gene transcriptions (the copying of genetic information). This approach may have implications for gene therapy.

Ethical concerns

While gene therapy holds promise as a revolutionary approach to treating disease, ethical concerns over its use

and ramifications have been expressed by scientists and lay people alike. For example, since much needs to be learned about how these genes actually work and their long-term effect, is it ethical to test these therapies on humans, where they could have a disastrous result? As with most clinical trials concerning new therapies, including many drugs, the patients participating in these studies have usually not responded to more established therapies and are often so ill that the novel therapy is their only hope for long-term survival.

Another questionable outgrowth of gene therapy is that scientists could possibly manipulate genes to genetically control traits in human offspring that are not health-related. For example, perhaps a gene could be inserted to ensure that a child would not be bald—a seemingly harmless goal. However, what if genetic manipulation were used to alter skin color or ensure good looks? If a gene is found that can enhance intelligence of children who are not yet born, will everyone in society, the rich and the poor, have access to the technology, or will it be so expensive that only the elite can afford it?

The Human Genome Project, which plays such an integral role for the future of gene therapy, also has social repercussions. If individual genetic codes can be determined, will such information be used against people? For example, will someone who is more susceptible to a disease have to pay higher insurance premiums or be denied health insurance altogether? Will employers discriminate between two potential employees, one with a “healthy” genome, and the other with genetic abnormalities?

Some of these concerns can be traced back to the eugenics movement, which was popular in the first half of the twentieth century. This genetic “philosophy” was a societal movement that encouraged people with “positive” traits to reproduce, while those with less desirable traits were discouraged from having children. Eugenics was used to pass strict immigration laws in the United States, barring less suitable people from entering the country lest they reduce the quality of the country's collective gene pool. Probably the most notorious example of eugenics in action was the rise of Nazism in Germany, which resulted in the Eugenic Sterilization Law of 1933. The law required sterilization for those with certain disabilities and even for some who were simply deemed “ugly.” To ensure that this novel science is not abused, many governments have established organizations specifically for overseeing the development of gene therapy. In the United States, the Food and Drug Administration and the National Institutes of Health require scientists to take a precise series of steps and meet stringent requirements before approving clinical trials.

Gene therapy has been immersed in more controversy and surrounded by more scrutiny in both the health and ethical arena than most other technologies (except, perhaps, for cloning) that promise to substantially change society. Despite the health and ethical questions surrounding gene therapy, the field will continue to grow and is likely to change medicine more quickly than any previous medical advance.

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Genetic anthropology

Definition

Genetic anthropology, also known as molecular anthropology, is a branch of science that combines genetic testing with archaeological, linguistic, historical, and cultural information to find out more about humans and learn how they relate to other species.

Description

The field of genetic anthropology was identified in 1962 when Émile Zuckerkandl first introduced the term *molecular anthropology*. The field of genetic anthropology at the time was primarily limited to the study of human evolution and human genetic relationship to other primates.

After that the field expanded, applying genetic information to analyze other subjects such as:

- the history of human populations
- the migration of different populations
- the characterization of DNA in extinct human ancestors
- human variation
- human adaptation to changing environments

Tools used in genetic anthropology

Genetic anthropology initially relied on rudimentary tools such as analyzing proteins. As the field advanced, so did the tools used in genetic anthropology. Genetic anthropologists learned how to use both nuclear and mitochondrial DNA in their research.

Nuclear DNA

Genetic anthropologists study nuclear deoxyribonucleic acid (DNA), the genetic material that contains the instructions for creating proteins. The nuclear DNA is packaged into chromosomes and is found in the control center (nucleus) of each cell of the body, apart from the red blood cells and platelets. All nuclear DNA in a cell, called the nuclear genome, is made up of approximately 3 billion bases. The nuclear genome contains DNA inherited from both parents.



A technician drills a sample of fossilized Neanderthal (*Homo neanderthalensis*) bone. The sample will have its genetic material extracted and sequenced as part of the Neanderthal genome project. Neanderthals were early humans who lived in Europe and the Middle East from 100,000 to 30,000 years ago. (Volker Steger/Science Source)

About 20% of the nuclear genome contains instructions for genes. A gene is a DNA sequence that contains the instructions for proteins. Ninety percent of the genome consists of DNA that does not have instructions for protein. This part of the nuclear genome includes repeated DNA sequences, some of which are found throughout the genome and some of which are clustered together. These repeated sequences are particularly important for the study of evolution and the relationship of humans to primates in the field of genetic anthropology.

Mitochondrial DNA

Genetic anthropologists also study mitochondrial DNA, structures found in the cell (organelles) surrounded by two layers of membrane. Mitochondria turn energy from food into energy that powers the cell. They also help the cell produce heat and store calcium, and they help determine which damaged cells need to be destroyed. Mitochondrial DNA (mtDNA) is the DNA found in the mitochondria. Mitochondrial DNA is similar in humans and non-human primates. There are many mitochondria in each cells, and, therefore, many copies of the mtDNA.

Ninety percent of the mitochondrial genome, in contrast to the nuclear genome, contains the instructions for proteins. The mitochondrial genome contains approximately 37 genes. These genes produce proteins that help the mitochondria function. There are few repetitive sequences in the mitochondrial genome.

MtDNA is only passed from a mother to her offspring through her egg; the fetus inherits an identical copy of the mother's mtDNA. Therefore, mtDNA offers a great vehicle for examining the history of various human populations and their migrations.

Research areas

The origin of modern humans

Two different models have been proposed for the origin of modern humans. One proposes that a single ancestor, *homo erectus*, gave rise to all modern humans. If this theory is correct, then the DNA of modern human individuals would be consistent and similar. Another theory is that modern humans derive from a single population from Africa. If this theory is correct, then

KEY TERMS

Cell—Building block that provides structure to the body and performs all the functions of the body. Cells contain genetic information and can copy themselves. The four main types of cells are: skin, nerve, muscle, and connective tissue.

Chromosome—The package of DNA found in each cell of the human body apart from the red blood cells. Humans have 22 pairs of autosomes (1 to 22) and one pair of sex chromosomes (XY). Females have two X chromosomes, and males have an X and Y. Normally, humans inherit one chromosome of each pair from their mother and one from their father.

DNA base—One unit in a DNA sequence. The four DNA bases are adenine (A), guanine (G), thymine (T), and cytosine (C). The sequence of these bases is the genetic code that contains the instructions for creating proteins.

DNA sequence—The order of DNA bases that contains the instructions for creating proteins. A three-base sequence in the DNA contains the instructions for making a particular amino acid.

Gene—The sequence of bases in DNA or RNA that encodes instructions for a gene product, which is either RNA or a protein.

Genome—The complete set of genetic instructions of an organism.

Hemoglobin—A protein found in the blood that transports oxygen from the lungs to the rest of the body.

Mitochondria—Structures found in the cell (organelles) surrounded by two layers of membrane. Mitochondria turn energy from food into energy that powers the cell. They also help the cell produce heat, store calcium, and choose which damaged cells need to be destroyed.

Mitochondrial mutation—Variation in the mitochondrial DNA that can affect how well the mitochondria function.

Nuclear DNA (deoxyribonucleic acid)—The genetic material that contains the instructions for creating proteins. The nuclear DNA is packaged into chromosomes and is found in the control center (nucleus) of the cell.

Nuclear genome—The complete set of nuclear DNA found in the nucleus of the cell.

presumably only African populations would have significant genetic variation.

To study which theory is more likely correct, genetic anthropologists analyzed mitochondrial DNA from Africans, Asians, and Europeans. This research supported the theory that modern humans descend from a single population in Africa since modern human genetic variation is generally small, and African populations exhibit the largest degree of genetic variation.

Evolution of humans and apes

Genetic anthropology has been used to study the evolution and similarities between humans and apes. For example, genetic anthropologists have used DNA sequencing to determine that chimpanzees are more closely related to humans than gorillas or orangutans. DNA sequencing of these species has also revealed that humans and chimpanzees diverged only about 5 million years ago.

Human adaptation to altitude

Genetic anthropologists have studied how people living in the mountainous regions of Tibet adapted to living in high altitude. Unlike visitors, who often get altitude sickness and

have higher levels of hemoglobin (a protein found in the blood that transports oxygen to the different parts of the body), mountain dwellers have adapted to low levels of oxygen without increased hemoglobin.

In one study, 1,000 women from this region were examined. Anthropologists conducted interviews, obtained family histories and collected blood and saliva samples. They found that normal hemoglobin concentrations increased the chances of a successful pregnancy. This advantage, acting over many generations, suggests how this group adapted to high altitude.

Factors contributing to high blood pressure

Researchers have studied the sociocultural and genetic factors that affect high blood pressure in African American adults. Certain genetic variants combined with exposure to racism appeared to increase the risk of high blood pressure in this population.

Genetic anthropology and tuberculosis

Anthropologists have studied the genome of tuberculosis bacteria in skeletons from Peru. Ancient Peruvians are believed to have lived several centuries before they had contact with Europeans. By sequencing the genome of

these bacteria, scientists were able to discover that these Peruvians likely contracted tuberculosis from exposure to seals. This research may foster future discoveries about how diseases mutate and jump from one species to another. It may also produce further insights into this ancient population from Peru.

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Genetic counseling

Definition

Genetic counseling is a communication process by which personal genetic risk information is translated into practical information for families. Genetic counselors are commonly health care professionals with specialized training and experience in the areas of medical genetics and counseling. They work as members of a health care team, providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions.

Purpose

Specifically, the process of genetic counseling assists families by:



A pregnant couple in genetic counseling. They had concerns about their baby after a relative tested positive for a genetic disorder. (Michelle Del Guercio/Science Source)

- Helping families understand information about birth defects or genetic disorders. This includes explaining patterns of inheritance, recurrence risks, the natural history of diseases, and genetic testing options.
- Providing nondirective supportive counseling regarding emotional issues related to a diagnosis or testing options.
- Helping individuals or families make decisions that they are comfortable with, based on their personal, ethical, and religious standards.
- Connecting families with appropriate resources, such as support groups or specific types of medical clinics, locally and nationally.

As of 2021, more than 50 universities offered genetic counseling study programs in the United States and Canada, meeting the rigorous accreditation criteria established by the American Board of Genetic Counseling (ABGC). Most genetic counseling programs are two-year programs that include course work, clinical rotations, and an independent research project. Most applicants enter the field from a variety of disciplines, including biology, genetics, psychology, and nursing.

Types of genetic counseling

Genetic counselors work with people who are concerned about the risk of an inherited disease. These patients represent several different patient populations. Prenatal genetic counseling is provided to couples who have an increased risk for birth defects or inherited conditions and are expecting a child or planning a pregnancy. Pediatric genetic counseling is provided to families with children suspected of having a genetic disorder or with children previously diagnosed with a genetic disorder. Adult genetic counseling is provided to adults with clinical features of an inherited disease or a family history of

one. Cancer genetic counseling is provided to those with a strong family history of certain types of cancer.

Prenatal genetic counseling

There are several different reasons a person or couple may seek prenatal genetic counseling. If a woman is age 35 or older and pregnant, there is an increased chance that the fetus may have a change in the number of chromosomes present. Changes in chromosome number may lead to intellectual disability and birth defects. Down syndrome is the most common change in chromosome number that occurs more often in the fetuses of older women. Couples may seek prenatal genetic counseling because of abnormal results of screening tests performed during pregnancy. A blood test called the alpha fetal protein (AFP) test is offered to all pregnant women. It tests for Down syndrome, open spine defects (spina bifida), and trisomy 18, a type of intellectual disability caused by a change in chromosome number. When this test yields abnormal results, further tests are offered in order to obtain more information about the chance of these conditions in the fetus.

Another reason that people seek prenatal genetic counseling is a family history of birth defects or inherited diseases. In some cases, blood tests of the parents may be available to indicate whether their children would be at risk of being affected. Genetic counselors assess risk in each case, help patients understand their risks, and explore how patients feel about or cope with these risks.

Prenatal tests that are offered during genetic counseling include level II ultrasounds, maternal serum AFP screening, chorionic villus sampling (CVS), and amniocentesis. Level II ultrasound is a detailed ultrasound surveying fetal anatomy for birth defects. Ultrasound is limited to detection of structural changes in anatomy and cannot detect changes in chromosome number. The maternal serum AFP screening is used to indicate whether a pregnant woman has a higher or lower chance of certain birth defects. This test can only determine the chances for a birth defect. The screening cannot diagnose a birth defect. CVS is a way to learn how many chromosomes are present in a fetus. A small piece of placental tissue is obtained for these studies during the 10th to 12th weeks of pregnancy. Amniocentesis is another way to learn how many chromosomes are present in a fetus. Amniotic fluid is obtained for these studies, usually between 16 and 18 weeks of pregnancy. There is a small risk for miscarriage with each of these tests.

Genetic counseling regarding these procedures involves the careful explanation of benefits and limitations of each testing option. The counselor also tries to explore how patients feel about prenatal testing and the

impact of such testing on the pregnancy. Genetic counselors are supportive of any decision a patient makes about whether to have prenatal tests performed.

Pediatric genetic counseling

Families or pediatricians seek genetic counseling when a child has features of an inherited condition. Any child who is born with more than one birth defect, intellectual disability, or dysmorphic features has an increased chance of having a genetic syndrome. One common type of intellectual disability in males for which genetic testing is available is fragile X syndrome. Genetic testing is also available for many other childhood illnesses, such as hemophilia and muscular dystrophy.

Genetic counselors work with medical geneticists to determine whether a genetic syndrome is present. This process includes a careful examination of family history, medical history of the child, review of pertinent medical records in the family, a physical examination of the child, and sometimes blood work or other diagnostic tests. If a diagnosis is made, then the medical geneticist and genetic counselor review what is known about the inheritance of the condition, the natural history of the condition, treatment options, further examinations that may be needed for health problems that are common in the diagnosed syndrome, and resources for helping the family.

The genetic counselor also helps the family adjust to the diagnosis by offering emotional support and counseling. Many families are devastated by receiving a diagnosis, by learning of the likely outcome for the child, and by the loss of the hoped-for healthy child. There would also be a discussion about recurrence risks in the family and who else in the family may be at risk.

Adult genetic counseling

Adults seek genetic counseling when a person in the family decides to be tested for a known genetic condition in the family, when an adult begins exhibiting symptoms of an inherited condition, or when there is a new diagnosis of someone with an adult-onset disorder in the family. In addition, sometimes the birth of a child with obvious features of a genetic disease leads to diagnosis of a parent who is affected more mildly. Genetic counseling for adults may lead to the consideration of presymptomatic genetic testing. Testing a person to determine whether they will be symptomatic for a condition before the symptoms occur is an area of controversy. Huntington's disease, a neurological disease resulting in dementia, is an example of a genetic disease for which presymptomatic testing is available. Onset of the condition occurs between 30 to 50 years of age. Huntington's disease is inherited in an autosomal dominant pattern. If a person has a parent with

QUESTIONS TO ASK YOUR DOCTOR

- Do health insurance policies normally pay for genetic counseling sessions?
- How can I be sure that the information I provide a genetic counselor will remain private and not be given to some other organization or individual?
- Should I share the information I receive from a genetic counselor with other members of my family?
- Will a genetic counselor make recommendations about possible steps to take in case our unborn child is at risk for certain genetic disorders?

the disease, their risk of being affected is 50%. Genetic counselors help patients sort through their feelings about such testing and whether the results would be helpful to them or cause anxiety.

Cancer genetic counseling

A family history of early-onset breast, ovarian, or colon cancer in multiple generations of a family is a common reason a person would seek a genetic counselor who works with cancer patients. While most cancer is not inherited, there are some families among whom a dominant gene is present and causing the disease. The genetic counselor can discuss with a patient the chance that the cancer in the family is related to a dominantly inherited gene. The counselor can also discuss the option of testing for the breast and ovarian cancer genes, *BRCA1* and *BRCA2*. In some cases, the person seeking testing has already had cancer, and in others they have not. Therefore, presymptomatic testing is also an issue in cancer genetics. Emotional support is important for these patients, as they have often lost close relatives from cancer and are fearful of their own risks. For families where a dominant form of cancer is detected through genetic testing, a plan for increased surveillance for the disease can be made.

The pedigree

In all types of genetic counseling, one important aspect of the genetic counseling session is information-gathering about family and medical history. Information-gathering is performed by drawing a chart called a pedigree, which is made of symbols and lines that represent the family history. To accurately assess the risk of inherited diseases, information about three generations of the family, including health status and/or cause of

death, is usually needed. If the family history is complicated, information from more distant relatives may be helpful, and medical records may be requested for any family members who have had a genetic disorder. Through an examination of the family history, a counselor may be able to discuss the probability of future occurrence of genetic disorders.

Ethnicity

In taking a family history, a genetic counselor asks for the patient's ethnicity or ancestral origin. There are some ethnic groups that have a higher chance of being carriers of specific genetic diseases. For instance, the chance that an African American is a carrier of a gene for sickle cell disease is one in 10 individuals. People of Jewish ancestry are more likely to be carriers of several conditions, including Tay–Sachs disease, Canavan disease, and cystic fibrosis. People of Mediterranean ancestry are more likely to be carriers of a type of anemia called thalassemia. Genetic counselors discuss inheritance patterns of these diseases, carrier risks, and genetic screening or testing options.

Consanguinity

Another question that a genetic counselor asks in taking a family history is whether the couple are related to one another by blood. The practice of marrying or having children with relatives is infrequent in the United States, but is more common in some countries. When two people are related by blood, there is an increased chance for their children to be affected with conditions inherited in a recessive pattern. In recessive inheritance, each parent of a child affected with a disease carries a single gene for the disease. The child gets two copies, one from each parent, and is affected. People who have a common ancestor are more likely than unrelated people to be carriers of genes for the same recessively inherited genes. Depending on family history and ethnic background, blood tests can be offered to couples to obtain more information about the chance for these conditions to occur.

Exposures during pregnancy

During prenatal genetic counseling, the counselor will ask about pregnancy history. If the patient has taken a medication or has had a harmful exposure (like radiation), the genetic counselor can discuss the possibility of harmful effects. Ultrasound is often a useful tool to look for some effects of exposures.

Ethical issues

Prenatal diagnosis of anomalies or chromosomal abnormalities leads to a decision about whether a couple

wishes to continue a pregnancy. Some couples chose to continue a pregnancy despite knowledge of a chromosomal abnormality. Prenatal diagnosis gives them additional time to prepare emotionally for the birth of the child and to gather resources. Others choose not to continue a pregnancy in which problems have been diagnosed. These couples have unique emotional needs. Often, the child is very much a desired addition to the family, and parents are devastated that he or she is not healthy. Presymptomatic testing for adult-onset disorders and cancer raises difficult issues regarding the need to know and the reality of dealing with abnormal results before signs of symptoms. The National Society of Genetic Counselors (NSGC) has established a code of ethics to guide genetic counselors in caring for patients. The NSGC Code of Ethics is based on four ethical principles:

- Beneficence is the promotion of personal well-being in others. The genetic counselor is an advocate for the patient.
- Nonmaleficence is the ethic of doing no harm to a patient.
- Autonomy is recognizing the value of the individual, the person's abilities, and their point of view. Important aspects of autonomy are truthfulness with patients, respecting confidentiality, and practicing informed consent.
- Justice is providing equal care for all, freedom of choice, and providing a high quality of care.

Informed consent applies to ensuring that patients fully understand the risks, benefits, and limitations of medical testing or procedures. For genetic testing and counseling, informed consent ensures that the patient fully understands the test or procedure, its benefits and limitations, and possible outcomes. Counselors and other professionals must make patients aware of possible negative outcomes as well as positive ones. Genetic counselors have the knowledge and skills to provide the appropriate information and support to patients for informed consent.

Perhaps the main ethical principle of genetic counseling is the attempt to provide nondirective counseling. This requires a patient-centered approach by providing care focused on the thoughts and feelings of the patient. New genetic tests and the transition to genomic tests, which involve multiple genes, have complicated the ethics and liability associated with genetics. Genetic counselors can help patients navigate through the unfamiliar territory of genetic testing.

Legal and social issues

Legal issues associated with the relatively new world of genetics in medicine, such as regulation of tests and

intellectual property, are broad issues for policymakers to address. Some ethical issues cross into important legal and social issues as part of genetic testing. Protecting patient health information is central to the Health Insurance Portability and Accountability Act (HIPAA), which makes all health information confidential. Genetic counselors must obtain permission from a patient in order to share test results or genetic diagnoses even before informing other family members who might be affected. Other legal and social issues associated with genetic counseling include:

- Coverage of genetic testing by insurance companies and how it might affect decisions.
- Avoiding genetic discrimination, and concerns about discrimination, that might affect patient testing decisions.
- Legal requirements or litigation involving informed consent and patient privacy.
- Liability issues related to failing to test a person.
- Failing to properly communicate test results or share them with the appropriate health providers, causing legal liability.
- Liability from over-testing or choice of tests.
- Gene editing and broad ethical and social concerns surrounding altering genes, as well as the benefits.

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Canadian Association of Genetic Counsellors (CAGC), P.O. Box 52083, Oakville, ON, L6J 7N5, Canada (905) 847-1363, (905) 847-3855, CAGCOffice@cagc-accg.ca, <http://cagc-accg.ca>

National Society of Genetic Counselors (NSGC), 330 N. Wabash Avenue, Suite 2000, Chicago, IL 60611, (312) 321-6834, (312) 673-6972, nsgc@nsgc.org, <http://www.nsgc.org>

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Genetic disorders

Definition

A genetic disorder is a disease or other health problem caused by an abnormality in a person's genome. Variations within the DNA sequence of a particular gene affect its function and may cause or predispose an individual to a particular disease. Alterations in the genome may increase the frequency of disorder and disease within entire populations.

Description

Although there are many types of genetic disorders, a specific disorder does not have to be heritable to have a genetic basis. For example, non-heritable disorders can also arise from mutations in somatic cells resulting from exposure to mutagenic factors in the environment. Mutations, whether inherited mutations that appear in every cell of the body or random mutations affecting a particular cell, can cause groups of cells to grow out of control, or inhibit the processes (contact inhibition processes) that normally prevent this from happening.

Some diseases and disorders are traced from the presence of a single form of a gene to a mutation in a specific normal gene. Other common conditions, including not only some cancers but also some forms of heart disease and diabetes, are polygenic. Variations in a number of genes, in combination with environmental conditions that determine the extent to which these genes are expressed, affect the risk that an individual will develop such conditions. The risk calculations associated with many of the disorders commonly regarded as genetic diseases are often predictable as functions of relatively simple Mendelian inheritance.

There are many types of genetic diseases and disorders resulting from a few well-established mechanisms. Autosomal dominant disorders, in which one deleterious gene or allele expresses itself over a normal complementary allele, is the mechanism underlying Crouzon disease. In contrast, phenylketonuria is an autosomal recessive disorder in which both harmful alleles must be present. There are also sex-linked diseases and disorders wherein the deleterious gene or genes lie on sex chromosomes (X and Y chromosomes). There are X-linked dominant disorders (e.g., hypoplastic amelogenesis imperfecta), X-linked recessive disorders (Menkes syndrome), and Y-linked disorders, in which the only mechanism of transmission is from father to son.

Not all genetic disorders depend on alterations to nuclear DNA. There are disorders, such as mitochondrial myopathy, that can result from alterations to mitochondrial DNA.

Genetic counseling deals with the problems associated with the diagnosis of a genetic disorder, the probable disease course, and possible treatments and management. Genetic testing is used to assess the risks of genetic disorders and the risks of recurrence. Options for dealing with the risk of a genetic disorder and its recurrence sometimes involve methods of contraception, adoption, insemination by donor sperm, and prenatal diagnosis.

Bayes' theorem is used in genetic epidemiology in order to obtain the probability of disease in a group of people with some characteristic. In addition, Bayes' theorem is able to calculate unknown conditional probabilities (PVP) from known conditional probabilities (detection rate or sensitivity). For example, biochemical and ultrasound marker-based screening use a derivation of Bayes' theorem to select patients for whom further testing for a particular disease or disorder may be appropriate.

A variation of Bayes' theorem, termed the Bart's test, is very popular in the prenatal screening projects. Bart's test allows an adjustment of the probability of the disease (expressed as 1/total) for an appropriate factor

named likelihood ratio, that is, the ratio between the detection rate and the false positive rate.

Except for genes appearing on the X or Y chromosomes in males, there are usually two copies of each gene in humans. This redundancy provides a buffer to genetic diseases and disorders. In many cases, only one correctly functioning copy of a gene is necessary. Only when an individual has obtained two copies of an abnormal recessive gene will the corresponding disease manifest itself. Inheritance of this type is called homozygous recessive.

A heterozygous individual with one allele for such a condition may be completely unaffected. In other cases, the individual may even be at an advantage, which provides a clue as to why the mutation remains in the population. Sickle cell disease, relatively common among people of African descent, is an often-fatal condition in which red blood cells become sickle-shaped when the oxygen content of the blood decreases, as it does during physical exertion. The deformed blood cells block small blood vessels, causing tissue death (necrosis) in affected areas. Although only an individual with two alleles for sickle cell will have the disease, individuals with one sickle cell allele (type pf gene) have sickle cell trait. Trait carriers only experience disease-like symptoms at extreme low-oxygen conditions such as those found at very high altitudes. On the other hand, such an individual actually gains a significant advantage relative to malarial resistance. Malaria is endemic in Africa, and the evolutionary benefit of having a large population of people who are heterozygous for the trait overcomes the disadvantage of a fatal condition affecting homozygotes with two copies of the allele. Therefore, this type of genetic disease may persist at a relatively high frequency in a population over a long period of time, even if the actual disorder is serious or potentially fatal.

With dominant alleles, one copy of a defective gene is enough to produce a disease or disorder. Genetic disorders with dominant inheritance that are lethal at an early age do not remain in the population because they kill the affected individual before he or she can reproduce. However, nonlethal dominant genetic disorders, such as the hand and foot malformation called camptobrachydactyly, do persist over time. Likewise, a lethal genetic disorder such as Huntington's disease that strikes after the individual has reached reproductive maturity can also be passed along to future generations.

If the gene associated with a disorder is found on the X chromosome, typically males are afflicted more often and/or more severely than females. That is because in females who are heterozygous for such an X-linked trait, there is a normal version of the gene to compensate. Males have only one X chromosome, so if an X-linked gene is mutated, it usually has a severe effect. X-linked genetic disorders include hemophilia and red-green color blindness.

Chromosome abnormalities, such as the addition or deletion of a chromosome, may result from errors that occur when gametes (sperm and egg) are formed, during fertilization, or during the early development of the zygote. Most chromosome aberrations are lethal, resulting in spontaneous abortion (miscarriage), or death in infancy. Only a few, including the extra copy of chromosome 21 that results in Down syndrome, produce individuals who, although affected by mental and physical abnormalities, can survive into adulthood.

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Genetic Alliance, 26400 Woodfield Road, #189, Damascus, MD 20872, (202) 966-5557, (202) 966-8553, info@geneticalliance.org, <http://www.geneticalliance.org>

Genetic Disease Foundation, Mount Sinai School of Medicine, One Gustavo L. Levy Place, Box 1497, New York, NY 10029, (212) 659-6704, <http://www.geneticdiseasefoundation.org>

National Human Genome Research Institute. National Institutes of Health, Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, (301) 402-2218, <http://www.genome.gov>

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Genetic gain

Definition

Genetic gain is a measure of achieved increase in desirable traits (characteristics) of an organism or

KEY TERMS

Carrier—Individual who has a pathogenic variant (mutation) in one copy of a gene that causes an autosomal recessive condition. Carriers often do not have symptoms. Two carriers of an autosomal recessive condition have a one-in-four (25%) chance of passing it on to their children.

DNA (deoxyribonucleic acid)—The genetic material that contains the instructions for creating proteins.

DNA base—One unit in a DNA sequence. The four DNA bases are adenine (A), guanine (G), thymine (T), and cytosine (C). The sequence of these bases is the genetic code that contains the instructions for creating proteins.

DNA sequence—The order of DNA bases that contains the instructions for creating proteins. A three-base sequence in the DNA contains the instructions for making a particular amino acid.

Gene—A unit of information on DNA that contains the instructions for making a protein.

Genetic marker—A DNA or RNA sequence variant. In plant breeding, markers can be linked to particular plant characteristic (traits).

Genome—The complete set of genetic instructions of an organism.

Genomic selection—A method in plant breeding that predicts the value of breeding stock based on genetic information.

Host—The body that the virus has infected.

Mutation rate—A measure of how often the virus makes errors when copying itself.

Pathogenic variant—Any change in the sequence of a genome that causes disease.

Protein—The building blocks for life that guide the development and functioning of the virus.

Recessive disease—Condition caused by a pathogenic variant (mutation) in both copies of a particular gene. Two carriers of an autosomal recessive condition have a one-in-four (25%) chance of passing it on to their children.

Replication—The process by which the virus makes copies of itself.

RNA (ribonucleic acid)—The genetic material that is involved in creating proteins.

Variant—Change in the sequence of a genome.

population as a result of genetic changes. Genetic gain is a key concept in the fields of quantitative genetics and breeding. Genetic gain is sometimes called gain-of-function when referring to increases in disease-causing capabilities of organisms accomplished in medical research.

Description

Genetic gain made through breeding programs improves crop yield and animal production. Genetic gain in microorganisms such as viruses results from variants that make the microorganisms more infectious or more deadly, which is useful in creating vaccines, treatments, and in biodefense research.

Genetic gain can happen naturally in the wild as the result of the increased survival of organisms with desirable genetic variants. It can also happen in the laboratory through selection of organisms with certain genetic traits or through the modification of the genome of the organism. Programs to increase genetic gain in food production work to insure that they are not resulting in too much inbreeding. Inbreeding decreases genetic variation and increases the likelihood of a recessive genetic disease. A

recessive disease develops when an offspring has a pathogenic variation in both copies of a particular gene. Offspring with a recessive disease have inherited a pathogenic variant from each carrier parent.

Genetic gain in agriculture

Genetic gain is an objective of crop breeding. Breeders seek to increase the frequency of genetic variants that increase the traits (characteristics) of interest such as disease resistance and increased yield. The factors that make it easier to achieve genetic gain for a particular trait in a particular crop include the following:

- the large role of genetics in the trait of interest
- a shorter breeding cycle
- a high degree of genetic variation
- plant stock available for breeding with the desired traits

Conventional breeding programs that increase genetic gain in agriculture are labor intensive and can take decades to complete. They involve breeding parent plants that have a high degree of variability and selecting plants for further breeding based on desirable traits.

Newer techniques use genetic markers to select plants that will be part of a breeding program. Genetic markers are DNA sequence variants that are linked to a particular plant trait or traits. Genome selection estimates the genetic worth of a plant based on analysis of a large number of genetic markers from the whole genome. Plants with higher genetic worth are more likely to contribute to genetic gain and are more valuable in breeding programs. Genetically modified crops increase genomic gain by artificially modifying the genome of the organism for better performance.

Genetic gain in infectious disease

Genetic gain can happen when viruses make copies of themselves (replicate) in order to infect a host. During replication, viruses need to make a copy of their genome. Errors can sometimes happen during replication, resulting in a new variant in the genome. Viruses with higher mutation rates are more likely to have genetic gain.

Some variants are significant enough to become dominant and increase genetic gain in the population. Variants that are more infectious or are more resistant to vaccines often become dominant because they can surpass other variants. For example, during the COVID-19 pandemic, the Alpha variant (UK) and the Delta variant (India) spread more quickly than the original virus because they were 50% to 60% more transmissible. These variants became dominant and increased the genetic gain of the virus. The potential for genetic gain also increases when the number increases of people infected with a virus. More infected people means more replication and increased likelihood of new variants.

Analyzing genetic gain in microorganisms such as viruses can help researchers study how viruses become more infectious and deadly. This type of research can involve creating genetically modified viruses with different variants in the laboratory. This activity allows researchers to improve management of viruses in the community and modify vaccines and treatments so that they work on viruses even as they evolve. This research is controversial, however, because it runs the risk that more lethal strains could mistakenly be released into the environment.

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Genetic Information Nondiscrimination Act (GINA)

Definition

The Genetic Information Nondiscrimination Act (GINA) of 2008 is a U.S. federal law that prevents discrimination in health insurance and employment based on an individual's genetic information or genetic profile.

Purpose

Genetic information is fast becoming a cornerstone of modern medicine. The use of genetic testing and genetic information for diagnosing disease and predicting susceptibility to conditions ranging from cancer to Alzheimer's disease to mental illness has increased dramatically, as has the amount of genetic information about individuals that can be obtained or bought. In 2014, approximately 700,000 Americans had their DNA sequenced, at least in part, at a cost of less than \$1,000 for a complete genome sequence. Genetic information can help people identify and understand inherited medical conditions that run in their families and their risk of having a child with a genetic disorder, as well as their risk of developing certain health conditions. This information can enable people to make lifestyle choices that may reduce their risk for certain conditions, as well as help them make important decisions about their medical care. However, the availability of genetic information leaves people increasingly vulnerable to discrimination and stigmatization based on genetic makeup.

The purpose of GINA is to encourage people to have genetic testing as an important part of their health care, without fear that the results could be used against them. Many people avoid genetic testing or revealing family medical histories that might improve their health care out of fear of genetic discrimination. For example, if genetic testing reveals a gene mutation that causes an inherited or other disorder, or increases the risk of developing a serious disease, employers might not hire or promote those people, or might even fire them. Before the enactment of the Affordable Care Act of 2010 (ACA or "Obamacare"), companies could deny people health insurance or charge them very high premiums based on their genetic information. GINA is intended to encourage people to have recommended genetic tests, as well as to feel comfortable about discussing their family medical histories, both with other family members and with healthcare providers. GINA is also intended to encourage people to volunteer for medical research and clinical trials of new tests, drugs, and therapies without fear of genetic discrimination.

The following are typical examples of genetic discrimination that GINA was designed to prevent:

- A child with a gene for a rare genetic disorder that could be controlled with therapy was denied coverage under her parents' health insurance policy, even after her state passed a law prohibiting genetic discrimination.
- A man's health insurance premiums skyrocketed after his mother tested positive for a gene causing a amyotrophic lateral sclerosis (ALS).

- A woman was fired from her job after her mother was diagnosed with familial cancer because the woman had a 50% risk of having inherited the disease.
- A 50-year-old woman was denied a promotion when it became known that early-onset Alzheimer's disease ran in her family.
- A company hoping to defend itself against potential workers' compensation claims administered genetic tests to employees without their consent; employees who refused to undergo testing faced possible dismissal.

Description

Genetic information is defined as information obtained from family medical histories and genetic test results—including test results of embryos and fetuses, and of family members up to fourth-degree relatives—as well as genetic counseling or genetic education requested or received by an individual or family member. Genetic tests are defined as analyses of DNA, RNA, chromosomes, and proteins or metabolites that detect the presence of genes, mutations, or chromosomal changes.

Title I of GINA prohibits genetic discrimination in obtaining health insurance. This means that health insurance providers cannot request, require, purchase, or use genetic information when making decisions about insurance eligibility, coverage, or premiums for individuals or their family members, nor can they require people to undergo genetic testing. Title I became effective on May 21, 2009. It is enforced by the Departments of Labor, Treasury, and Health and Human Services. However, Title I was made largely redundant by the ACA, which prohibits genetic discrimination by insurance providers in both the individual and group health insurance markets.

Title II of GINA prohibits genetic discrimination in employment. This means that employers cannot request, require, or use an individual's genetic information to make decisions about hiring, firing, promotion, pay, job assignments, or certain other terms of employment. In addition to employers, Title II applies to employment agencies, labor organizations, joint labor-management training programs, and apprenticeship programs. It went into effect on November 21, 2009. Title II is under the jurisdiction of the Equal Employment Opportunity Commission (EEOC).

GINA also requires that people participating in clinical research projects be informed of any risks associated with the project and be provided with a description of how the researchers will maintain the confidentiality of any personal genetic information obtained in the study. Health insurers or group health plans engaged in research

KEY TERMS

Affordable Care Act (ACA)—The Patient Protection and Affordable Care Act (“Obamacare”); signed into law by President Barack Obama in March of 2010, the ACA overhauled the U.S. healthcare system.

Equal Employment Opportunity Commission (EEOC)—The U.S. Government agency charged with enforcing Title II of GINA, which covers employment discrimination.

Genetic discrimination—Discrimination against people in employment or health insurance on the basis of their genetic information, including genetic testing results or a family medical history that suggests genetic predisposition to a disease.

Genetic testing—Testing of chromosomes and genes from an individual or unborn baby for a genetic condition. Genetic testing can only be done if the gene is known.

may request, but not require, that their members undergo genetic testing for clinical research.

Origins

The EEOC declared in 1995 that genetic discrimination in employment and other areas was prohibited under the Americans with Disabilities Act (ADA); however, this decision was not legally binding. That same year, Congresswoman Louise Slaughter and Senator Olympia Snow introduced federal legislation that would limit genetic discrimination in health insurance coverage. Their bill failed, as did similar legislation introduced in each successive congressional session. Subsequent introduced bills were expanded to include genetic discrimination in employment as well as health insurance. However, it took 14 years before GINA passed unanimously in the Senate and by 414 to 1 in the House of Representatives. GINA was signed into law by President George W. Bush on May 22, 2008.

Limitations

GINA does not apply to employers with fewer than 15 employees; to health benefits provided to federal employees or military personnel (TRICARE); or to health care provided by the Veterans Health Administration (VHA) or the Indian Health Service. However, these groups are protected by other regulations. The ACA protects against genetic discrimination by private individual and group health insurers. President Bill Clinton

protected federal workers from genetic discrimination by executive order in 2000. The military adopted GINA policies for TRICARE in 2008. The VHA has covered genetic and hereditary conditions since 1990, on the grounds that such conditions could be “service aggravated.” State laws may also protect people from genetic discrimination, although these vary widely. In 1991, Wisconsin became the first state to prohibit discrimination based on genetic tests. Although some state laws are more protective than GINA, most are less protective.

GINA does not prevent health insurers from basing eligibility, coverage, and premiums on an individual’s health or on symptoms, diagnosis, or treatment of a genetic condition, although it does protect against discrimination based on health information about family members. As of January 1, 2014, the ACA prohibited the denying of coverage or the institution of higher premiums based on a person’s health or preexisting conditions, including genetic conditions. Other limitations of GINA remain in effect:

- GINA is not retroactive. It does not apply to discrimination that occurred before the law’s effective dates. However, it does apply to genetic information that was collected prior to the law.
- GINA does not prohibit healthcare providers from recommending genetic tests; nor does it require health insurers to cover specific genetic tests and treatments.
- GINA does permit health insurers to ask for the minimum genetic information necessary for coverage decisions for certain medical tests or treatments. For example, in deciding whether to cover a prophylactic mastectomy (preventive breast removal), the insurer may determine whether a woman has a *BRCA* gene that greatly increases her risk of breast cancer. However, the insurer cannot use this information to discriminate against her.

Most significantly, Title I of GINA applies only to health insurance. It does not protect people from genetic discrimination in other types of insurance coverage, such as life, disability, and long-term-care insurance. As of 2015, California, Oregon, and Vermont were the only states with regulations prohibiting the use of genetic information in determining eligibility, coverage, and premiums for these types of insurance. At least one large insurance company asks prospective customers about genetic testing and informs them that refusal to disclose genetic testing results could cause their application to be denied or result in higher premiums. Other insurers were expected to eventually follow suit. Even companies that do not request genetic information can often find it in applicants’ medical records.

QUESTIONS TO ASK YOUR DOCTOR

- Do you recommend that I have genetic testing?
- What information will genetic testing provide?
- Will my genetic test results be available to my employer or insurance company?
- Could my genetic test results increase my life insurance premiums or prevent me from getting life insurance?
- How will my genetic information be kept confidential?

It appears that many people are declining genetic testing that might improve disease prevention or facilitate early diagnosis and treatment because they fear losing their life, long-term-care, or disability insurance or facing skyrocketing premiums due to test results. A Harvard Medical School study found that people who learned that they carried a gene for early-onset Alzheimer's disease were five times more likely than a control group to buy long-term-care insurance; however, they were very worried about insurance company discrimination if the test results appeared in their medical records. GINA's legislative sponsors recognized the significance of these omissions, but after the 14-year battle to pass GINA they were willing to settle for what they could get. For their part, long-term-care and life insurers argue that they need genetic information from applicants in order to make sound business decisions.

Results

People who believe that they suffered genetic discrimination in the workplace can file charges with the EEOC. As of 2014, the EEOC had received hundreds of claims from employees, former employees, and job applicants charging that companies had asked them for genetic information or used it to discriminate against them. Although many complaints have been dismissed, as of December 2013, the EEOC had filed more than 1,000 charges under GINA. The EEOC settled its first lawsuit for a GINA violation in 2013, and a second class-action lawsuit was pending in federal court as of 2014. Both cases charged employers with asking about family medical histories, such as cancer and mental disorders, during pre-employment medical exams and, in the second case, on an annual basis. In the first lawsuit, a fabrics manufacturer agreed to pay \$50,000 in compensation to a temporary worker who, when offered a permanent job, was asked to disclose her family medical history. Other job applicants at this company were also asked to provide genetic information. In settling the

complaint, the company admitted no wrongdoing but agreed to provide employees in charge of hiring with antidiscrimination training.

A 2015 federal case in Atlanta, Georgia, took GINA in an unexpected direction. Two workers were suspected of leaving feces in a grocery company warehouse. Fearing they would lose their jobs, they agreed to have DNA testing to clear themselves. However, they became the brunt of humiliating jokes and subsequently sued the company. Although the only disclosed genetic information was that the men were not responsible for the acts, the judge ruled that the DNA tests fell under GINA. The jury awarded the workers \$2.2 million.

As of 2015, it was unclear whether GINA was preventing genetic discrimination and alleviating fears among the general public. Concerns over genetic discrimination by life, disability, and long-term-care insurers are increasing with growing awareness of predictive testing for diseases such as Alzheimer's disease and breast and colon cancers. Up to 25% of volunteers in a DNA sequencing study at Harvard dropped out because of insurance concerns. Genetic counselors report that clients frequently express fear over the confidentiality of their genetic test results and ask that the results be kept out of their medical records. This, however, undermines the usefulness of genetic testing. Although some experts believe that such concerns are exaggerated, genetic discrimination can be subtle—people do not necessarily know why they are turned down for insurance coverage.

GINA controversies

Some experts argue that the repercussions of GINA are broader than many employers realize. For example, GINA limits the information that companies can use to assess their workers' fitness and to promote healthy lifestyle choices. Most large U.S. employers sponsor employee wellness programs; however, these programs can ask about family medical histories only with the participant's explicit permission, which may limit their effectiveness. Employers that have mandatory pre-employment physicals or exams can be prohibited from asking for relevant information, which some critics argue is in conflict with good medical practices. Furthermore, company physical exams are the only preventive healthcare that some people receive. Supporters of GINA argue that employers are not in a position to understand or properly utilize genetic information. In the case of the lawsuit against the fabrics manufacturer, the family medical history was requested by a third-party medical provider, but the EEOC says that employers must inform such providers about GINA restrictions.

Some researchers and bioethicists argue that typical patient consent forms do not adequately inform people

about the risk of release, re-identification, and misuse of their genetic information. For example, in 2013, researchers used genealogy websites to readily identify many supposedly anonymous individuals who had their DNA analyzed for research purposes. A Presidential Commission for the Study of Bioethical Issues recommended additional measures to safeguard genetic information. Nevertheless, legions of people are perfectly willing to share their genetic information, posting genetic test results online for anyone to see.

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- Genetic Alliance, Inc., 26400 Woodfield Road, #189, Damascus, MD 20872, (202) 966-5557, (202) 966-8553, info@geneticalliance.org, <http://www.geneticalliance.org>

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Genetic mapping

Definition

The aim of genetic mapping is to determine the linear sequence of genes in genetic material. The mapping can be performed at several levels of detail (resolution) that fall into two broad types: traditional genetic, or linkage, mapping and more detailed physical mapping.

Description

Linkage mapping shows the relative, rather than absolute, positions of genes along a chromosome and is a technique that has been used since the early 1900s. Early geneticists determined that genes were found on chromosomes. They also reasoned that because the various forms of genes, or alleles, could be precisely exchanged during meiosis through crossovers between homologous chromosomes, the genes for specific characteristics must lie at precise points along each chromosome. It followed that the mapping of chromosomes could, therefore, be made from the observation of crossovers.

Between 1912 and 1915, the American scientist Thomas Hunt Morgan (1866–1945) hypothesized that if genes were arranged linearly along chromosomes, then those genes lying closer together would be separated by crossovers less often than those lying further apart. Genes lying closer together would thus have a greater probability of being passed along as a unit. It follows that the percentage of crossovers would be proportional to the distance between two genes on a chromosome. The percentage crossover can be expressed as the number of crossovers between two genes in meiosis. One genetic map unit (m.u.) is defined as the distance between gene pairs for which one product out of 100 is recombinant (a product of crossover). S recombinant frequency (R.F.) of 0.01 (1%) is defined as 1 m.u., and a map unit is sometimes referred to as a centimorgan (cM) in honor of Thomas Hunt Morgan.

As an example of how linkage mapping might work, suppose two characteristics, A and B, show a 26% crossover. Assign 26 crossover units to the distance between these two genes. If a characteristic C turns out in breeding experiments to have 9% crossover with B and 17% crossover with A, it would then be located between A and B at a point 9 units from B and 17 units from A. Compiling the information from many such breeding experiments creates a chromosome map that indicates the relative positions of the genes that code for certain characteristics. Accordingly, the further apart any two genes are on the same chromosome, the greater the incidence of crossing over between them.

A linkage map is limited because recombination frequencies can be distorted relative to the physical distance between sites. As a result, the linkage map is not always the best possible representation of genetic material.

While linkage maps only indicate relative positions of genes, physical maps are more accurate and aim to show the actual number of nucleotides between each gene. Restriction maps are constructed by cleaving DNA into fragments with restriction enzymes. These enzymes recognize specific short DNA sequences and cut the duplex. The distances between the sites of cleavage are then measured. The positions of the target restriction sites for these enzymes along the chromosome can be used as DNA markers. Restriction sites generally exist in the same positions on homologous chromosomes, so the positions of these target sites can be used rather like milestones along a road and can act as reference points for locating significant features in the chromosome.

A map of the positions of restriction sites can be made for a localized region of a chromosome. It is made by comparing the sizes of single enzyme breakages (digests) of the region of interest with double digests of the same region. This means that two different restriction enzymes are applied, one to each of two separate chromosome extracts of the region of interest, and subsequently the two enzymes are used together in a third digestion with the chromosome extract. The chromosome fragments resulting from the three digestions are then subjected to a biochemical procedure known as gel electrophoresis, which separates them and gives an estimation of their size. Comparison of the sizes of the chromosome fragments resulting from single and double restriction enzyme digestions allows for an approximate location of the target restriction sites. Thus, such maps represent linear sequences of restriction sites. As this procedure determines the sizes of digested chromosome fragments, the distances between sites in terms of the length of DNA can be calculated, because the size of a fragment estimated from an electrophoresis experiment is proportional to the number of base pairs in that fragment.

A restriction map does not intrinsically identify sites of genetic interest. For it to be of practical use, mutations have to be characterized in terms of their effects upon the restriction sites. In the 1980s, it was shown how restriction fragment length polymorphisms (RFLPs) could be used to map human disease genes. RFLPs are inherited by Mendelian segregation and are distributed in populations as classical examples of common genetic polymorphisms. If such a DNA variant is located close to a defective gene (which cannot be tested directly), the DNA variant can be used as a marker to detect the presence of the disease-causing gene. The prenatal examination of DNA for particular enzyme sites associated with

certain hereditary diseases has proved to be an important method of diagnosis. Clinically useful polymorphic restriction enzyme sites have been detected within the beta-like globin gene cluster. For example, the absence of a recognition site for the restriction enzyme HpaI is frequently associated with the allele for sickle-cell anemia, and this association has been useful in prenatal diagnosis of this disease.

The ultimate genetic map is the complete nucleotide sequence of the DNA in the whole chromosome complement, or genome, of an organism. Several completed genome maps already exist. Simple prokaryotic organisms, such as bacteria, with their relatively small chromosomes of one to two million base pairs, were the first to be mapped. Later, eukaryotic organisms such as the yeast *Saccharomyces cerevisiae* and the nematode worm *Caenorhabditis elegans* were mapped. In 2000, the Human Genome Project produced the first draft of the human genome. The project adopted two methods for mapping the three billion nucleotides. The earlier approach was a “clone by clone” method. In this, the entire genome was cut into fragments up to several thousand base pairs long and inserted into synthetic chromosomes known as bacterial artificial chromosomes (BACs). The subsequent mapping step involved positioning the BACs on the genome’s chromosomes by looking for distinctive marker sequences called sequence tagged sites (STSs), whose location had already been pinpointed. Clones of the BACs are then broken into smaller fragments in a process known as shotgun cloning. Each small fragment was then sequenced and computer algorithms that recognize matching sequence information from overlapping fragments were used to reconstruct the complete sequence inserted into each BAC. It was later argued that the first mapping step was unnecessary and that the algorithms used to reassemble the shotgunned DNA fragments could be applied to cloned random fragments taken directly from the whole genome. In this whole-genome shotgun strategy, fragments were first assembled by algorithms into larger scaffolds and the correct position of these scaffolds on the genome was worked out by STSs. The latter method speeded up the whole procedure considerably, and is currently being used to sequence genomes from other organisms.

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Genetic testing

Definition

A genetic test seeks to identify changes in a person's chromosomes, genes, or proteins that are associated with inherited disorders. Genetic testing is performed to determine if a person has or will develop a certain disease or could pass a disease to his or her offspring. Genetic tests also determine whether or not couples are at a higher risk than the general population for having a child affected with a genetic disorder.

Purpose

Some families or ethnic groups have a higher incidence of a certain disease than does the population as a whole. For example, individuals from Eastern European, Ashkenazi Jewish descent are at higher risk for carrying genes for rare conditions that occur much less frequently in populations from other parts of the world. Before having a child, a couple from such a family or ethnic group may want to know if their child would be at risk of having that disease. Genetic testing for this type of purpose is called genetic screening.

During pregnancy, the baby's cells can be studied for certain genetic disorders or chromosomal problems such as Down syndrome. Chromosome testing is most commonly offered when the mother is 35 years or older at the time of delivery. When there is a family medical

history of a genetic disease, or there are individuals in a family affected with developmental and physical delays, genetic testing may also be offered during pregnancy. Genetic testing during pregnancy is called prenatal diagnosis.

Prior to becoming pregnant, couples who are having difficulty conceiving a child or who have had multiple miscarriages may be tested to see whether a genetic cause can be identified.

A genetic disease may be diagnosed at birth by doing a physical evaluation of the baby and observing characteristics of the disorder. Genetic testing can help to confirm the diagnosis made by the physical evaluation. In addition, genetic testing is used routinely on all newborns to screen for certain genetic diseases that can affect a newborn baby's health shortly after birth.

There are several genetic diseases and conditions in which the symptoms do not occur until adulthood. One such example is Huntington's disease. This is a serious disorder affecting the way in which individuals walk, talk, and function on a daily basis. Genetic testing may be able to determine if someone at risk for the disease will in fact develop the disease.

Some genetic defects may make a person more susceptible to certain types of cancer. Testing for these defects can help predict a person's risk. Other types of genetic tests help diagnose, predict, and monitor the course of certain kinds of cancer, particularly leukemia and lymphoma.

Precautions

Because genetic testing is not always accurate, and because there are many concerns surrounding insurance and employment discrimination for the individual receiving a genetic test, genetic counseling should always be performed prior to genetic testing. A genetic counselor is an individual with a master's degree in genetic counseling. A medical geneticist is a physician specializing and board certified in genetics.

A genetic counselor reviews the person's family history and medical records and the reason for the test. The counselor explains the likelihood that the test will detect all possible causes of the disease in question (known as the sensitivity of the test), and the likelihood that the disease will develop if the test is positive (known as the positive predictive value of the test).

Learning about the disease in question, the benefits and risks of both a positive and a negative result, and what treatment choices are available if the result is positive will help prepare the person undergoing testing. During the genetic counseling session, the individual



A scientist performing genetic testing in a laboratory. (Alexander Rath/Shutterstock)

interested in genetic testing will be asked to consider how the test results will affect his or her life, family, and future decisions.

After this discussion, the person should have the opportunity to indicate in writing that he or she gave informed consent to have the test performed, verifying that the counselor provided complete and understandable information.

A variety of genetic tests are now increasingly being offered directly to consumers, usually over the Internet. Such genetic testing usually involves scraping a few cells from inside the cheek and mailing the sample to a test laboratory where the test is performed. People considering such genetic tests should discuss the issue with their healthcare provider or a genetic counselor.

Background

Genes and chromosomes

Deoxyribonucleic acid (DNA) is a long molecule made up of two strands of genetic material coiled around each other in a unique double helix structure. This

structure was discovered in 1953 by Francis Crick and James Watson.

DNA is found in the nucleus, or center, of most cells (some cells, such as a red blood cell, do not have a nucleus). Each person's DNA is a unique blueprint, giving instructions for a person's physical traits, such as eye color, hair texture, height, and susceptibility to disease. DNA is organized into structures called chromosomes.

The instructions are contained in DNA's long strands as a code spelled out by pairs of bases, which are four chemicals that make up DNA. The bases occur as pairs, because a base on one strand lines up with and is bound to a corresponding base on the other strand. The order of these bases forms the DNA's code. The order of the bases on a DNA strand is important to ensuring a person is not affected with any genetic disorders. When the bases are out of order or missing, cells may often not produce important proteins; this can lead to a genetic disorder. While genes are found in every cell of the body, not every gene is functioning all of the time. Some genes are turned on during critical points in development and then remain

silent for the rest of an individual's life. Other genes always remain active so that cells can produce important proteins such as those that help digest food properly or fight off the common cold.

The specific order of the base pairs on a strand of DNA is important in order for the correct protein to be produced. A grouping of three base pairs on the DNA strand is called a codon. Each codon, or three base pairs, comes together to spell a word. A string of many codons together can be thought of as a series of words all coming together to make a sentence. This sentence is what instructs cells to make a protein that helps bodies function properly.

DNA strands containing a hundred to several thousand copies of genes are found on structures called chromosomes. Each cell typically has 46 chromosomes arranged into 23 pairs. Each parent contributes one chromosome to each pair. The first 22 pairs are called autosomal chromosomes, or non-sex chromosomes, and are assigned a number from 1 to 22. The last pair are the sex chromosomes and include the X and the Y chromosomes. If a child receives an X chromosome from each parent, the child is female. If a child receives an X from the mother and a Y from the father, the child is male.

Just as each parent contributes one chromosome to each pair, so each parent contributes one gene from each chromosome. The pair of genes produces a specific trait in the child. In autosomal dominant conditions, it takes only one copy of a gene to influence a specific trait. The stronger gene is called dominant; the weaker gene is called recessive. Two copies of a recessive gene are needed to control a trait, while only one copy of a dominant gene is needed. Our sex chromosomes, the X and the Y, also contain important genes. Some genetic diseases are caused by missing or altered genes on one of the sex chromosomes. Males are most often affected by sex chromosome diseases when they inherit an X chromosome with missing or mutated genes from their mother.

Types of genetic mutations

Genetic disease results from a change, or mutation, in a chromosome or in one or several base pairs on a gene. Some of us inherit these mutations from our parents, called hereditary or germline mutations, while other mutations can occur spontaneously, or for the first time in an affected child. For many of the adult-onset diseases, genetic mutations can occur over the lifetime of the individual. These are called acquired or somatic mutations, and occur while the cells are making copies of themselves or dividing in two. There may be some environmental effects, such as

radiation or other chemicals, that can contribute to these types of mutations as well.

There are a variety of different types of mutations that can occur in the genetic code to cause a disease; and for each genetic disease, there may be more than one type of mutation to cause the disease. For some genetic diseases, the same mutation occurs in every individual affected with the disease. For example, the most common form of dwarfism, called achondroplasia, occurs because of a single base pair substitution. This same mutation occurs in all individuals affected with the disease. Other genetic diseases are caused by different types of genetic mutations that may occur anywhere along the length of a gene. For example, cystic fibrosis, the most common genetic disease of the Caucasian population, is caused by hundreds of different mutations along the gene. Individual families may carry the same mutation as each other, but not as the rest of the population affected with the same genetic disease.

Some genetic diseases occur as a result of a larger mutation that can occur when the chromosome itself is either rearranged or altered, or when a baby is born with more than the expected number of chromosomes. There are only a few types of chromosome rearrangements that are possibly hereditary, or passed on from the mother or the father. The majority of chromosome alterations occur sporadically or for the first time with a new baby.

The type of mutation that causes a genetic disease will determine the type of genetic test to be performed. In some situations, more than one type of genetic test will be performed to arrive at a diagnosis. The cost of genetic tests vary: chromosome studies can cost hundreds of dollars and certain gene studies can cost thousands. Insurance coverage also varies with the company and the policy. It may take several days or several weeks to complete a test. Research testing where the exact location of a gene has not yet been identified can take several months or years for results.

Types of genetic testing

Gene tests

Gene tests look for signs of a disease by examining DNA taken from a person's blood, body fluids, or tissues. The tests can look for large changes, such as a gene that has a section missing or added, or small changes, such as a missing, added, or altered chemical base within the DNA strand. Other important changes can be genes with too many copies, genes that are too active, genes that are turned off, or those that are lost entirely.

Various techniques are used for gene tests. Direct DNA sequencing examines the direct base pair sequence

of a gene for specific gene mutations. Some genes contain more than 100,000 bases; a mutation of any one base can make the gene nonfunctional and cause disease. The more mutations possible, the less likely it is for a test to detect all of them. This test is usually done on white blood cells from a person's blood, but can also be performed on other tissues. There are different ways in which to perform direct DNA mutation analysis. When the specific genetic mutation is known, it is possible to perform a complete analysis of the genetic code, also called direct sequencing. There are several different lab techniques used to test for a direct mutation. One common approach begins by using chemicals to separate DNA from the rest of the cell. Next, the two strands of DNA are separated by heating. Special enzymes (called restriction enzymes) are added to the single strands of DNA; they then act like scissors and cut the strands in specific places. The DNA fragments are then sorted by size through a process called electrophoresis. A special piece of DNA called a probe is added to the fragments. The probe is designed to bind to specific mutated portions of the gene. When bound to the probe, the mutated portions appear on x-ray film with a distinct banding pattern.

Another gene test technique is indirect DNA testing. Family linkage studies are done to study a disease when the exact type and location of the genetic alteration is not known, but the general location on the chromosome has been identified. These studies are possible when a chromosome marker has been found associated with a disease. Chromosomes contain certain regions that vary in appearance between individuals. These regions are called polymorphisms and do not cause a genetic disease to occur. If a polymorphism is always present in family members with the same genetic disease, and absent in family members without the disease, it is likely that the gene responsible for the disease is near that polymorphism. The gene mutation can be indirectly detected in family members by looking for the polymorphism.

To look for the polymorphism, DNA is isolated from cells in the same way it is for direct DNA mutation analysis. A probe is added that will detect the large polymorphism on the chromosome. When bound to the probe, this region will appear on x-ray film with a distinct banding pattern. The pattern of banding of a person being tested for the disease is compared to the pattern from a family member affected by the disease.

Linkage studies have disadvantages not found in direct DNA mutation analysis. These studies require multiple family members to participate in the testing. If key family members choose not to participate, the incomplete family history may make testing other members useless. The indirect method of detecting a mutated gene also causes more opportunity for error.

Chromosome tests

Various genetic syndromes are caused by structural chromosome abnormalities. To analyze a person's chromosomes, his or her cells are allowed to grow and multiply in the laboratory until they reach a certain stage of growth. The length of growing time varies with the type of cells. Cells from blood and bone marrow take one to two days; fetal cells from amniotic fluid take 7–10 days.

When the cells are ready, they are placed on a microscope slide using a technique to make them burst open, spreading their chromosomes. The slides are stained: the stain creates a banding pattern unique to each chromosome. Under a microscope, the chromosomes are counted, identified, and analyzed based on their size, shape, and stained appearance.

Types of chromosome tests include the karyotype test and the FISH (fluorescence in situ hybridization) test. In a karyotype test, the chromosomes are counted, and a photograph is taken of the chromosomes from one or more cells as seen through the microscope. Then the chromosomes are cut out and arranged side-by-side with their partner in ascending numerical order, from largest to smallest. The karyotype is done either manually or using a computer attached to the microscope. The FISH test identifies specific regions on chromosomes using fluorescent DNA probes. FISH analysis can find small pieces of chromosomes that are missing or have extra copies and that can be missed by the karyotype test.

Biochemical tests

Genes contain instructions for making proteins and abnormal protein levels can be indicative of a genetic disorder. Biochemical tests look at the level of key proteins. This level can identify genes that are not working normally. These types of tests are typically used for newborn screening. For example, this screening can detect infants who have metabolic conditions such as phenylketonuria (PKU).

Applications of genetic testing

Newborn screening

In the United States, genetic testing is used most often for newborn screening, a major public health program that can find disorders in newborns that have long-term health effects. Newborn screening tests infant blood samples for abnormal or missing gene products. Every year, millions of newborn babies have their blood samples tested for potentially serious genetic diseases. As of 2021, newborn screening programs were testing for disorders that can cause infectious disease, premature death, hearing disorders, metabolic disorders, and heart problems. A

technology called tandem mass spectrometry allows screening of more than 30 other metabolic disorders.

Carrier testing

An individual who has a gene associated with a disease but never exhibits any symptoms of the disease is called a carrier. A carrier is a person who is not affected by the mutated gene he or she possesses, but can pass the gene to an offspring. Genetic tests have been developed that tell prospective parents whether or not they are carriers of certain diseases. If one or both parents are a carrier, the risk of passing the disease to a child can be predicted.

To predict the risk, it is necessary to know whether the gene in question is autosomal or sex-linked. If the gene is carried on any one of chromosomes 1–22, the resulting disease is called an autosomal disease. If the gene is carried on the X or Y chromosome, it is called a sex-linked disease.

Sex-linked diseases, such as the bleeding condition hemophilia, are usually carried on the X chromosome. A woman who carries a disease-associated gene on one of her X chromosomes has a 50% chance of passing that gene to her son. A son who inherits that gene will develop the disease because he does not have another normal copy of the gene on a second X chromosome to compensate for the abnormal copy. A daughter who inherits the disease-associated gene from her mother will be at risk for having a son affected with the disease.

The risk of passing an autosomal disease to a child depends on whether the gene is dominant or recessive. A prospective parent carrying a dominant gene has a 50% chance of passing the gene to a child. A child needs to receive only one copy of the mutated gene to be affected by the disease.

If the gene is recessive, a child needs to receive two copies of the mutated gene, one from each parent, to be affected by the disease. When both parents are carriers, their child has a 25% chance of inheriting two copies of the mutated gene and being affected by the disease; a 50% chance of inheriting one copy of the mutated gene, and being a carrier of the disease but not affected; and a 25% chance of inheriting two normal genes. When only one parent is a carrier, a child has a 50% chance of inheriting one mutated gene and being an unaffected carrier of the disease, and a 50% chance of inheriting two normal genes.

Cystic fibrosis is a disease that affects the lungs and pancreas and is discovered in early childhood. It is the most common autosomal recessive genetic disease found in the Caucasian population: 1 in 25 people of Northern European ancestry are carriers of a mutated cystic fibrosis

gene. The gene, located on chromosome 7, was identified in 1989.

The gene mutation for cystic fibrosis is detected by a direct DNA test. Over 600 mutations of the cystic fibrosis gene have been found; each of these mutations causes the same disease. Tests are available for the most common mutations. Tests that check for 86 of the most common mutations in the Caucasian population will detect 90% of carriers for cystic fibrosis. The percentage of mutations detected varies according to the individual's ethnic background. If a person tests negative, it is likely but not guaranteed that he or she does not have the gene. Both parents must be carriers of the gene to have a child with cystic fibrosis.

Tay-Sachs disease, also autosomal recessive, affects children primarily of Ashkenazi Jewish descent. Children with this disease die between the ages of two and five. This disease was previously detected by looking for a missing enzyme. The mutated gene has now been identified and can be detected using direct DNA mutation analysis.

Presymptomatic testing

Not all genetic diseases show their effect immediately at birth or early in childhood. Although the gene mutation is present at birth, some diseases do not appear until adulthood. If a specific mutated gene responsible for a late-onset disease has been identified, a person from an affected family can be tested before symptoms appear.

Huntington's disease is one example of a late-onset autosomal dominant disease. Its symptoms of mental confusion and abnormal body movements do not appear until middle to late adulthood. The chromosome location of the gene responsible for Huntington's chorea was located in 1983 after studying the DNA from a large Venezuelan family affected by the disease. Ten years later the gene was identified. A test is now available to detect the presence of the expanded base pair sequence responsible for causing the disease. The presence of this expanded sequence means the person will develop the disease.

Another late-onset disease, Alzheimer's, does not have as well an understood genetic cause as Huntington's disease. The specific genetic cause of Alzheimer disease is not as clear. Although many cases appear to be inherited in an autosomal dominant pattern, many cases exist as single incidents in a family. Like Huntington's, symptoms of mental deterioration first appear in adulthood. Genetic research has found an association between this disease and genes on four different chromosomes. The validity of looking for these genes in a person without

symptoms or without family history of the disease is still being studied.

Cancer susceptibility testing

Cancer can result from an inherited (germline) mutated gene or a gene that mutated sometime during a person's lifetime (acquired mutation). Some genes, called tumor suppressor genes, produce proteins that protect the body from cancer. If one of these genes develops a mutation, it is unable to produce the protective protein. If the second copy of the gene is normal, its action may be sufficient to continue production, but if that gene later also develops a mutation, the person is vulnerable to cancer. Other genes, called oncogenes, are involved in the normal growth of cells. A mutation in an oncogene can cause too much growth, which is the beginning of cancer.

Direct DNA tests are currently available to look for gene mutations identified and linked to several kinds of cancer. People with a family history of these cancers are those most likely to be tested. If one of these mutated genes is found, the person is more susceptible to developing the cancer. The likelihood that the person will develop the cancer, even with the mutated gene, is not always known because other genetic and environmental factors are also involved in the development of cancer.

Cancer susceptibility tests are most useful when a positive test result can be followed with clear treatment options. In families with familial polyposis of the colon, testing a child for a mutated *APC* gene can reveal whether or not the child needs frequent monitoring for the disease. In families with potentially fatal familial medullary thyroid cancer or multiple endocrine neoplasia type 2, finding a mutated *RET* gene in a child provides the opportunity for that child to have preventive removal of the thyroid gland. In the same way, *MSH1* and *MSH2* mutations can reveal which members in an affected family are vulnerable to familial colorectal cancer and would benefit from aggressive monitoring.

In 1994, a mutation linked to early-onset familial breast and ovarian cancer was identified. *BRCA1* is located on chromosome 17. Women with a mutated form of this gene have an increased risk of developing breast and ovarian cancer. A second related gene, *BRCA2*, was later discovered. Located on chromosome 13, it also carries increased risk of breast and ovarian cancer. Although both genes are rare in the general population, they are slightly more common in women of Ashkenazi Jewish descent.

When a woman is found to have a mutation in one of these genes, the likelihood that she will get breast or ovarian cancer increases, but not to 100%. Other genetic and environmental factors influence the outcome.

Testing for these genes is most valuable in families where a mutation has already been found. *BRCA1* and *BRCA2* are large genes; *BRCA1* includes 100,000 bases. More than 1,600 mutations to this gene have been discovered, but a mutation could occur in any one of the bases. Studies show tests for these genes may miss 30% of existing mutations. The rate of missed mutations, the unknown disease likelihood in spite of a positive result, and the lack of a clear preventive response to a positive result make the value of this test for the general population uncertain.

Prenatal and postnatal chromosome analysis

Chromosome analysis is performed on fetal cells primarily when the mother is age 35 or older at the time of delivery, has experienced multiple miscarriages, or reports a family history of a genetic abnormality. Prenatal testing is done on the fetal cells from a chorionic villus sampling (from the baby's developing placenta) at 10–12 weeks or from the amniotic fluid (the fluid surrounding the baby) at 16–18 weeks of pregnancy. Cells from amniotic fluid grow for 7–10 days before they are ready to be analyzed. Chorionic villi cells have the potential to grow faster and can be analyzed sooner.

Chromosome analysis using blood cells is done on a child who is born with or later develops signs of mental retardation or physical malformation. In the older child, chromosome analysis may be done to investigate developmental delays.

Extra or missing chromosomes cause mental and physical abnormalities. A child born with an extra chromosome 21 (trisomy 21) has Down syndrome. An extra chromosome 13 or 18 also produces well-known syndromes. A missing X chromosome in a female causes Turner syndrome, and an extra X in a male causes Klinefelter syndrome. Other abnormalities are caused by extra or missing pieces of chromosomes. Fragile X syndrome is a sex-linked disease that causes mental retardation in males.

Chromosome material may be rearranged, such as the end of chromosome 1 moving to the end of chromosome 3. This is called a chromosomal translocation. If no material is added or deleted in the exchange, the person may not be affected. Such an exchange, however, can cause infertility or abnormalities if passed to children.

Evaluation of a man and woman's infertility or repeated miscarriages includes blood studies of both to check for a chromosome translocation. Many chromosome abnormalities are incompatible with life; babies with these abnormalities often miscarry during the first trimester. Cells from a baby that died before birth can be

QUESTIONS TO ASK YOUR DOCTOR

- Under what circumstances should my spouse and I consider genetic testing on our unborn child?
- How are those genetic tests conducted?
- Is there a risk to the fetus as a result of genetic testing? If so, how serious is that risk?
- What kinds of information can we expect to get from genetic tests on our unborn child?

studied to look for chromosome abnormalities that may have caused the death.

Diagnostic testing

This type of genetic testing is used to confirm a diagnosis when a person has signs or symptoms of a genetic disease. The genetic test used depends on the disease for which a person is tested. For example, if a patient has physical features indicative of Down syndrome, a chromosomal test is used. To test for Duchenne muscular dystrophy, a gene test is done to look for missing sections in the dystrophin gene.

Chromosome tests are used to diagnose certain cancers, particularly leukemia and lymphoma, which are associated with changes in chromosomes: extra or missing complete chromosomes, extra or missing portions of chromosomes, or exchanges of material (translocations) between chromosomes. Studies show that the locations of the chromosome breaks are at locations of tumor suppressor genes or oncogenes.

Chromosome analysis on cells from blood, bone marrow, or solid tumors helps diagnose certain kinds of leukemia and lymphoma and often helps predict how well the person will respond to treatment. After treatment has begun, periodic monitoring of these chromosome changes in the blood and bone marrow gives the physician information as to the effectiveness of the treatment.

A well-known chromosome rearrangement is found in chronic myelogenous leukemia. This leukemia is associated with an exchange of material between chromosomes 9 and 22. The resulting smaller chromosome 22 is called the Philadelphia chromosome.

Pharmacogenetic testing

The latest type of genetic testing is pharmacogenetic testing. This test examines a person's genes to gain

information on how drugs would be broken down by the body. Pharmacogenetic testing aims to design drug treatments that are specific to each person. For example, a test used in patients who have chronic myelogenous leukemia can show which patients would benefit from a medicine called Gleevec. Another test looks at a liver enzyme called cytochrome P450, which breaks down certain types of drugs. Gene mutations can affect the ability of the body to break down certain drugs, and people with a less active form of P450 might be taking excessive levels of a drug. Pharmacogenetic testing seeks to help patients obtain the right dosage of a medication.

Preparation

Most tests for genetic diseases of children and adults are done on blood. To collect the 5–10 mL of blood needed, a healthcare worker draws blood from a vein in the inner elbow region. Collection of the sample takes only a few minutes.

Prenatal testing is done either on amniotic fluid or a chorionic villus sampling. To collect amniotic fluid, a physician performs a procedure called amniocentesis. An ultrasound is done to find the baby's position and an area filled with amniotic fluid. The physician inserts a needle through the woman's skin and the wall of her uterus and withdraws 5–10 mL of amniotic fluid. Placental tissue for a chorionic villus sampling is taken through the cervix. Each procedure takes approximately 30 minutes.

Bone marrow is used for chromosome analysis in a person with leukemia or lymphoma. The person is given local anesthesia. Then the physician inserts a needle through the skin and into the bone (usually the sternum or hip bone). One-half to 2 mL of bone marrow is withdrawn. This procedure takes approximately 30 minutes.

Aftercare

After blood collection, the person can feel discomfort or bruising at the puncture site, or may become dizzy or faint. Pressure to the puncture site until the bleeding stops reduces bruising. Warm packs to the puncture site relieve discomfort.

The chorionic villus sampling, amniocentesis, and bone marrow procedures are all done under a physician's supervision. The person is asked to rest after the procedure and is watched for weakness and signs of bleeding.

Risks

Collection of amniotic fluid and chorionic villus sampling have the risk of miscarriage, infection, and bleeding; the risks are higher for the chorionic villus

sampling. Because of the potential risks for miscarriage—0.5% following the amniocentesis and 1% following the chorionic villus sampling procedure—both of these prenatal tests are offered to couples, but not required. A woman should tell her physician immediately if she has cramping, bleeding, fluid loss, an increased temperature, or a change in the baby's movement following either of these procedures.

After bone marrow collection, the puncture site may become tender and the person's temperature may rise. These are signs of a possible infection.

Genetic testing involves other nonphysical risks. Many people fear the possible loss of privacy about personal health information. Results of genetic tests may be reported to insurance companies and affect a person's insurability. Some people pay out-of-pocket for genetic tests to avoid this possibility. Laws have been proposed to deal with this problem. Other family members may be affected by the results of a person's genetic test. Privacy of the person tested and the family members affected is a consideration when deciding to have a test and to share the results.

A positive result carries a psychological burden, especially if the test indicates the person will develop a disease, such as Huntington's chorea. The news that a person may be susceptible to a specific kind of cancer, while it may encourage positive preventive measures, may also negatively shadow many decisions and activities.

A genetic test result may also be inconclusive, meaning no definitive result can be given to the individual or family. This may cause the individual to feel more anxious and frustrated and experience psychological difficulties.

Prior to undergoing genetic testing, individuals need to learn from the genetic counselor the likelihood that the test could miss a mutation or abnormality.

Normal results

A normal result for chromosome analysis is 46, XX or 46, XY. This means there are 46 chromosomes (including two X chromosomes for a female or one X and one Y for a male) with no structural abnormalities. A normal result for a direct DNA mutation analysis or linkage study is no gene mutation found.

There can be some benefits from genetic testing when the individual tested is not found to carry a genetic mutation. Those who learn with great certainty they are no longer at risk for a genetic disease may choose not to undergo prophylactic therapies and may feel relieved and less anxious.

Abnormal results

An abnormal chromosome analysis report includes the total number of chromosomes and identifies the abnormality found. Tests for gene mutations report the mutations found.

There are many ethical issues to consider with an abnormal prenatal test result. Many of the diseases tested for during a pregnancy cannot be treated or cured. In addition, some diseases tested for during pregnancy may have a late onset of symptoms or have minimal effects on the affected individual.

Before making decisions based on an abnormal test result, the person should meet again with a genetic counselor to fully understand the meaning of the results, learn what options are available based on the test result, and learn the risks and benefits of each of those options.

Resources

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"Genetic Testing." Mayo Clinic. April 14, 2020. <https://www.mayoclinic.org/tests-procedures/genetic-testing/about/pac-20384827> (accessed June 9, 2021).

ORGANIZATIONS

Centers for Disease Control and Prevention Office of Public Health Genomics (OPHG), 1600 Clifton Road, Atlanta, GA 30329-4027, (800) 232-4636, <http://www.cdc.gov/genomics>

March of Dimes, 1550 Crystal City Drive, Suite 1300, Arlington, VA 22202, (888) 663-4637, <http://www.marchofdimes.org>

National Human Genome Research Institute (NHGRI). National Institutes of Health., Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, (301) 402-2218, <http://www.nhgri.nih.gov>

National Society of Genetic Counselors (NSGC), 330 N. Wabash Ave., Suite 2000, Chicago, IL 60611, (312) 321-6834, (312) 673-6972, nsgc@nsgc.org, <http://www.nsgc.org>

Katherine S. Hunt, MS

Genetics and congenital anomalies

Definition

Any unusual variation or abnormality in the shape, structure, and/or function of an organ, body part, or tissue is commonly referred to as a birth defect. However, *congenital anomaly* is the more accurate and preferred term, since birth defect can be misinterpreted to mean a defect produced by the birthing process. Congenital anomalies may be external or internal, single (isolated) or multiple, major or minor, and by definition are present at (and almost always before) birth, although in some cases detection/diagnosis occurs well after birth. As a group, congenital anomalies are common, have a wide range of clinical severity, and can develop in one form or another in any anatomical structure or location. There are many different causes of congenital anomalies, known and unknown, but in terms of how they develop, there are four major types: malformations, deformations, disruptions, and dysplasias.

Description

Variation among individuals in physical characteristics, both external and internal, is an essential attribute of any organism that reproduces sexually, including humans. Although less obviously, but no less importantly, people also differ in their metabolism and other cellular/chemical processes that help form and maintain the body. The process of normal development in the body is called morphogenesis, while abnormal development is known as dysmorphogenesis. Dysmorphology, then, is the study of congenital anomalies, including their formation, causes, and patterns of occurrence.

An important task in both medical and sociocultural contexts lies in determining what constitutes a congenital anomaly, and what qualifies as an accepted morphological variant. Further, what distinguishes a major anomaly from a minor one? In other words, what is normal, and what is abnormal? In some cases, the distinction is obvious; in others it is not. Terms such as *normal* and *abnormal* are generally agreed to be subjective, and thus not applicable when applied to individuals in a broad context. The same can be said of terms such as defective, anomalous, deformed, malformed, aberrant, irregular, and the like. Even though some terms and phrases are perceived as subjective, negative, and offensive when misapplied as generalities, they are nonetheless necessary in a medical context. With due sensitivity and care, these same terms can be used clinically in an objective and instructive manner.

Compared with the complex and evolving social issues of perception and acceptance, the medical approach to distinguishing normal variants from minor and major anomalies is more objective and direct. Regardless of the anatomical structure or process, the primary criterion involves evaluating whether its function, shape, structure, and/or size fall within or outside the normal (expected) range. To help answer that question, measurements of every conceivable type have been taken and catalogued over the years on countless individuals. Statistical formulas are applied to the data for a given characteristic or function (e.g., height, weight, blood pressure, serum enzyme levels, etc.) to determine its normal range. If needed, adjustments for age, sex, race, ethnicity, and many other variables can also be made. The results are often graphed and, for most human characteristics, a line drawn through the data points on the graph produces the well-known bell curve, a name derived from its shape. Calculations based on such factors as the total number of individuals studied and the range of measurements obtained, among others, are used to mark off a section in the middle of the curve such that most individuals (usually between 80% and 95%) fall within that range. Therefore, any values above or below (i.e., outside) that range are considered anomalous or abnormal. Measured values for minor anomalies might fall several percentage points on either side of the upper and lower boundaries of the normal range, while major anomalies lie at the ends of the curve.

Among other new challenges, parents and families of children with congenital anomalies are exposed to a bewildering array of new medical terms and phrases, and asked to understand, process, and remember these while likely under a great deal of stress. The practice of medical genetics consists primarily of communicating with individuals and families about difficult and complex issues. Geneticists and genetic counselors are especially sensitive to the psychosocial impact terminology can have on perception and understanding of congenital anomalies/genetic disorders. Parents of a newly diagnosed child inevitably want to know how the anomaly or genetic syndrome occurred. An understanding of the different types of anomalies is the basis for answering that question.

Malformations

A malformation is an abnormality in the shape or structure of an organ, body part, or larger section of the body resulting from an intrinsically dysfunctional developmental process. In other words, the genetic instructions for development are faulty, interfered with, or both.

All cells in the body carry the same set of genes, copied from the original set provided by the sperm and the

KEY TERMS

Association—A non-random occurrence in two or more individuals of the same group of anomalies that are not otherwise known to be a sequence or syndrome.

Congenital—Present at birth.

Deformation—Abnormal shape or function in otherwise normal tissue produced by unusual mechanical forces on the embryo/fetus.

Disruption—A type of anomaly formation in which a breakdown or inhibition of normal tissue development occurs.

Dysmorphic—Literally meaning misshapen, it is most often used as a general descriptive term for individuals with one or more anomalous physical characteristics.

Dysplasia—The structural and functional results of the abnormal organization of cells into tissues, affecting one or more of the derivatives of a primary tissue type (endoderm, mesoderm, or ectoderm).

Etiology—The cause of a disease, syndrome, or anomaly.

Idiopathic—One or more anomalies of unknown cause in an individual.

Malformation—An abnormality in an organ or body structure caused by a dysfunctional developmental process.

Morphogenesis—The normal developmental process of the body's structure and form.

Sequence—The combination of both a primary structural or functional anomaly, and the secondary anomalies produced by any abnormal forces or processes it generates.

Syndrome—A pattern of multiple major and minor anomalies that occur as a group more often than would be expected by chance alone, implying the same underlying cause or mechanism in all affected individuals.

egg at conception. Some genes are primarily responsible for directing a portion of embryonic/fetal development, and their influence may be anywhere from general (entire body or entire tissue) to specific (small component of one organ). This is why many single-gene (inherited) and most chromosomal disorders are characterized by multiple major and minor malformations in various anatomic locations. Any disorder, including most with a genetic basis, that can be uniquely characterized by a specific

group of anomalies that occur more frequently together in that condition than would be expected by chance is defined as a syndrome. Multiple malformation patterns that have no discernible or consistent genetic pattern or teratogenic cause are known as associations (e.g., the VACTERL or VATER association).

Most isolated malformations follow a multifactorial inheritance pattern, and often involve incomplete morphogenesis of a midline organ or structure (e.g., septal defects [holes] in the heart, cleft lip/palate, diaphragmatic hernia, or spina bifida). These same types of malformations occur in some syndromes, in combination with a wide variety of other malformation types. Organs, body parts, or other structures may be extra/missing, abnormally positioned, overdeveloped (hyperplastic), underdeveloped (hypoplastic), or any of a number of minor variations.

Deformations

A deformation is an anomaly in the form, shape, or position of a body part or section that results from mechanical forces on the embryo/fetus. Deformations can have extrinsic (outside the fetus) or intrinsic (internal) causes. Examples of possible extrinsic causes include small maternal stature, oligohydramnios (decreased amniotic fluid volume), breech presentation, uterine malformation, and multiple pregnancy (i.e., twins, triplets, etc.). Some intrinsic (fetal) factors capable of producing deformations include neuromuscular disease, connective tissue defects, central nervous system disorders, and kidney malformations.

Joint contractures, such as talipes equinovarus (club-foot), are the most common type of deformation, and have both extrinsic and intrinsic causes. As the fetus develops and grows, it must be able to move (flex and extend) the joints or they can become locked in position (contracted). Chronic oligohydramnios produces intrauterine constraint (IUC), which compresses and immobilizes the fetus, causing joint contractures. Oligohydramnios itself may be caused by leakage of fluid from the amniotic sac (extrinsic cause), or result from decreased fluid production secondary to malformation or absence (agenesis) of the fetal kidneys. (Amniotic fluid is comprised mostly of fetal urine in the later stages of pregnancy.)

Agenesis of the fetal kidneys also exemplifies a malformation/deformation sequence. Specifically, an original isolated malformation (renal agenesis) produces a sequence of events (oligohydramnios plus IUC plus fetal compression) that results in deformations, such as joint contractures and a characteristic facial pattern, which is sometimes referred to as the Potter sequence. A neuromuscular disease that causes partial or total prenatal

paralysis of the limbs (decreased mobility) is another example of an intrinsic cause of joint contractures.

Disruptions

A disruption is an anomaly of an organ or body structure resulting from an extrinsic factor that interferes with, or disrupts, an originally normal developmental process. For example, certain types of maternal infection or drug use at a critical time in pregnancy have the potential to arrest the developmental process in specific fetal tissues. Another type of disruption can occur when a strip of the amniotic membrane surrounding the fetus detaches and wraps around one of the developing limbs or a section of the body. Known as an amniotic band, it acts somewhat like a tourniquet, restricting blood flow and inhibiting further growth.

Dysplasias

Dysplasia refers to an abnormal organization of cells in a particular tissue type, and any resulting abnormal morphological development. Dysplasias usually have a genetic basis, and examples include skeletal dysplasias (e.g., fragile, short, and/or abnormally curved bones), ectodermal dysplasias (skin, hair, nails, and associated tissues), and renal dysplasias (multiple cysts or tumors in the kidneys).

Genetic profile

Of all major congenital malformations, 60% have an undetermined cause, and 20% are attributed to multifactorial inheritance. The remaining 20% are divided roughly equally between single-gene disorders, chromosomal syndromes, and teratogenic causes. Considering that inclusion in the multifactorial group does not imply a specifically determined cause in any particular case, about 80% of all major malformations have no readily identifiable cause. The most frequently malformed organs are the brain, heart, and urinary tract (kidneys, ureters, bladder, and urethra). Deformations and disruptions most often affect the extremities (hands and feet), limbs (arms and legs), skull, and face.

Multifactorial inheritance is assumed for most isolated congenital anomalies, with a risk for recurrence in subsequent pregnancies of 3%–5%. Single-gene (e.g., autosomal dominant, autosomal recessive, sex-linked, etc.) and chromosomal syndromes present a broad range of recurrence risks, but most often are 1%–3% for chromosomal syndromes, and 25% or 50% for single-gene disorders.

Demographics

Considered individually, most anomalies and genetic syndromes are uncommon, and some are quite rare. As a category, however, they are quite common. Major congenital anomalies are the leading cause of death for children less than one year old, and the second and third most frequent cause for those less than five and fifteen years old, respectively. Approximately 40% of all pediatric hospital admissions are related to congenital anomalies.

Malformations may be isolated or multiple, with minor or major clinical significance. Of all newborns, about 14% have a single minor malformation, 3% have a single major malformation, and up to 0.7% have multiple major malformations. The frequency of major malformations is even higher at conception, estimated at 10%–15%, but most of these result in spontaneous pregnancy loss. About 2% of newborns are found to have a disruption of some type. In the presence of a major congenital malformation, especially if it affects the central nervous system or urinary tract, there is an 8% risk that a deformation will also occur. Skeletal dysplasias have an overall incidence of about 0.5%, with diagnosis of some of the milder forms often delayed until childhood. Ectodermal dysplasias occur in about 0.7% of individuals, but only several types associated with major malformations are usually diagnosed at birth. Other forms of congenital dysplasias are rare.

Diagnosis

Many anomalies are now detected/diagnosed prenatally, either through testing chosen because of a known or suspected risk factor; as a coincidental finding during testing chosen for another purpose; or as a chance finding during routine prenatal evaluations. Prenatal testing is done either through imaging studies, most often routine (level I) or detailed (level II) obstetric ultrasound, or through direct biochemical or genetic testing of the fetus using chorionic villus sampling (CVS) or amniocentesis. Fetal echocardiography is sometimes used to confirm heart defects, and some rare conditions might require x-rays or magnetic resonance imaging (MRI) of the fetus (via the mother), while a few others can only be diagnosed by a fetal skin biopsy. Some tests are designed only to screen for certain anomalies or syndromes (increase or decrease the likelihood).

Evaluating congenital anomalies postnatally usually involves attempts to confirm the suspected or most likely diagnosis, while at the same time excluding other possible diagnoses. Major external anomalies are easily detected, but those affecting internal organs require recognition of the signs and symptoms they produce (e.g., a baby with breathing difficulty who turns blue [cyanotic]

while crying may have a heart defect), which could be subtle and/or not appear until well after birth.

Any child with an apparently isolated congenital anomaly should have it confirmed (i.e., exclude subtle or hidden signs of an association or syndrome). Multiple congenital anomalies are best evaluated by a geneticist, if possible, even in cases involving an obvious diagnosis, such as a common condition like Down syndrome. The family may wish to have a consultation in a genetics clinic, where a comprehensive approach helps to ensure that a thorough evaluation and explanation of the condition are provided. In addition, psychosocial issues are addressed, appropriate referrals can be made (e.g., other specialists, support groups, or more extensive psychological assistance as needed), and the most complete and current information on testing and other options are available. In cases with an unusual presentation of symptoms, or rare syndromes, geneticists have the best chance of establishing a diagnosis, often in consultation with colleagues who specialize in a particular syndrome or class of disorders. In other situations, a geneticist might suggest periodic reevaluations if a diagnosis is unclear initially, since some children grow into a syndrome (i.e., the defining characteristics only become apparent as the child grows). Unfortunately, all too often a diagnosis is never established, regardless of effort expended or specialists consulted. Even in these cases, a geneticist may be able to offer a reasonable estimation as to a cause and recurrence risk, based on a process of eliminating some factors, making others more likely, and applying any available empirical data from similar cases.

Regardless of situation, a genetics evaluation includes as many of the following as possible:

- a complete physical examination of the affected child
- a review of medical records
- evaluation of the pregnancy history
- a consultation to obtain and evaluate the medical history of the immediate and extended family

Based on these evaluations, one or more of a wide variety of possible medical tests could be suggested. If a hereditary syndrome is suspected, physical examination, medical record review, and testing might also be requested of one or more family members to help establish a diagnosis. The importance of making a diagnosis rests in the ability it provides to answer other questions parents inevitably have. The diagnostic process also attempts to determine how a malformation, deformation, disruption, dysplasia, or some combination occurred.

Treatment and management

Deformations are typically more amenable to successful treatment and correction than other types of anomalies. For instance, infants with dislocated hips or clubfeet can usually achieve normal function after a regimen of bracing, casting, and movement therapy, although in some cases minor surgery is necessary. Many malformations can also be successfully repaired, especially those that are isolated. However, invasive and complex surgery is often needed, with only partial improvement in some cases. Certain malformations, such as cleft lip/palate, require multiple surgeries performed in stages as the child grows. For the most part, disruptions and dysplasias are minimally treatable, if at all. However, an exception could be the use of a prosthetic device for a limb amputation anomaly caused by a disruption such as an amniotic band.

Prognosis

The prognosis for any particular congenital anomaly, whether isolated or part of a sequence or syndrome, can vary greatly. Medical complications from one anomaly may adversely affect the prognosis of another, or affect the course of an entire syndrome. In general, however, children with extrinsically caused deformations tend to fare better than those with other types of anomalies. Likewise, isolated malformations usually carry a better prognosis than multiple malformations/deformations, intrinsically derived deformations, and most types of tissue dysplasia. Disruption anomalies have widely varying prognoses based on various factors, such as the organ or body parts affected, the degree of disruption, and the timing during morphogenesis at which the disruption began.

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 March of Dimes, 1550 Crystal City Drive, Suite 1300, Arlington, VA 22202, (888) 663-4637, <http://www.marchofdimes.org>
 National Society of Genetic Counselors, 330 N. Wabash Ave., Suite 2000, Chicago, IL 60611, (312) 321-6834, nsgc@nsgc.org, <http://www.nsgc.org>

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Genome

Definition

A genome is the complete set of genetic material needed to create and maintain a living organism. In humans, a genome consists of 24 chromosome pairs and between 20,000 and 25,000 individual genes.

Description

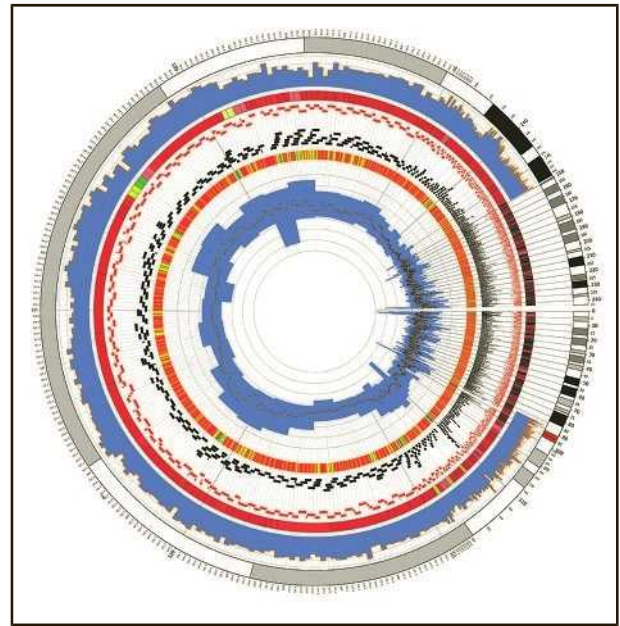
Within each cell there is a substance called deoxyribonucleic acid or DNA. Groups of DNA pairs join to form genes, and genes join to form chromosomes. A genome is the complete grouping of this material. It contains all the instructions necessary for life. Every function of the body, all that makes a human a unique individual, and all information needed to reproduce is controlled by genes within the genome.

Genes are composed of specific sequences of building blocks called nucleotides. There are only four specific nucleotides that make up all genetic material. They are commonly abbreviated as A, C, G, and T for adenine, cytosine, guanine, and thymine. These four nucleotides only appear in specific pairings. A and T will only pair with each other or with another A or T nucleotide, and C and G will only pair with each other or with another C or G. The entire human genome is based on pairings of these four nucleotides. There are more than three billion of these pairs in a human genome.

Genes comprise only approximately 2% of the entire human genome. The remaining parts of the genome consist of areas called noncoding regions that regulate production of proteins necessary to strengthen genes, regulate the expression of genes, and conduct other biochemical functions.

Gene sequencing

More commonly known as gene sequencing, genetic profiling is the process by which the genetic



Genome map showing the genetic content with a chromosome (outer ring). Within the circle are graphs and histograms displaying the guanine and cytosine content of the genes within the chromosome. (Martin Krzywinski/*Science Source*)

characteristics of individuals are identified. Through a process called personal DNA analysis, DNA profiling, or DNA sequencing, researchers are able to create a map of an organism's DNA by identifying the individual base nucleotides. Because each person's genetic profile is unique, it is sometimes called a genetic fingerprint.

Genetic sequencing was first completed using ribonucleic acid (RNA) material and then DNA. RNA is genetic material essential in the production of proteins and in the transmission of genetic information. Genetic sequencing may be performed using samples of hair, skin, saliva, or blood, and an instrument known as a sequencer.

Beginning in the 1970s, researchers sought to identify and map the human genome. At that time, it took several months to sequence a single base pair. In 1990, researchers began the Human Genome Project with the goal of identifying the entire human genome. This goal was accomplished in 2003 with the sequencing of the complete human genome. The mapping of the human genome has inspired ongoing investigation and discoveries of the significance of genes and human health.

Gene sequencing may be broken into two main types: whole exome sequencing (WES) and whole genome sequencing (WGS). WES focuses on only the portion of the human genome known as coding DNA. Coding DNA contains material that actively produces

KEY TERMS

DNA—Deoxyribonucleic acid, the main component in chromosomes and the substance that carries all genetic material.

Gene sequencing—The process of mapping the order of DNA or genetic material in an organism.

Nucleotides—The building blocks of genes, which are arranged in specific order and quantity.

Pharmacogenetics—The study of how medication metabolism is affected by genetic inheritance.

RNA—Ribonucleic acid, the intermediate step between DNA and its final expression product. DNA is transcribed into RNA, and RNA is translated into protein.

proteins needed to create genetic material that expresses traits. WGS maps the entire genome, both coding and non-coding sections of the genome. Non-coding DNA is estimated to be more than 80% of the total material in the human genome. When this material was first discovered, it was believed that it served no purpose and was sometimes referred to as “junk DNA.” As the human genome has been sequenced and studied, functional activities for non-coded DNA have been discovered. In some cases, it is believed that this non-coded DNA may interact with environmental factors to produce medical conditions such as bipolar disorder and some types of cancer.

For many years the Sanger method was the gold standard for gene sequencing. Developed in 1977 by geneticist Frederick Sanger, this method uses single strands of DNA that have been separated from the matching pair by a chemical process. This single chain is then subjected to another process that limits the chain to a shortened, specific length. The shortened sections are then ordered by length. Then the base nucleotides are identified. Based on this identification, the entire gene sequence may be known. While the Sanger method is still used in many laboratories, newer methods called next-generation sequencing (NGS) are used in larger commercial laboratories to produce maps of various genes and genetic material.

NGS uses small fragments of DNA to identify individual nucleotide sequences by using a generic DNA strand template and recreating the sequence from the sample DNA provided. The advantage to NGS is that by using modern sequencing equipment, it may be performed across millions of DNA strands at once rather

than the limited number of strands that may be sequenced via the Sanger method.

Multiple programs have researched and are currently researching the potential of whole-genome sequencing (WGS) in predicting disease. In January 2015, the results of a study exploring the efficacy of WGS in diagnosing the risk of developing cancer were published. The researchers in this study examined the whole genome of individuals with cancer who have mutations in the *BRCA* gene. Mutations in the *BRCA* gene may cause an increased risk of developing breast and ovarian cancer. They compared the WGS results of these patients with cancer patients who did not have *BRCA* mutations and discovered that while many of the mutations they discovered were mutations of unknown significance, they were able to predict cancer risk in 21% of patients who did not have the *BRCA* mutations.

The Human Genome Project

In 1990, the National Institutes of Health (NIH), the U.S. Department of Energy, and other international organizations began a program called the Human Genome Project. The NIH called it one of the greatest feats of exploration in history. The goal was to sequence the complete set of DNA in the human body. Completed in April 2003, the Human Genome Project led to the ability for the first time to read the complete genetic blueprint of a human being.

The completion of the Human Genome Project and advancing technology that has made genetic testing more affordable have led to an increase in medical centers and genetics labs that routinely perform gene sequencing. As a result, more than 80 million unique differences in genes and in uncoded regions have been discovered. The challenge doctors and researchers face is determining which of these differences or variants is important.

Implications

Discoveries found within the human genome determine all biological characteristics of an individual. This genetic material also determines signs and symptoms of genetically caused diseases and medical conditions. Therefore, gene sequencing of the human genome is used to diagnose many medical conditions, specifically conditions with known genetic causes. Researchers have discovered several genetic markers that may be useful in predicting which lung cancer patients may develop metastatic cancer in the future, while other studies have found that genomic markers are not as effective at determining survival rates for cancer patients as are other molecular features that control transcription and other biological

QUESTIONS TO ASK YOUR DOCTOR

- Will I benefit from whole genomic sequencing or whole exome sequencing?
- Are there other genetic screenings or tests that may be more helpful?
- Could my treatment be improved by the information from genomic sequencing?

functions involved with genetics rather than functions of DNA expression.

Genetic mapping may also be useful when treating patients. According to the National Institutes of Health (NIH), more than two million Americans have serious side effects from prescription medicines each year, and as many as 100,000 die from these effects. Using genomics, doctors may be able to tailor medications to an individual's specific genome and improve medication safety and efficacy. The science of pharmacogenetics seeks to improve health outcomes by combining the science of genomics and pharmacology.

Genetic sequencing is used to help identify a person's risk for developing certain diseases, diagnose medical conditions, and determine the best course of treatment. In the future, individualized, custom medical treatment may be developed based on an individual's specific genome.

The future of human genetics lies in the quest to determine the significance of the information discovered in the Human Genome Project and in the ongoing discoveries of the human genome.

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ORGANIZATIONS

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Genome- and epigenome-wide association studies

Definition

The completion of the Human Genome Project and the development of time- and cost-effective methods of sequencing the genome of an individual have changed how we understand genetics and genetic variants. In this post-genome-association era, many more studies can be done to further understand the role of genes in organisms in both coding and non-coding regions of the genome we inherited, and the epigenome it turns into as we change over time and are impacted by our environment. Genome-wide association studies (GWASs) and epigenome-wide association studies (EWAS) are utilized to help understand the human genome and its relationship to mutations, as well as how the sum of interactions between genes, and between genes and the environment, makes us who we are. This information can then be applied to understanding the pathogenesis and heritability of genetic disorders.

Description

The Human Genome Project has had a major impact on the world of genetics. The result of the project—the mapping of every gene and the sequence of the billions of nucleotides that make up these genes in the entire human genome—has led to new understanding of the role of genes and their interactions in regard to the structure and function of the human body, both normal and abnormal. Other projects and technologies such as Sanger sequencing, genome sequencing, and next-generation sequencing have been instrumental in the timely sequencing of individual genomes from DNA (deoxyribonucleic acid). Comparing and associating the genome of an abnormal gene sequence to the known normal human genome sequence, known as the HapMap, has allowed doctors and scientists to diagnose and treat patients more efficiently. Many genetics-related diseases can now be associated with mutations in specific genes, creating an entire database of genetic diseases.

GWAS and EWAS are studies that utilize the human genome sequence to scan for markers in the genome associated with certain disorders. Understanding of the role of

KEY TERMS

Allele—One of two or more different genes encoding specific and inheritable characteristics that occupy corresponding locations on a pair of chromosomes.

Chromosome—A microscopic thread-like structure found within each cell of the body and consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

DNA methylation—The addition of methyl groups (CH_3) to nucleotide bases of DNA to regulate gene expression.

Genome—The entire DNA sequence of a cell or organism.

Human Genome Project—An international effort begun in 1990 and completed in 2003 to locate and identify the 100,000 genes on the 46 human chromosomes.

Locus—The position occupied by a gene on a chromosome.

Nucleotides—The building blocks of genes, which are arranged in specific order and quantity.

Single-nucleotide polymorphism—Single nucleotide variant (SNV); a variation or point mutation in a single nucleotide building block of DNA.

these genes has proven to be integral to understanding genetic diseases. GWAS and EWAS are carried out by comparing the genomes of persons with the disease and similar persons without the disease. If the result of the study shows an increase in particular variations in the genomes of those with the disease, using biomarkers on SNPs, then the variations are said to be associated. With this information, researchers can target the roles of these genes to up-regulate or down-regulate as needed to alter the treatment and management of the disease. One example is the use of tyrosine kinase inhibitors in certain cancers such as breast and prostate cancer, since an alteration in the genes related to tyrosine kinase is linked to these cancers. Complex diseases can now be further researched in this post genome- and epigenome-association era.

In the post-genome-association era, there are many more studies that can be done to determine the relationship between multiple genes and gene variants that

contribute to or are the primary causes of complex diseases. These gene variants, typically single-nucleotide polymorphisms (SNPs), are the current challenge in understanding the mechanisms behind complex diseases, either inherited or non-inherited. SNPs are single nucleotide variations in one of the billions of nucleotides that make up the chain of DNA and, therefore, genes in the human genome. SNPs can cause a wide range of changes in the genome, from no changes at all to severe changes such as in the development of a chromosome that leads to the termination of a developing fetus, depending on the location and amount of SNPs that occur.

A new era

Studies being done in the post-genome-association era are focused toward understanding the role and effect of SNPs and also non-coding regions in the human genome, particularly SNPs in the non-coding regions. SNPs can be very complex, as some have a role in the regulation of other genes. Studies are also being performed on complex osteoarthritis diseases such as rheumatoid arthritis (RA); systemic lupus erythematosus, also referred to as lupus (SLE); ankylosing spondylitis (AS); osteoporosis; and osteosarcomas, among others. Genome-wide association studies have determined multiple gene loci related to these bone and autoimmune disorders. Although this information is available, there are still many questions related to their inheritability and the relationship between the loci alterations that account for the sum total of the changes in each disorder.

Using what is already known about osteoarthritic disorders, studies are being done to determine the molecular pathways and mechanism of pathology, to further understand and then treat and possibly even prevent these disorders from occurring in an individual. One such study has determined an altered methylation in the genome of people with osteoarthritic disorders. Methylation is extremely important in the structure and function of genes, and the regulation of the expression of genes. These findings can be used by pharmaceutical researchers for the development of more effective drugs to treat the symptoms or suppress the expression of methylation-related disorders.

Studies are also being performed using the information available about SNPs to fully understand the inheritance of disorders and apply that information to other complex diseases such as cancer. One such study has worked to quantify local inheritability, and has shown groups of diseases such as autoimmune diseases to have alterations in similar loci. Information such as this can be utilized in further studies regarding the loci and inheritability of common diseases such as cancer that are not well understood in terms of genetics and inheritance.

Although much information is available, there are still many questions related to the inheritability of genetic disorders and the relationship between the loci of alterations that account for the changes in each disorder. GWAS may, in the future, help researchers to understand genetic variance between people and the relationship between gene expression and the environment.

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Genome sequencing

Definition

Genome sequencing is a method of determining the order of the genetic code of the human body, comparing normal and potentially abnormal sequences. The human genome project has mapped the entire human genome, helping researchers better understand how the genetic code works and why. By understanding the genetic code, scientists can learn how genes work together for the overall structure and function of the human body. Scientists can then compare the genome of individuals for diagnostic purposes and learn more about genetic variations and disorders.

Description

The human genome is the foundational code that makes up not only our structure and function, but also what we are as a genus and species. Each species has its own unique genome. This explains the many differences between species with the same genus, as well as the reason why reproduction can only occur within the same species.

The genome is comprised of the complete set of DNA (deoxyribonucleic acid) and all of its associated genes. The Human Genome Project, an international genome research project conducted from 1990 to 2003, determined the roughly three billion sequences of four nucleic acids that the human genome is made up of. With this information, the research alliance was also able to determine the 25,000 (approximately) genes that are coded based on the DNA sequence and the location of these genes on each of the autosomal and sex chromosomes in the human body.

Ninety-nine percent of humans share the exact same genome. Variations from the norm in the genetic code result in abnormalities and genetic disorders. These variations occur when the code is being replicated to produce new individuals as seen in meiosis, or when the code is being replicated for cell growth and proliferation as seen in mitosis. Comparing abnormal code to normal code will help scientists understand the relationship between the genome and genetic abnormalities such as disorders and pathologies.

Genome sequencing has led to the correlation of genetic disorders and their underlying gene abnormality. Many more phenotypes can be diagnosed and associated to a genotype now that this information is confirmed. This information can also be applied to the development of pharmaceuticals and other treatment and management protocols that are essential in improving the prognosis of an individual with a genetic variation. Knowing and understanding the exact location and mechanism by which a genetic variation is formed, and therefore inherited, has also allowed for in vitro genetic screenings and diagnosing to be effectively performed. Additionally, the human genome and genome sequencing will ideally help researchers fully understand not only genetic anomalies, but also the development of pathologies such as cancers, and how to best treat those cancers.

Genome sequencing in non-humans has also allowed researchers to better understand the biological functions of organisms such as viruses, bacteria, protozoa, and prions among others. Much like the way researchers use the information gained from the human genome sequence, researchers can utilize the information obtained from these organisms and apply it to treatment and



A laboratory assistant analyzes a DNA sequence on the computer. (*science photo/Shutterstock*)

management protocols to fight against the diseases they cause within humans.

Methods

Genome sequencing of an individual is very useful in determining the genetic cause of a disorder for all Mendelian genetic disorders. This information can lead to a development of treatment and management options, genetic testing of future offspring, and possibly prevention of a disorder. There are many methods by which genome sequencing is currently performed, and advancements to the efficiency and cost-effectiveness of these methods are being updated as research becomes applicable.

Next-generation sequencing

Next-generation sequencing is the most current type of sequencing utilized. It is widely used due to its ability to sequence a large portion of the genome in a short amount of time, making it very useful and also cost-effective. With next-generation sequencing, an entire genome can be sequenced in roughly one hour. This type of sequencing is

used when a differential diagnosis is complex and an exact gene correlation is not known.

The reaction is done by extracting DNA from an individual (either through white blood cells or saliva), breaking the DNA down into fragments, and then amplifying the information via polymerase chain reactions. Whole genome sequencing and whole exome sequencing are also performed to ensure all pieces of the DNA are sequenced. This is done in millions of parallel sequences called multiplexing, as opposed to a single sequence done by older genome sequencing methods. Next-generation sequencing can also be more specific to certain genes or chromosomes as needed, depending on what the test is looking for. Because next-generation sequencing is still a new tool, more research is needed to validate its clinical efficacy. In addition, bioinformatics, computer technology, and trained personnel need to be available in order for this sequencing technique to reach its fullest clinical potential.

Sanger sequencing

Sanger sequencing was the previously preferred method of genome sequencing. It uses a strand of DNA, a polymerase chain reaction, a gel electrophoresis, and

KEY TERMS

DNA—Deoxyribonucleic acid, the main component in chromosomes and the substance that carries all genetic material.

Genetic code—A set of instructions for transferring genetic data stored in the form of DNA or RNA into proteins.

Genome—The entire genetic material of an organism.

Meiosis—The cellular process that results in the number of chromosomes in gamete-producing cells being reduced to one half and involves a reduction division in which one of each pair of homologous chromosomes passes to each daughter cell and a mitotic division.

Mitosis—A process that takes place in the nucleus of a dividing cell, typically a series of steps consisting of prophase, metaphase, anaphase, and telophase, and resulting in the formation of two new nuclei, each having the same number of chromosomes as the parent nucleus.

Nucleic acids—Any of various acids (such as DNA or RNA) that are found in living cells.

fluorescent tags on each of the four nucleotides to determine the order of nucleotides in the original strand of DNA.

Sanger sequencing is widely used when the differential diagnosis is being confirmed by genetic testing, typically after signs and symptoms are associated with a certain disorder. This is because Sanger sequencing can only sequence one DNA segment at a time, taking up to a few days to a few weeks to complete the sequence of one portion of the genome. It is not a good method to use when the genetic basis of a disorder is not narrowed down to a particular gene because it would take a lot of trial and error, and therefore time and money, to determine a genetic cause of a DNA using this method.

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Genomic medicine

Definition

Genomic medicine involves personalizing health care and treatment based on each person's unique genetic makeup. Genomic medicine is also sometimes called personalized medicine, precision medicine, or individualized medicine.

Description

Historically, medical study focused on treating rather than preventing disease and was based on a one-size-fits-



A technician monitors a beaker containing a yeast-tryptone culture medium, which will grow yeasts or bacteria that contain human DNA strands for genomic research. (James King-Holmes/Science Source)

KEY TERMS

Biomarker (biological marker)—A chemical, physical, or biological indicator that can be measured and can be used to assess health and disease.

Cell—Building block that provides structure to the body and performs all the functions of the body. Cells contain genetic information and can copy themselves. The four main types of cells are: skin, nerve, muscle, and connective tissue.

DNA (deoxyribonucleic acid)—The genetic material that contains the instructions for creating proteins.

DNA base—One unit in a DNA sequence. The four DNA bases are adenine (A), guanine (G), thymine (T), and cytosine (C). The sequence of these bases is the genetic code that contains the instructions for creating proteins.

DNA sequence—The order of DNA bases that contains the instructions for creating proteins. A three-base sequence in the DNA contains the instructions for making a particular amino acid.

Gene—A sequence of bases in a DNA sequence that contains the instructions for a protein.

Genetic biomarker—A variant in DNA, RNA, or protein that can be measured and is an indicator of

disease. These biomarkers can be used to assess the expression, function, or regulation of a gene.

Genome—The complete set of genetic instructions of an organism.

Mitochondria—Structures found in the cell (organelles) surrounded by two layers of membrane. Mitochondria turn energy from food into energy that powers the cell. They also help the cell produce heat, store calcium, and choose which damaged cells need to be destroyed.

Mitochondrial DNA (mtDNA)—The DNA (genetic material) found in the mitochondria. MtDNA contains the instructions for about 37 genes. These genes produce proteins that help the mitochondria function. MtDNA is only passed from the mother to her offspring.

Pathogenic variant—Any change in the sequence of a genome that causes disease.

RNA (ribonucleic acid)—The genetic material that is involved in creating proteins.

Variant—Change in the sequence of a genome.

all approach. This approach does not work for some people because common diseases are caused by a complex combination of genetic and environmental factors that vary among individuals. A study by the U.S. Food and Drug Administration (FDA) found that 38% to 75% of individuals with a common disease such as heart disease or diabetes do not significantly improve with treatment. One explanation is that medical treatment is based on statistical averages rather than on each patient's specific genetics.

Genomic medicine addresses this problem by personalizing treatment to each person's unique genotype. This approach holds promise for improving the quality of life, decreasing mortality, and reducing healthcare costs.

Genomic medicine has many benefits:

- predicting how susceptible a person is to a disease
- helping providers prescribe more effective drugs with fewer side effects
- increasing efficiency of pharmaceutical trials
- preventing disease rather than just treating it
- improving disease detection

- reducing the amount of trial and error involved in disease treatment

Examples of genomic medicine

Genetic testing

Genetic testing seeks the cause of a disease by looking for pathogenic variants (mutations) in DNA, RNA and in some cases mitochondrial DNA. Early genetic testing was based on symptoms and looked for large changes in chromosomes or variants in one or two genes. This approach is time-consuming and often does not yield results.

Subsequent approaches, such as whole genome sequencing and whole exome sequencing, helped to expedite a diagnosis and led to more effective treatment. Whole genome sequencing looks for variants in the whole genome. Whole exome sequencing looks for variants in the protein-coding parts of the genome that contain the genes.

Pharmacogenomics

Pharmacogenomics studies how certain gene variations affect the safety of certain medications and how well

QUESTIONS TO ASK YOUR DOCTOR

- Could my condition be better treated using genomic medicine?
- Could pharmacogenomic testing help me?
- Should my family have genetic testing?

they will work. Advances in this field have produced genetic tests that can help doctors choose the best medication and dose for each patient.

For example, variations involving the *CYP2D6* gene can influence the metabolism of codeine into morphine. Ultra-rapid metabolizers, people who have a duplicate of this gene, turn codeine into morphine faster and make greater amounts of morphine. They are at greater risk of having an overdose if they use codeine and may have serious problems as a result. Breastfeeding mothers with this variation who use codeine may provide excessive amounts of morphine to their baby and thus cause serious breathing problems in the infant and even death. People with another variant in *CYP2D6* do not metabolize codeine very well. Codeine does not work very well for these people, and they may need to use an alternative pain reliever.

Targeted drug therapies

Genomic medicine has helped researchers design targeted drug therapies based on genetic biomarkers. A genetic biomarker is usually a variant in DNA, RNA, or protein that can be measured and is an indicator of disease. Many targeted therapies based on the measurement of biomarkers have been developed to treat cancer. For example, 20% to 25% of women with breast cancer produce too much HER2 protein. This protein causes the tumor cells to grow more rapidly. HER2 is measured in women with breast cancer, and those with higher levels of this protein see improved outcomes if they are given the antibody trastuzumab along with their chemotherapy.

Gene therapy

Gene therapy involves treating a disease by adding, removing, or changing the genetic material in the cells of a patient. The transferred genetic material is typically DNA or RNA. DNA is genetic material that contains the genes that have the instructions for the production of proteins. Proteins are responsible for the structure and all the functions of our body and cells. RNA is the genetic material that carries out the instructions for the production

of proteins coded in the DNA. Gene therapy seeks to correct abnormal genes that are not functioning properly. The goal of gene therapy is to cure disease rather than just treat symptoms.

Using genomic medicine to prevent disease

Genomic medicine can help prevent disease by identifying those who would benefit from specific treatments before they have symptoms. For example, women with pathogenic variants in a *BRCA* gene have a high risk of developing breast and ovarian cancer. Prophylactic surgeries before the onset of symptoms, such as bilateral removal of the breasts (mastectomy) and ovaries, can reduce the risk of breast cancer by about 95%, the risk of ovarian cancer by 80%, and the risk of death by 68%.

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Genotype see **Genotype and phenotype**

Genotype and phenotype

Definition

The term “genotype” describes the actual set (complement) of genes carried by an organism. In contrast, “phenotype” refers to the observable expression of characters and traits coded for by those genes. Although phenotypes are based upon the content of the underlying genes composing the genotype, the expression of those genes in observable traits (phenotypic expression) is also, to varying degrees, influenced by environmental factors.

Description

The term “genotype” was first used by the Danish geneticist Wilhelm Johannsen (1857–1927) to describe the entire genetic or hereditary constitution of an organism. In contrast, Johannsen described displayed characters or traits (for example, anatomical traits, biochemical traits, physiological traits, etc.) as an organism’s phenotype.

Genotype and phenotype represent very real differences between genetic composition and expressed form. The genotype is a group of genetic markers that describes the particular forms or variations of genes (alleles) carried by an individual. Accordingly, an individual’s genotype includes all the alleles carried by that individual. An individual’s genotype, because it includes all of the various alleles carried, determines the range of traits possible (for example, an individual’s potential to be afflicted with a particular disease). In contrast to the possibilities contained within the genotype, the phenotype reflects the manifest expression of those possibilities (potentialities). Phenotypic traits include obvious observable traits as height, weight, eye color, hair color, etc. The presence or absence of a disease, or symptoms related to a particular disease state, is also a phenotypic trait.

A clear example of the relationship between genotype and phenotype exists in cases where there are

dominant and recessive alleles for a particular trait. Using a simplified monogenetic (one gene, one trait) example, a capital “T” might be used to represent a dominant allele at a particular locus coding for tallness in a particular plant, and the lowercase “t” used to represent the recessive allele coding for shorter plants. Using this notation, a diploid plant will possess one of three genotypes: TT, Tt, or tt (the variation tT is identical to Tt). Although there are three different genotypes, because of the laws governing dominance, the plants will be either tall or short (two phenotypes). Those plants with a TT or Tt genotype are observed to be tall (phenotypically tall). Only those plants that carry the tt genotype will be observed to be short (phenotypically short).

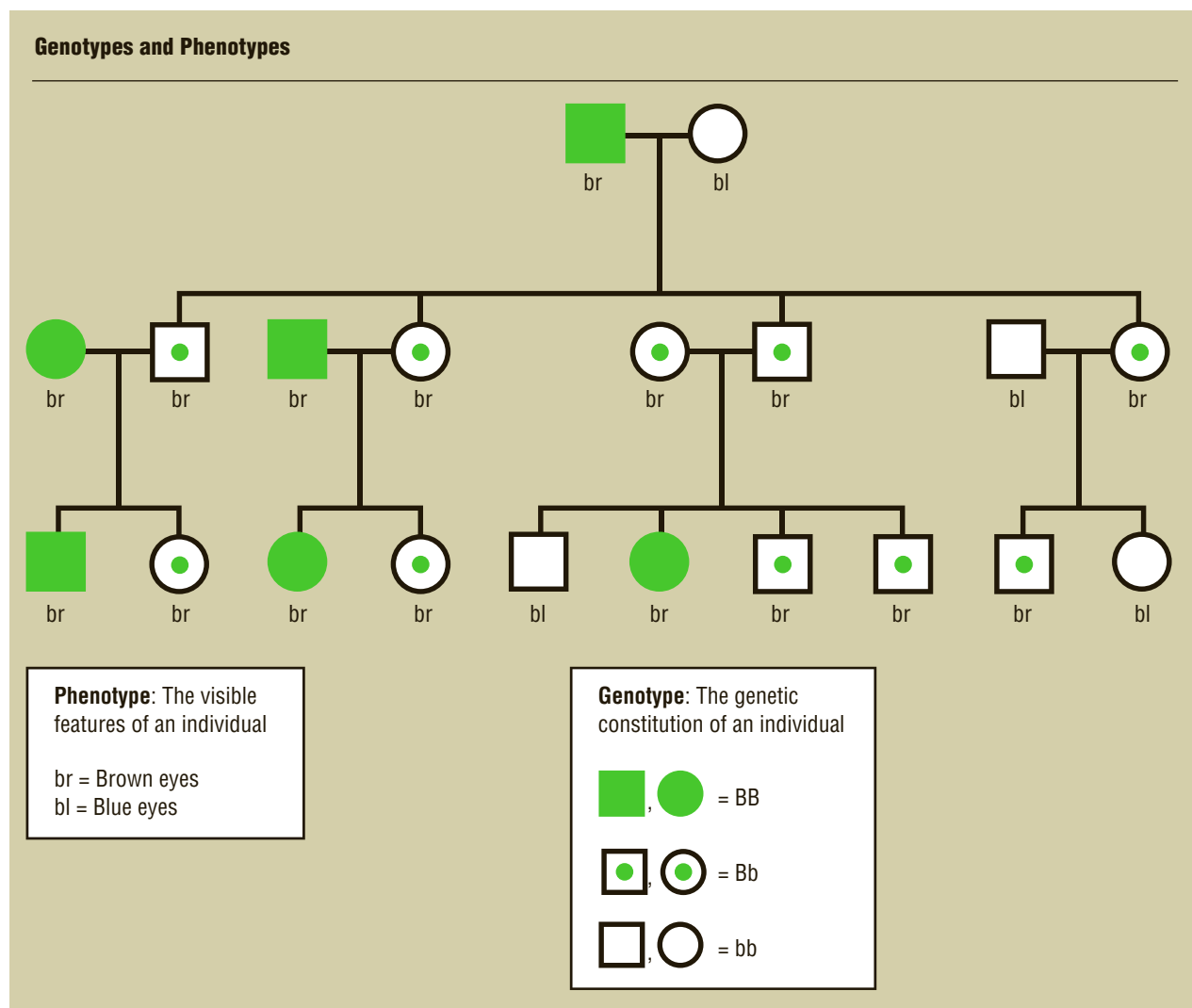
In humans, there is genotypic sex determination. The genotypic variation in sex chromosomes, XX or XY, decisively determines whether an individual is female (XX) or male (XY), and this genotypic differentiation results in considerable phenotypic differentiation.

Although the relationships between genetic and environmental influences vary (i.e., the degree to which genes specify phenotype differs from trait to trait), in general, the more complex the biological process or trait, the greater the influence of environmental factors. The genotype almost completely directs certain biological processes. Genotype, for example, strongly determines when a particular tooth develops. How long an individual retains a particular tooth is to a much greater extent determined by environmental factors such diet, dental hygiene, etc.

Because it is easier to determine observable phenotypic traits that it is to make an accurate determination of the relevant genotype associated with those traits, scientists and physicians place increasing emphasis on relating (correlating) phenotypes with certain genetic markers or genotypes.

There are, of course, variable ranges in the nature of the genotype-environment association. In many cases, genotype-environment interactions do not result in easily predictable phenotypes. In rare cases, the situation can be complicated by a process termed phenocopy, when environmental factors produce a particular phenotype that resembles a set of traits coded for by a known genotype not actually carried by the individual. Genotypic frequencies reflect the percentage of various genotypes found within a given group (population) and phenotypic frequencies reflect the percentage of observed expression. Mathematical measures of phenotypic variance reflect the variability of expression of a trait within a population.

The exact relationship between genotype and disease is an area of intense interest to geneticists and physicians, and many scientific and clinical studies focus on the



Genotypes and phenotypes: pedigree analysis chart (Gale)

relationship between the effects of genetic changes (for example, changes caused by mutations) and disease processes. These attempts at genotype/phenotype correlations often require extensive and refined use of statistical analysis.

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Genotype tissue expression project (GTEx)

Definition

The genotype tissue expression project (GTEx) is an NIH Common Fund program with the purpose of examining the differences in how genes are expressed and regulated in different tissues of the body. The GTEx project was established with the goal of creating an information resource and associated tissue bank for scientific researchers.

Description

The GTEx project was established by the NIH (National Institutes of Health) in 2010 to address a gap in the knowledge of how genetic variation correlates with gene expression in multiple tissues. Previous studies using genome wide association studies (GWAS) had identified thousands of single nucleotide polymorphisms (SNPs) at chromosome locations within the human genome. A large number of SNPs have been linked to disease; however, because many SNP variants do not result in a change in the protein, the link between how specific SNPs effected changes in gene expression in a specific tissue or disease was not clear. To address this knowledge gap, the NIH funded the GTEx project with the goal of examining the link between tissue-specific gene expression and genetic variation. This included the development of a tissue bank for samples and the development of a website to function as a resource database.

By analyzing RNA expression levels as quantitative traits within individual tissues, variations in expression that are tightly linked with genetic variation will be identified as expression quantitative trait loci (eQTLs). SNPs that are correlated with gene expression level are known as eSNPs. Approximately 10% or more of gene transcripts are eSNPs located close to the gene (cis-eQTLs), while trans-eQTLs are those in which the eSNP is located far from the gene. The interpretation of GWAS study findings is one application of the identification of cis- and trans-eQTLs, which will create a foundation for studying gene regulation.

The primary goals outlined in the 2008 GTEx Workshop included development of coordination centers and storage locations, with the initial collection of tissues from 160 autopsy/transplant donors and 160 surgery patients to begin in 2010. Long-term goals of the GTEx project included the collection of tissues from an additional 900 donors over the following three years. During this process, a standard group of tissues (50–70 per autopsy donor) are collected and processed using

KEY TERMS

caHUB Acquisition of Normal Tissues—The Cancer Human Biobank, a section of which is dedicated to the storage of tissues for the GTEx project.

Donor Recruitment and Tissue Collection Centers (DRTCCs)—Several locations designated for identifying and enrolling donors and acquiring multiple tissue samples from each, using best practices for sample collection, handling, fixation, and storage.

Expression quantitative trait loci (eQTL)—Locations within the genomic loci that contribute to expression of mRNAs.

Gene expression—The process in which a gene is transcribed into mRNA, and then translated into a protein. Multiple methods of regulation are used by cells to tightly control the levels of gene expression.

Genome-wide association study (GWAS)—A study of common genetic variants between individuals to identify whether a variant is linked to a trait. Primarily used in assessing the link between SNPs and an associated disease.

Laboratory, Data Analysis, and Coordinating Center (LDACC)—The center designated for the coordination for the GTEx project, including sample processing and de-identification, database management, and eQTL analysis.

Single nucleotide polymorphisms (SNPs)—Single nucleotide variant (SNV); a variation or point mutation in a single nucleotide building block of DNA.

consistent methods. Collected tissues are then sent for processing at the Laboratory, Data Analysis, and Coordinating Center (LDACC).

The LDACC is responsible for the coordination of the overall GTEx project. These duties include:

1. Tracking and receiving samples and the de-identification of patient data.
2. Performing nucleic acid extraction and purification, genotyping, and RNA quantification by microarray and next-generation sequencing.
3. Performing statistical analyses to identify eQTLs.
4. Management and integration of all phenotypic and molecular data into the GTEx database at the National Center for Biotechnology Information (NCBI).
5. Organization of major GTEx activities, including working group meetings.

QUESTIONS TO ASK YOUR DOCTOR

- What information associated with my illness is available in the GTEx?
- If I were interested in donating tissues to the GTEx project, how would I proceed?
- What are the risks associated with tissue donation to GTEx?

The Cancer Human Biobank (caHUB) plays a key role in the GTEx project. The caHUB Acquisition of Normal Tissues in Support of the GTEx Project was a key initiative that allowed for the collection and storage of samples associated with the GTEx project. Additionally, the Brain Bank repository has provided the resources needed for the storage of brain tissue samples.

The data generated by the GTEx project have been designated by the NIH as a community resource. The majority of the data will be easily available through NIH resources on the Internet, with limitations placed on the accessibility of data that may impact donor identification. Some elements of the data that include sensitive identifiers will be accessible to the scientific community only through a controlled access system called the database of Genotypes and Phenotypes (dbGAP). As of 2015, research analyses were currently being published using data from 175 individual donors enrolled in the pilot study.

The GTEx project is a powerful tool for understanding the links between genetic variation and gene expression across many tissue types. The project provides a resource and a framework for understanding eQTLs in many tissues and will aid in the interpretation of GWAS findings in the ongoing research of many diseases.

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GTEx Consortium, National Human Genome Research Institute, GTExInfo@mail.nih.gov, <https://commonfund.nih.gov/GTEx/index>

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Germline genome editing

Definition

Germline genome editing makes changes to the genetic material (genome) in eggs, sperm, or early embryos that can be passed down to future generations. The main goal of germline editing is to fix pathogenic (disease-causing) mutations and prevent genetic disease in offspring and future generations. Although considered unethical, it could also, potentially, be used to change characteristics of offspring such as height or intelligence.

Description

Early genome editing involved inducing mutations through radiation or chemical treatment in the laboratory. These techniques were not targeted and produced changes at random sites in the genome. The first experiments involving targeted editing of the genome were done on yeast and mice in the 1970s and 1980s. This early targeted editing was inefficient and could not be easily used in other species.

Many modern techniques of genome editing, which had their advent in the 2000s, rely on programmable (targeted) nucleases. Programmable nucleases cut DNA or RNA at a specific site and stimulate the desired change in the sequence. One of the most powerful genome editing techniques that uses programmable nucleases is CRISPR/Cas, a tool derived from the immune system of bacteria. CRISPR/Cas can be used to change an organism's DNA by making a cut in the DNA at a specific location and tricking the body's DNA repair mechanism to make the desired change. Doing so allows researchers to repair errors in the

KEY TERMS

Cell—Building block that provides structure to the body and performs all the functions of the body. Cells contain genetic information and can copy themselves. The four main types of cells are: skin, nerve, muscle, and connective tissue.

DNA (deoxyribonucleic acid)—The genetic material that contains the instructions for creating proteins.

DNA base—One unit in a DNA sequence. The four DNA bases are adenine (A), guanine (G), thymine (T) and cytosine (C). The sequence of these bases is the genetic code, which contains the instructions for creating proteins.

DNA sequence—The order of DNA bases that contains the instructions for creating proteins. A three-base sequence in the DNA contains the instructions for making a particular amino acid.

Gene—A sequence of bases in a DNA sequence that contains the instructions for one protein.

In vitro fertilization (IVF)—A form of assisted reproductive technology (ART) in which embryos are formed in the lab by mixing eggs and sperm, culturing the embryos, and then transferring the embryos to a recipient's uterus.

Mitochondria—Structures found in the cell (organelles) surrounded by two layers of membrane. Mitochondria turn energy from food into energy that powers the cell. They also help the cell produce heat, store calcium, and choose which damaged cells need to be destroyed.

Mitochondrial DNA (mtDNA)—The DNA (genetic material) found in the mitochondria. MtDNA contains the instructions for about 37 genes. These genes produce proteins that help the mitochondria function. MtDNA is only passed from the mother to her offspring.

Mitochondrial mutation—Variation in the mitochondrial DNA that can affect how well the mitochondria functions.

Pathogenic variant—Any change in the sequence of a genome that causes disease.

Programmable nucleases—DNA or RNA cutting enzymes from bacteria that can be programmed for genome editing to cut at a specific location and stimulate changes in the sequence.

RNA (ribonucleic acid)—The genetic material that is involved in creating proteins.

Variant—Change in the sequence of DNA.

sequence. Unfortunately, it can also cause unintended changes in the genome in other locations. Germline genome editing using CRISPR/Cas can result in a mosaic embryo, in which some cells are without the genetic change while other cells contain the genetic change. This effect can result in abnormalities in the embryo.

Genome editing can be performed in either somatic or germline cells. Somatic gene editing involves changing the genetic material in a tissue or cell other than sperm or egg cells. Somatic gene editing is often used to correct an error in the genetic material that results in a missing or abnormal protein. Somatic gene editing fixes that error so that a functioning protein is produced in the cells that are targeted. This can be done on cells outside the body that are transferred back to the patient or directly on cells in the body.

Somatic gene editing changes are not passed on to offspring. For example, in one trial, researchers removed cells from a patient who had a genetic variant (mutation) that caused the production of defective hemoglobin protein. Hemoglobin is used to transfer oxygen to the various parts of the body. Researchers corrected the variation in the removed cells that subsequently produced normal

hemoglobin. The repaired cells were then transferred back into the patient and produced normal hemoglobin. This treatment fixed the blood cells, but not the egg or sperm cells; it could, therefore, not be passed on to their offspring.

If the researchers had changed the hemoglobin variation in the egg or sperm cells or an early embryo, then this procedure would be called germline genome editing. These types of changes cause permanent changes in the individual and the person's offspring.

Germline genome editing can involve the transfer of mitochondrial DNA from a donor female to an egg cell. This technique can be used to improve fertility and fix errors in the mitochondrial DNA of offspring. Mitochondria are structures found in the cell that produce most of the energy needed to power the cell. Mitochondria contain mitochondrial DNA (mtDNA), which is only passed from the mother to her offspring. Although this technique has resulted in the birth of healthy children, it has also resulted in miscarriages and children with abnormalities.

Ethical issues

Germline genome editing performed in the laboratory rather than on humans can help researchers discover

how genetic variants affect disease and how they can be treated. In human medicine, germline genome editing has the potential to be a powerful tool to cure genetic disease and prevent its transmission to future generations.

There are, however, potential ethical concerns when germline editing is applied to humans:

- It could increase prejudice against people with genetic disease.
- It could be used to improve desirable traits rather than curing disease, which can have unintended societal consequences.
- It could result in unintended changes in the genome, which could cause cancer, genetic disease, and other problems.

An example of how germline genome editing can go wrong occurred in 2018 when Chinese scientists performed germline editing using CRISPR/Cas on twin girls to make them more resistant to HIV. Unfortunately, the gene variation introduced into the babies may also have made them and future generations more susceptible to other infections, such as influenza. This germline editing using CRISPR/Cas may also have introduced other unintended mutations. This experiment received international condemnation and renewed calls for an international moratorium on germline editing. The scientists involved were sent to prison and fined as a result.

Most scientists support a moratorium on using CRISPR/Cas for germline editing until more research is done and global ethical guidelines are developed. The United States has a moratorium on this type of germline editing, and it is banned in many other countries.

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Germline mosaicism

Definition

Germline mosaicism occurs when some of the eggs or sperm have a different genetic makeup than others within the same organism. The term is often used to describe mosaicism for a pathogenic variant that causes disease and can be passed on to future offspring.

Description

Mosaicism happens after conception, and it results when only some cells of the body have a genetic variant and others do not. Humans start from one cell, which results from the fusion of an egg and sperm. This one cell, the zygote, normally contains 23 chromosome from the egg and 23 from the sperm. The chromosomes are made up of DNA packaged with protein, and contain the instructions for the development and functioning of the human body.

All the cells in the body are derived from this zygote and ideally should be identical copies. However, sometimes these cells are not identical copies because one of the cells acquires a genetic variant. If this happens, then all of the cells that come from this cell will have this variant. As of 2021, what causes this variant was unknown, but in some cases it may result from certain types of environmental exposure. Mosaicism happens if the variant occurs only in some of the cells of the body and not in others.

Germline mosaicism occurs when some of the reproductive (germline) cells have a genetic variant while others do not. If the variant originates in one of the germline cells, then the person will have isolated germline mosaicism, which does not affect the other cells of the body. Somatic mosaicism happens if the variant is found in some of the somatic cells, which are cells other than the egg or sperm cells and that are not involved in reproduction. If the variant happens early in embryonic development before the germline cells and somatic cells have separated into two different cell lines, then the person will have both somatic and germline mosaicism. If the variant

occurs in a somatic cell after the cell lines branch off, then the person will only have somatic mosaicism.

In some cases the variant is minor and does not cause disease. If it does cause disease, then it is called a pathogenic variant. In many cases when people refer to germline mosaicism, they are referring to a pathogenic variant.

Parents with germline mosaicism of pathogenic variants are at increased risk for having children with the genetic disease caused by the variant. The chances that this variant will be passed on to a child depend on how many germline cells have the variant and the type of condition. The number of affected germline cells cannot be measured. The recurrence risks range from 1% to 30%.

If an egg or sperm with the variant results in a zygote, then the resulting fetus will have the variant in all of its cells. The child will have inherited the genetic disease caused by the variant. This child will not have mosaicism, but will have a higher chance of passing the genetic disease on to offspring. People who only have somatic mosaicism are not at increased risk for having a child with the condition.

People with isolated germline mosaicism do not have symptoms since they do not have the pathogenic variant in any of their somatic cells. People with combined somatic and germline mosaicism may have symptoms of the disease. The severity of the symptoms depends on how many somatic cells have the variant. The symptoms that an individual with only somatic mosaicism will have depend on how many cells have the variant.

The frequency of germline mutations depends on the condition. Some conditions, such as Alport syndrome, which results in progressive kidney failure, seem to have a low rate of germline mosaic. Other conditions, such as some hemophilia and muscular dystrophies, have a relatively high germline mosaicism rate of 11% to 20% in cases in which the disease seems to originate in the child.

Germline mosaicism can be hard to detect, especially in women, and is often inferred if someone has multiple children with a variant that is not found in the blood cells of either parent. If the variant is present in enough sperm cells, then germline mosaicism can be confirmed through analysis of the sperm.

Examples

The variants in germline mosaicism are sometimes chromosome abnormalities. More commonly they are point mutations or small pieces missing or duplicated or added to the DNA. A point mutation is an error in the DNA sequence in which one DNA base is substituted for another or inserted or deleted.

Germline mosaicism usually occurs in autosomal dominant and X-linked disorders. An autosomal dominant disorder is caused by a pathogenic variant in one copy of a particular gene. This gene is found on one of the 22 autosomes, the non-sex chromosomes. Autosomal dominant conditions are inherited from one of the parents. Parents who have an autosomal dominant condition and do not have germline mosaicism have a 50% chance of passing the disease on to their offspring. The risk is lower for parents with germline mosaicism but hard to estimate.

An X-linked condition is caused by a pathogenic variant on the X chromosome. Females have two X chromosomes, and males have an X and Y chromosome. These are called the sex chromosomes. Females get one X chromosome from their mother and one from their father. Males get one X chromosome from their mother and one Y chromosome from their father. Males are affected when they inherit the gene variant from their mother. In most cases, a female who inherits a pathogenic variant in one copy of the gene that causes the X-linked condition does not have symptoms. She is called a carrier female. There are exceptions; some carrier females can have symptoms. Carrier females without germline mosaicism have a one-in-two (50%) chance that their sons will be affected and one-in-two (50%) chance that their daughters will be carriers. Daughters of affected males will be carriers, and sons of affected males will not be affected.

There have been rare case reports of germline mosaicism in autosomal recessive disorders. A person who has an autosomal recessive condition has a pathogenic variant (mutation) in both copies of a gene that causes this condition. This gene is found on one of the 22 autosomes. Their parents are each carriers of one variant. A carrier for an autosomal recessive genetic disease has a pathogenic variant (mutation) in one copy of a gene and one functioning copy of that same gene. Carriers often do not have symptoms because they have one functioning copy of the gene. Two carriers of an autosomal recessive condition who do not have germline mosaicism have a one-in-four (25%) chance of passing it on to their children.

Most cases of germline mosaicism (80%) happen in males. Germline mosaicism happens more frequently in sperm as male germline cells undergo many more cell divisions to produce sperm. This increases the likelihood that a variant will occur. Advanced paternal age seems to increase the risk of germline mosaicism.

Germline mosaicism in females is rarer. It is mainly seen in X-linked conditions such as Duchenne muscular dystrophy. Occasionally, autosomal dominant conditions

KEY TERMS

Autosomal dominant—Condition caused by a pathogenic variant (mutation) in one copy of a particular gene. Individuals with an autosomal dominant condition have a one-in-two (50%) chance of passing it on to their children.

Autosomal recessive—Condition caused by a pathogenic variant (mutation) in both copies of a particular gene. Two carriers of an autosomal recessive condition have a one-in-four (25%) chance of passing it on to their children.

Carrier—Person who has a pathogenic variant in one copy of a gene that causes an autosomal recessive condition. Carriers often do not have symptoms. Two carriers of an autosomal recessive condition have a one-in-four (25%) chance of passing it on to their children.

Cell—Building block that provides structure to the body and performs all the functions of the body. Cells contain genetic information and can copy themselves. The four main types of cells are: skin, nerve, muscle, and connective tissue.

Chromosome—The package of DNA found in each cell of the human body apart from the red blood cells. Humans have 22 pairs of autosomes (1 to 22) and one pair of sex chromosomes (XY). Females have two X chromosomes, and males have an X and Y. Normally, humans inherit one chromosome of each pair from their mother and one from their father.

DNA (deoxyribonucleic acid)—The genetic material that contains the instructions for creating proteins.

DNA base—One unit in a DNA sequence. The four DNA bases are adenine (A), guanine (G), thymine (T), and cytosine (C). The sequence of these bases is the genetic code that contains the instructions for creating proteins.

DNA sequence—The order of DNA bases that contains the instructions for creating proteins. A three-base sequence in the DNA contains the instructions for making a particular amino acid.

Gene—A sequence of bases in a DNA sequence that contains the instructions for one protein.

Germ cells—The cells that create the egg and sperm cells (gametes).

Germline—Cells, including the egg, sperm, and fertilized egg that pass on their genetic material to the next generation of cells.

In vitro fertilization (IVF)—A form of assisted reproductive technology (ART) in which embryos are formed in the lab by combining eggs and sperm, culturing the embryos, and then transferring the embryos to the recipient's uterus.

Mosaicism—A condition in which a single multicellular organism has more than one genetic line in its cells as the result of genetic mutation.

Pathogenic variant—Any change in the sequence of a genome that causes disease.

Point mutation (DNA)—Error in the DNA sequence in which one DNA base is substituted for another or inserted or deleted.

Somatic cells—Cells of the body that are not involved in reproduction.

Variant—Change in the sequence of DNA.

X-linked—A condition caused by a pathogenic variant on the X chromosome. Most X-linked conditions are found in males who have one X chromosome and one Y chromosome. Females are less likely to have symptoms if only one of their X chromosomes has a pathogenic variant (mutation), since they have two X chromosomes.

result from female mosaicism. In most of these cases, the female has somatic mosaicism as well.

A parent who has no symptoms and has multiple children with an autosomal dominant or X-linked genetic condition might have germline mosaicism. For example, there is a case report of a healthy truck driver without symptoms who fathered three children with different mothers along his truck route in Brazil, with each of the children having the same genetic disease. Genetic testing discovered that all three half-siblings had the same pathogenic variant. The variant was not found in this man's

blood cells, indicating that he did not have the condition. Sequencing of his sperm cells, however, revealed that he had germline mosaicism.

Germline mosaicism is known to occur in female carriers of X-linked disorders such as alpha-thalassemia X-linked intellectual disability syndrome. This condition is characterized by severe intellectual disability, characteristic facial features, and mild anemia. Females with germline mosaicism for this condition have a variant for this disorder in some of their egg cells but not in their blood cells.

QUESTIONS TO ASK YOUR DOCTOR

- Is it possible that my partner or I have germline mosaicism?
- What is the chance that I will have another child with the condition?
- Can I have prenatal testing for my next pregnancy?

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Giant congenital melanocytic nevus

Definition

Congenital melanocytic nevi (CMN) are pigmented skin growths that can vary in shape and size across the surface of the body. They are present at birth and can cover all regions of the body. CMN are also called birthmarks or moles. When they cover large areas of the skin, CMNs can be classified as giant melanocytic nevi.

Description

CMNs can present as light brown to black patches of various sizes on the skin. In extreme cases of giant CMNs, these patches can cover nearly the entire surface of the body. These nevi are present at birth and usually grow in proportion to the body size as the child develops. Those afflicted with giant nevi will likely have many smaller satellite nevi of various sizes that can develop during the first few years of life.

There are three forms of CMN: small-sized nevi that are less than two centimeters in diameter (0.78 in), medium-sized nevi that are greater than two centimeters but less than 20 centimeters (7.87 in) in diameter, and giant-sized nevi that are characterized by one or more large, darkly pigmented patches that are heterogeneous in composition and may have excess hair. A giant CMN is also referred to as a bathing trunk nevus, garment nevus, and giant hairy nevus.

Some congenital nevi may be light in color or not pigmented at all, but may develop over time into darker, more prominent nevi. CMNs can be superficial or span several layers of the dermis. They can also associate with neurovascular bundles, hair follicles, and subcutaneous fat cells. CMNs can resemble melanomas, but multiple benign nevi are characteristic of the congenital condition. Abnormal and normal melanocytes develop from populations of embryonic cells that also contribute to the development of the central nervous system. Giant CMNs can develop on the tissue covering the brain and spinal cord in an associated condition called neurocutaneous melanosis. The growth of CMNs in these tissues can put pressure on the brain and lead to symptoms such as headaches, seizures, mobility problems, and sometimes brain tumors.

Genetic profile

Congenital melanocytic nevus conditions are associated with somatic mutations in genes that are responsible for the regulation of protein signaling pathways associated with cell proliferation and development. Approximately four out of five cases are caused by mutations affecting the NRAS enzyme, and one in six cases are caused by mutations affecting the BRAF enzyme. Single mutations in these genes can cause abnormal and unregulated enzyme activity.

NRAS is a member of a family of genes that code for GTPase proteins. These proteins are important for the regulation of signaling pathways that mediate cell division and differentiation in a number of tissue types. BRAF is an enzyme called a serine/threonine protein kinase; these proteins are often involved in signaling cascade pathways that regulate cellular growth. GTPase proteins modulate kinase activity, and mutations in either a GTPase or a kinase can alter the ability of cells to divide, grow, and differentiate properly. In CMN, mutations in the *BRAF* or

KEY TERMS

Lesion—A defective or injured section or region of the brain (or other body organ).

Melanocyte—A cell that can produce melanin.

Melanocytic nevus—A nevus that contains pigmented skin cells called melanocytes. Melanocytic nevi are skin lesions that are also commonly described as moles.

Melanoma—Cancer that develops in melanocytes, the pigmented skin cells.

Nevus (plural, nevi)—Any anomaly of the skin present at birth, including moles and various types of birthmarks.

NRAS genes that make them constantly active in skin tissue can contribute to an overproduction of melanocytes.

Mutations in *NRAS* or *BRAF* are usually sporadic but can be inherited as autosomal dominant mutations. Multifactorial inheritance may contribute more to CMN occurrence than direct parental inheritance.

Demographics

Giant CMN occurs in 0.002% of births worldwide. It occurs in all races and genders equally.

Signs and symptoms

Symptoms of giant CMN include the presence of a large, darkly colored patch of skin, usually on the trunk of the body. CMN is present at birth, and additional nevi of various sizes can also be present or develop over the life of the individual. Nevi can be raised from the surface of the skin, have a different texture from other parts of the skin, and range from light brown to black in color. Most nevi do not cause any pain, although nevi that are associated with nerves can be sensitive or itchy. In rare cases, CMN can develop on brain and spinal cord tissues, which can complicate neurological function.

Diagnosis

Congenital nevi can resemble melanoma, and larger nevi are at a higher risk of being or becoming malignant. In fact, melanoma develops in 1%–2% of people with CMN, and at earlier life stages than those without CMN. Diagnosis of the various forms of CMN depends on clinical and dermoscopic features. Size, topology, extension into the dermis, and the association with nerves, hair follicles, and blood vessels are all part of diagnosing cases

QUESTIONS TO ASK YOUR DOCTOR

- Is nevus skin different from “normal” skin?
- What are the causes of CMN?
- Are there health concerns associated with CMN that I should be aware of?
- Are there treatment options that are reasonable for my condition?

of CMN. Biopsies can be taken to characterize the histological features of the nevi and also to check for cancerous growth. Oftentimes lifelong monitoring is necessary to check for any changes in the nevi.

Treatment and management

Removal of nevi is often considered to reduce chances of cancer development and also for aesthetic reasons. Some nevi are superficial and easy to remove; other nevi with extensions that reach into the deeper layers of the skin require more invasive surgical removal. Excess hair and some superficial pigmentation can be removed with the use of laser treatments. There are risks of scarring, pain during recovery, and recurrence with nevus removal, so it is not always acceptable in all cases of CMN.

Palliative treatment tries to address itching or other discomfort that is sometimes associated with larger nevi. Some commercial creams and lotions are available, but they do not work for everyone.

Prognosis

With the exceptions of having a higher risk of developing melanoma and some rare cases of neurological complications associated with CMN, it is not a life-threatening condition.

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Nevus Outreach, 361 Southwest Drive, #353, Jonesboro, AR 72404, (918) 331-0595, (877) 426-3887, <http://www.nevus.org>

Skin Cancer Foundation, 205 Lexington Avenue, 11th Floor, New York, NY 10016, (212) 725-5176, <http://www.skincancer.org>

Emily R. Larson, PhD

Glanzmann thrombasthenia

Definition

Glanzmann thrombasthenia (GT) is an extremely rare inherited disorder in which there is abnormal function of a component of the blood called the platelets, leading to abnormalities in blood clotting and increased bleeding.

Description

Blood clotting, or coagulation, is the process by which several factors in the blood stick together to form a physical barrier that prevents bleeding. In response to a disruption in blood flow or bleeding because of injury, several factors in the blood clump together at the site of injury, sealing off the blood vessel and stopping blood loss in a process called hemostasis. If any of the factors that contribute to the process of coagulation and hemostasis are abnormal, dangerous bleeding conditions can result.

One of the factors involved in hemostasis is called the platelet. Platelets are small disc-shaped structures that circulate in the blood stream in an inactive state. When an injury occurs, platelets become activated and stick to fibrous proteins, called fibrinogen, that are also circulating in the blood stream. Because there are multiple sites on the fibrinogen proteins for platelets to bind, and vice versa, a cross-linked net or mass called a platelet plug is formed, which seals off the injury and prevents further bleeding. Next, the platelet mass actively contracts to form an even more solid mass in a process called clot retraction. Over time, repair cells can use this mass as a

scaffolding to lay down new tissue and thereby effect a permanent repair of the injury.

Platelets attach to fibrinogen through the use of specialized sugar proteins (glycoproteins) that are present on the platelet surface. There are two specific glycoproteins that form a complex responsible for the platelet-fibrinogen interaction: glycoprotein IIb and glycoprotein IIIa.

The platelet disorder GT results from an inherited defect in the glycoprotein IIb/IIIa complex (GP IIb/IIIa). As a result of this glycoprotein defect, platelets fail to stick to fibrinogen, leading to defective hemostasis and prolonged bleeding. GT is sometimes subdivided into different groups: type I, in which there is no functional GP IIb/IIIa; type II, in which small amounts of working GP IIb/IIIa can be detected; and variant thrombasthenia, in which the amount of working GP IIb/IIIa may vary. Glanzmann thrombasthenia has also been referred to by other names including thrombasthenia of Glanzmann and Naegeli, diacyclothrombopathia IIb-IIIa, Glanzmann disease, and glycoprotein complex IIb/IIIa deficiency.

GT was first described by the Swiss physician Edward Glanzmann in 1918. Glanzmann used the term “thrombasthenia,” meaning “weak platelets,” because clots from patients with the disorder did not retract well. Although the disease is exceedingly rare, platelets taken from people with the disease have been very useful in the research that first discovered how normal platelets function.

Genetic profile

GT is a genetic condition and can be inherited or passed on in a family. The disorder results from any number of different mutations that can occur in either the gene for glycoprotein IIb or the gene for glycoprotein IIIa (*ITGB3* and *ITGA2B*, both located on chromosome 17, locus 17q21.32), with defects split equally between the two genes.

In the majority of cases, it appears that the genetic abnormality for the disorder is inherited as an autosomal recessive trait, meaning that two abnormal genes are needed to display the disease. A person who carries one abnormal gene does not display the disease and is called a carrier. A carrier has a 50% chance of transmitting the gene to his or her children, who must inherit one abnormal gene from each parent to display the disease. People who are carriers of the abnormal gene appear to have only half-normal amounts of working GP IIb/IIIa, which is still sufficient for normal platelet function.

There are reports of a few families in which the defect is inherited in an autosomal dominant fashion. In this pattern of inheritance, only one abnormal gene is

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance in which only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are needed to display the trait or disease.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Coagulation—The process by which a liquid becomes a solid, as in blood clotting.

Fibrinogen—A fibrous protein that circulates in blood and participates in blood clotting by attaching to platelets.

Glycoprotein IIb/IIIa (GP IIb/IIIa)—Sugar proteins on the surface of platelets that bind to the fibrous protein, fibrinogen. These sugar proteins are defective in Glanzmann's thrombasthenia.

Hemostasis—The arrest of bleeding by blood coagulation.

Mutation—A change in the genetic material that may alter a trait or characteristic of an individual or manifest as disease.

Platelets—Small disc-shaped structures that circulate in the blood stream and contribute to blood clotting.

Transfusion—The injection of a component of the blood from a healthy person into the circulation of a person who is lacking or deficient in that same component of the blood.

needed to display the disease, and the chance of passing the gene to offspring is 50%.

Demographics

GT is exceedingly rare, with fewer than 1,000 cases identified. There are several groups in which the majority of cases of thrombasthenia have been discovered, including Iraqi Jews, Arabs living in Israel and Jordan, populations of south India, and French Gypsies of the Manouche tribe.

Signs and symptoms

Most people with GT will have a major bleeding event before the age of five. Common manifestations of the disease include nosebleeds, bleeding from the gums,

or skin rashes caused by bleeding into the skin (known as purpura or petechiae). Larger amounts of bleeding into underlying tissue may result in diffuse black bruises, usually seen on the arms and the legs. Normal handling of infants can cause superficial bruises and may be mistaken for abuse. As a result of chronic bleeding, patients may have lower amounts of red blood cells in their blood (anemia) and suffer from iron deficiencies. Rarely, there may be bleeding into the joints, causing disfigurement. Bleeding after traumatic accidents or after surgical operations and dental procedures may be profuse and require vigorous medical treatment. Prolonged untreated or unsuccessfully treated bleeding associated with GT may be life-threatening. For reasons that are unclear, severity of bleeding events appears to decrease with increasing age.

There are other concerns when GT is diagnosed in a woman. Because of the platelet disorder, women may experience particularly heavy menstrual bleeding. In fact, the first occurrence of menstrual bleeding in a young woman may be so severe that it requires prompt medical attention and treatment. Further, pregnancy and delivery represent severe bleeding risks and may not always be manageable with medical treatment.

Diagnosis

Glanzmann thrombasthenia is diagnosed through a combination of medical history, physical examination, and laboratory testing. Bleeding episodes and physical manifestations of the disease may prompt an investigation for the underlying cause. The presence of a bleeding disorder in more than one close or distant relative is especially important, as it may indicate that a genetic cause of the condition is involved.

Blood tests will reveal normal amounts of platelets. Tests performed with substances that stimulate platelet clumping though GP IIb/IIIa will show minimal effects as a result of the platelet defect. Conversely, tests performed using a different substance, ristocetin, which causes platelet clumping through different mechanisms, will provoke a brisk and appropriate platelet response. Other blood tests will reveal a longer than normal bleeding time, poor clot retraction, and may demonstrate low numbers of red blood cells and iron deficiency.

The diagnosis of GT is ultimately confirmed by investigating the GP IIb/IIIa glycoprotein complex. Antibodies that are specifically designed to distinguish between normal and abnormal GP IIb/IIIa can be used in a technique known as immunofluorescence (in which the antibody is attached to a fluorescent dye) or a test called a Western blot (in which proteins are first separated by size and then exposed to antibodies). These methods can also be used to detect people who are carriers of a mutant gene for GT by demonstrating only

QUESTIONS TO ASK YOUR DOCTOR

- Which technique do you recommend to confirm the diagnosis?
- Should family members be tested to see if they are appropriate platelet donors?
- How often are dental checkups recommended?
- What are the risks of bone marrow transplant?

half-normal amounts of GP IIb/IIIa. Prenatal diagnosis may also be possible but is not recommended as sampling of the blood in an affected fetus may lead to uncontrollable bleeding that could prove fatal.

Molecular genetic testing for both genes associated with GT is available as of 2021 from the Institute of Human Genetics in Germany. The test can be done on fibroblasts, peripheral whole blood, isolated DNA, or a white blood cell prep.

Treatment and management

Several medications can aid in the treatment of GT, while others should be avoided. Some patients will demonstrate shortening of their bleeding time with DDAVP, a medication that improves the function of platelets. Women who have heavy bleeding may benefit from birth control pills to prevent their menstrual periods. Nutritional iron supplements may alleviate or prevent the development of iron deficiency and will aid in restoring normal levels of red blood cells. Medications to be avoided are those that interfere with platelet function and predispose to bleeding, including aspirin, ibuprofen and ibuprofen-like drugs, heparin, warfarin, ticlopidine, clopidogrel, abciximab, streptokinase, urokinase, or tissue plasminogen activator.

The treatment of choice for stopping active bleeding is through transfusion of normal platelets that are obtained from donors without the disease. Studies have shown that most people (approximately 85%) with the disorder will require platelet transfusions during their lifetime. For individuals with GT, transfusion with one unit of platelets for every 11–22 lb. (5–10 kg) of body weight will correct the defect in blood clotting and may be life-saving. Pre-emptive transfusions are especially important before surgical operations or dental procedures. Transfusions should be continued until wound healing is complete.

Over time, platelet transfusion may become less effective. Platelets obtained from donors and given to a patient with GT are recognized by the immune system as foreign

cells. The immune system, in turn, generates antibodies that attach to the donor platelets and impair their function, ultimately leading to their destruction. Because of this unfortunate effect, platelet transfusions are best reserved for life-threatening bleeding or before procedures in which bleeding is likely. Using platelets from donors closely related to the patient may delay the immune response and extend the benefits of transfusion therapy.

Patients with GT should be followed closely by a hematologist, and should be vaccinated against the hepatitis B virus because of the high risk of exposure to the virus with ongoing blood-product transfusions. Patients should also be seen regularly by a dentist to prevent gum disease that could result in profuse bleeding. Genetic counseling can be offered to affected individuals or couples with a family history of the disorder.

Bone marrow transplantation is currently the only curative form of treatment for patients with GT. However, this is generally considered more hazardous than the disease itself, except in exceptional circumstances.

Prognosis

Although there is no cure, the prognosis for people with Glanzmann thrombasthenia is quite good. Despite the fact that the majority of people with this disorder will require medical treatment to control bleeding, patients rarely die of massive blood loss. Interestingly, the severity of bleeding appears to decrease with increasing age. Barring any catastrophic accident that results in uncontrollable bleeding, lifespan is approximately the same as the general population.

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Oren Traub, MD, PhD

Glaucoma

Definition

Glaucoma is a group of eye disorders that result in vision loss due to a failure to maintain the normal fluid balance within the eye. If fluid pressure builds up, damage to the optic nerve occurs, leading to vision loss. If detected in its early stages, vision loss can be prevented through the use of medications or surgical procedures that restore the proper fluid drainage of the eye. Glaucoma usually develops in older adults; however, early-onset glaucomas—primary congenital glaucoma (PCG) and juvenile open-angle glaucoma—are genetic disorders, and susceptibility genes have been identified for adult forms of glaucoma.

Description

Vision is an important and complex sense by which the qualities of an object, such as color, shape, and size, are perceived through the detection of light. Light that bounces off an object first passes through the cornea (outer layer) of the eye and then through the pupil and the lens, where it is projected onto a layer of cells at the back of the eye called the retina. When the retina is stimulated by light, signals pass through the optic nerve to the brain, resulting in a visual image of an object.

The front chamber of the eye is bathed in a liquid called the aqueous humor. This liquid is produced by a nearby structure called the ciliary body and is moved out of the eye into the bloodstream by a system of drainage canals known as the trabecular meshwork. The proper amount of fluid within the chamber is maintained by a balance between fluid production by the ciliary body and fluid drainage through the trabecular meshwork. When fluid accumulates in the front chamber, either because of an overproduction of fluid or because of a failure of the normal drainage routes, fluid pressure builds up within the eye. Over time, this increased fluid pressure causes damage to the optic nerve, resulting in progressive visual impairment. Increased eye fluid pressure leading to vision loss is known as glaucoma.



Close-up of the eye of a patient suffering from glaucoma, where the lens of the eye is peeling away from the iris; this pseudo-exfoliation is seen as grey within the pupil. Glaucoma is caused by a structural abnormality in the drainage angles of the eyes. (Sue Ford/Science Source)

Glaucoma is a group of many different eye disorders that can manifest alone; as a sign of more than 60 different diseases; or as a result of an injury to the eye. Glaucoma can also be classified by the age of the affected individual: infantile or congenital glaucoma affects infants at birth or children up to three years old; juvenile glaucoma affects individuals from age three to 30; and adult glaucoma affects people older than 30.

Types of glaucoma

The National Eye Institute (NEI) defines five types of glaucoma according to the abnormality in the eye drainage system:

- **Open-angle glaucoma.** This is the most prevalent type of glaucoma. It occurs when the eye drainage passage is narrowed but still open. The narrowing of the passage increases intraocular pressure (the pressure inside the eye), damaging the optic nerve. Juvenile open-angle glaucoma is a primary glaucoma that develops during childhood or early adulthood and is caused by a genetic mutation.
- **Low-tension or normal-tension glaucoma.** In this type of glaucoma, the intraocular pressure is normal, but optic nerve damage and narrowed side vision occur.
- **Angle-closure glaucoma.** This type of glaucoma is a medical emergency. The fluid at the front of the eye cannot reach the angle and leave the eye, because the angle is blocked by part of the iris. People with this type of glaucoma have a sudden increase in intraocular pressure.
- **PCG.** Children with this genetic condition are born with a defect in the angle of the eye that slows the normal



Collateral vessels of the optic disc in a glaucoma patient.
(Paul Whitten/Science Source)

drainage of fluid. It is also called childhood, pediatric, or infantile glaucoma.

- **Secondary glaucomas.** These glaucomas can develop as complications of other medical conditions. They can sometimes result from eye surgery, advanced cataracts, eye injuries, certain eye tumors, or uveitis (eye inflammation).

Genetic profile

Glaucoma usually develops in older adults, but abnormalities that impede fluid drainage in the eye may be present at birth (congenital glaucoma), with early onset of symptoms by about five years of age (juvenile glaucoma). Genome wide association studies have identified more than 125 genetic locations (loci) with gene mutations that can cause different types of glaucoma, and at least nine of the genes themselves have been identified.

There are at least eight mapped gene loci for open-angle glaucoma, and two of these genes (*MYOC* and *CYP11B1*) account for a fraction of cases. Approximately 10% to 33% of people with juvenile open-angle glaucoma have mutations in the *MYOC* gene. *MYOC* mutations can also result in primary congenital glaucoma (PCG). The *MYOC* gene provides instructions for producing a protein called myocilin that is found in the trabecular meshwork and the ciliary body of the eye that regulates the intraocular pressure. It is believed that defective myocilin may accumulate in the trabecular meshwork and ciliary body, thus preventing the flow of fluid from the eye and causing the increased intraocular pressure of glaucoma. Research has also shown that 20% to 40% of people with PCG and some people with

juvenile open-angle glaucoma have mutations in the *CYP11B1* gene. This gene provides instructions for producing a form of the cytochrome P450 protein found in the trabecular meshwork, the ciliary body, and other structures of the eye. Defects in the *CYP11B1* protein may interfere with development of the trabecular meshwork and/or regulation of fluid secretion from the inside of the eye. Other research has shown that the protein may interact with myocilin. Individuals with mutations in both the *MYOC* and *CYP11B1* genes may develop earlier-onset glaucoma and have more severe symptoms.

Mutations in other genes also appear to be involved in congenital or early-onset glaucoma. Mutations in the *LTBP2* gene, encoding latent-transforming growth factor beta-binding protein 2, can cause PCG. Two other loci also have been linked to PCG.

Glaucoma can be inherited in either an autosomal recessive (PCG) or an autosomal dominant manner (juvenile open-angle glaucoma). In autosomal recessive inheritance, two abnormal genes are needed to cause the disease. A person who carries one abnormal gene does not have symptoms of the disease and is known as a carrier. A carrier has a 50% chance of transmitting the gene to a child, who must inherit one abnormal gene from each parent in order to develop the disease. Alternately, in autosomal dominant inheritance, only one abnormal gene is needed to develop the disease, and the chance of passing the gene and the disease to offspring is 50%. PCG is also inherited in an autosomal dominant pattern in some families. The presence of two mutated *CYP11B1* genes increases the risk of severe disease and glaucoma in both eyes and is linked to a family history of PCG as well as parental consanguinity (relatedness). If the mutations (pathogenic variants) have been identified in the parents or other affected family members, prenatal diagnosis and carrier testing are available for *CYP11B1* and *LTBP2* mutations. Genetic testing is also available for *CYP11B1* and *MYOC* mutations that cause open-angle juvenile glaucoma.

Other gene variants associated with the development of primary open-angle glaucoma (POAG) include *SVEP1*, *RERE*, *VCAM1*, *ZNF638*, *CLIC5*, *SLC2A12*, *YAP1*, *MXRA5*, and *SMAD6*.

Demographics

Glaucoma is the leading cause of preventable blindness in the United States and the third leading cause of blindness worldwide. It can develop at any age, but people over 45 are at higher risk. The prevalence of glaucoma increases with advancing age, reaching 10%

Types of glaucoma and related genetic information

Disorder	Alternative names	Inheritance	Abnormal protein	Abnormal gene	Gene location
Glaucoma 1, open angle, A (GLC1A)	Juvenile onset primary open-angle glaucoma; Hereditary juvenile glaucoma	Autosomal dominant	Trabecular meshwork-induced glucocorticoid response protein (myocilin)	MYOC, (also known as TIGR, GLC1A, JOAG, GPOA)	1q24.3–q25.2
Glaucoma 1, open angle, B (GLC1B)	Adult onset primary open-angle glaucoma; Hereditary adult glaucoma	Autosomal dominant	Unknown	Unknown	9q34.1 2qcen-q13; (additional loci under investigation)
Glaucoma 1, open angle, C (GLC1C)	Adult onset primary open-angle glaucoma; Hereditary adult glaucoma	Autosomal dominant	Unknown	Unknown	3q21–q24
Glaucoma 1, open angle, D (GLC1D)	Adult onset primary open-angle glaucoma; Hereditary adult glaucoma	Autosomal dominant	Unknown	Unknown	8q23
Glaucoma 1, open angle, E (GLC1E)	Adult onset primary open-angle glaucoma; Hereditary adult glaucoma	Autosomal dominant	Unknown	Unknown	10p15–p14
Glaucoma 1, open angle, F (GLC1F)	Adult onset primary open-angle glaucoma; Hereditary adult glaucoma	Autosomal dominant	Unknown	Unknown	7q35–36
Glaucoma 3, primary infantile, A (GLC3A)	Congenital glaucoma; Buphthalmos	Autosomal recessive	Cytochrome P4501B1	CYP1B1	2p22–p21
Glaucoma 3, primary infantile, B (GLC3B)	Congenital glaucoma	Autosomal recessive	Unknown	Unknown	1p36.2–36.1
Iridogoniodysgenesis, type 1 (IRID1)	Iridogoniodysgenesis anomaly; familial glaucoma iridogoniodysgenesis	Autosomal dominant	Forkhead transcription factor	FKHL7	6P25
Iridogoniodysgenesis, type 2 (IRID2)	Iridogoniodysgenesis anomaly; Iris hypoplasia with early-onset glaucoma	Autosomal dominant	Paired-like homeodomain transcription factor-2	PITX2 (also known as IDG2, RIEG1, RGS, IGDS2)	4q25–q26
Rieger syndrome, type 1 (RIEG1)	Iridogoniodysgenesis with Somatic anomalies	Autosomal dominant	Paired-like homeodomain transcription factor-2	PITX2 (also known as IDG2, RIEG1, RGS, IGDS2)	4q25–q26
Rieger syndrome, type 2 (RIEG2)	Iridogoniodysgenesis with Somatic anomalies	Autosomal dominant	Unknown	Unknown	13q14
Glaucoma-related pigment dispersion syndrome (GPDS1)	Pigment dispersion syndrome and pigmentary glaucoma	Autosomal dominant	Unknown	Unknown	7q35–q36

Types of glaucoma and related genetic information (Gale)

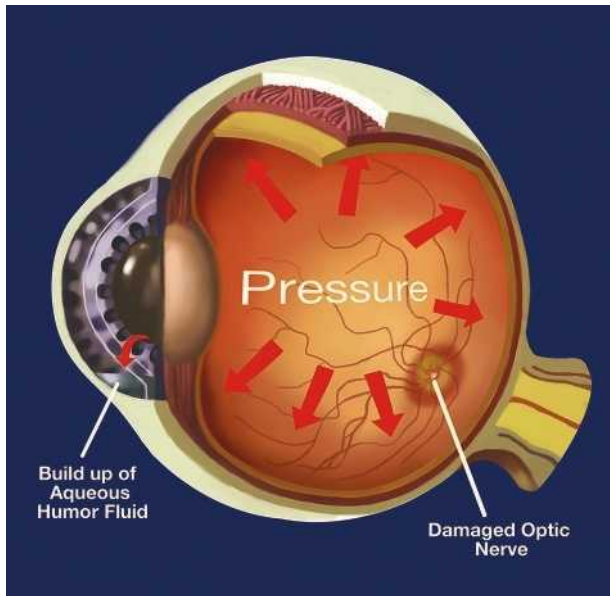
in persons age 90 and older. Primary congenital glaucoma (PCG) affects approximately one in 10,000 people. The frequency is higher in the Middle East. Juvenile open-angle glaucoma affects about one in 50,000 people. Primary open-angle glaucoma (POAG) affects about 1% of the population over age 40. Asians are more prone to angle-closure glaucoma, as are the Inuit in Canada and Greenland.

Signs and symptoms

In the adult and juvenile forms of open-angle glaucoma, vision loss begins at the periphery (outer edges) of

the visual field, resulting in tunnel vision. Because the visual loss is not in the individual's central vision, he or she might not notice this change. However, if the glaucoma is left untreated, loss of vision progresses, and central vision is often affected, sometimes resulting in blindness. The average time from development of high eye fluid pressure to the appearance of visual loss is 18 years in the adult form, but much shorter in the juvenile form.

In contrast to the adult and juvenile forms, congenital or infantile open-angle glaucoma is noted at birth or within the first three years of life. Symptoms include cloudy corneas, excessive tearing, and sensitivity to light.



Glaucoma is an eye disease in which increased fluid pressure in the eye causes damage to the optic nerve. Glaucoma will damage vision or cause blindness if left untreated. If the condition is detected early enough, it is possible to halt or arrest the progression of the disease.
(Spencer Sutton/Science Source)

Because the eye is very flexible in infants, increased fluid pressure may cause bulging of the eye (buphthalmos or “ox eye”). Children with glaucoma in only one eye are usually diagnosed earlier because a difference in eye size is noticeable. When the disorder affects both eyes, many parents view the large eyes as attractive and do not seek medical help until other symptoms develop, delaying the diagnosis.

With angle-closure glaucoma, symptoms come on suddenly. People may experience blurred vision, severe pain, headache, sensitivity to light, and nausea. The development of this type of glaucoma is an emergency and requires immediate treatment.

Diagnosis

The diagnosis of glaucoma may be suggested by certain physical findings, especially in infants, but it is confirmed by tests with special instruments. Parents may bring their young infant to a physician if they notice changes in the eye shape and size, both of which are signs of infantile glaucoma. Diagnosis of PCG and open-angle juvenile glaucoma may be confirmed with genetic testing.

In adults who do not show obvious signs of glaucoma, the condition is frequently detected by routine eye exams and other tests. Using an ophthalmoscope (a handheld or machine-mounted instrument with a light

source), a physician or optometrist will look through the pupil to the back of the eye. There, he or she may detect characteristic changes in the region where the optic nerve meets the eye, called the optic disk.

In another portion of a routine eye exam, an ophthalmologist or optometrist will measure the fluid pressure of the eye through the use of a special instrument called a tonometer. The test is painless and involves brief contact of a small probe with the surface of the eye. Presence of elevated pressure (more than 21 mm Hg) means that a person is at risk for glaucoma.

Once high pressure or changes in the optic disk are noted, an ophthalmologist can also use a gonioscope (a small lens with a reflecting mirror) to inspect the drainage passageways of the eye and determine whether they are blocked. Visual field tests (in which individuals indicate whether they can see small flashing lights that are directed at different spots in their visual field) are used as a final indicator for the presence of glaucoma or a measurement of how far glaucoma-related visual loss has progressed.

Treatment and management

Although there is no treatment for the optic nerve injury and vision loss caused by glaucoma, it is possible to prevent further visual loss by lowering eye fluid pressure. In adults, this is primarily achieved through medications, which can reduce eye fluid pressure by either decreasing fluid production or increasing fluid drainage from the eye. The medications can be taken orally (by mouth) or applied to the eye through drops. The different classes of medications used to treat glaucoma include beta-blockers, alpha agonists, carbonic anhydrase inhibitors, and prostaglandin analogues.

For infantile glaucoma, the treatment is usually surgical. Laser surgery or microsurgery to open the drainage canals can be effective in increasing drainage of eye fluid. Other types of surgery can be performed to reduce the amount of fluid production. Many children require several operations to lower or maintain their eye fluid pressure adequately, and long-term treatment with medications may be necessary.

For angle-closure glaucoma, immediate hospitalization and treatment with medication is required. Once the person’s condition has been stabilized, laser surgery is used to create a passageway for fluid drainage.

All individuals with glaucoma should see an ophthalmologist regularly to evaluate progression of the condition and whether it is being adequately treated. Beginning at the age of 40, all people should have regular screening exams to detect early signs of glaucoma.

KEY TERMS

Angle-closure glaucoma—An increase in the fluid pressure within the eye due to a complete and sometimes sudden blockage of the fluid-drainage passages.

Aqueous humor—Fluid produced by the ciliary body and contained within the front chamber of the eye.

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a non-sex chromosome is required for a disease or inherited trait to develop in an individual.

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are needed to display the trait or disease.

Buphthalmos—A characteristic enlargement of one or both eyes associated with infantile glaucoma.

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light, resulting in blurry vision. Surgery may be performed to remove the cataract.

Ciliary body—A structure within the eye that produces aqueous humor.

Cornea—The transparent structure of the eye over the lens that is continuous with the sclera in forming the outermost, protective layer of the eye.

Gonioscope—An instrument used to examine the trabecular meshwork; it consists of a magnifier and a lens equipped with mirrors.

Open-angle juvenile glaucoma—Hereditary glaucoma that develops in childhood or early adulthood

and can be caused by mutations in the *MYOC* or *CYPB1* genes.

Ophthalmologist—A physician specializing in the medical and surgical treatment of eye disorders.

Ophthalmoscope—An instrument with special lighting designed to view structures in the back of the eye.

Optic disk—The circular area at the back of the eyeball where the optic nerve connects to the retina.

Optic nerve—A bundle of nerve fibers that carries visual messages from the retina in the form of electrical signals to the brain.

Optometrist—A medical professional who examines and tests the eyes for disease and treats visual disorders by prescribing corrective lenses and/or vision therapy. In many states, optometrists are licensed to use diagnostic and therapeutic drugs to treat certain ocular diseases.

Primary congenital glaucoma (PCG)—Glaucoma that is present at birth or develops during the first year of life and can be caused by mutations in the *CYPB1* or *LTBP2* genes.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Tonometer—A device used to measure fluid pressures in the eye.

Trabecular meshwork—A sponge-like tissue that drains the aqueous humor from the eye.

People with a family history of glaucoma or with diabetes should be screened beginning in young adulthood.

Promising research

In 2021, researchers from Santen Inc., Massachusetts Eye and Ear, and Ulster University announced the formation of a global research initiative to study and develop new treatments for glaucoma. Research will focus on ways to preserve vision by preventing, slowing, or reversing damage caused by glaucoma. The same year, another international collaboration between the Moscow Institute of Physics and Technology and Harvard Medical School reported the first successful attempt to grow and transplant retinal ganglion cells, specialized neurons that are damaged in glaucoma, developed from stem cells.

Retinal ganglion cells are responsible for transmission of visual information. Although this first attempt was an animal study, researchers hope that this technology will be ready for use in humans in about 10 years.

Clinical trials

Clinical trials on glaucoma are sponsored by the National Institutes of Health (NIH) and other agencies. As of 2021, the NIH listed 245 recruiting, ongoing, and active clinical trials for PCG. Clinical trial information is continually updated.

Prognosis

Since even small degrees of vision loss due to glaucoma cannot be reversed, early detection of the condition

QUESTIONS TO ASK YOUR DOCTOR

- Which type of early-onset glaucoma does my child have?
- What is the inheritance pattern for early-onset glaucoma?
- Should we have genetic testing for genes that cause glaucoma?
- What is our risk of having another child with early-onset glaucoma?
- Is prenatal testing available for early-onset glaucoma?

through regular eye examinations is critical. If glaucoma is detected early, lifelong medical treatment can halt the progress of the disease and maintain relatively normal vision. If left undiagnosed or untreated, many people with glaucoma progress to blindness.

Angle-closure glaucoma is an emergency, and the prognosis depends on the severity of the attack and how quickly medical attention is obtained. Left untreated, the condition can quickly lead to total vision loss in the affected eye.

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- American Academy of Ophthalmology, P.O. Box 7424, San Francisco, CA 94120-7424, (415) 561-8500, (415) 561-8533, <http://www.aao.org>
- American Optometric Association, 243 N. Lindbergh Boulevard, St. Louis, MO 63141-7881, (314) 991-4100, <http://www.aoa.org>
- Glaucoma Foundation, 80 Maiden Lane, Suite 700, New York, NY 10038, (212) 285-0080, info@glaucomafoundation.org, <http://www.glaucomafoundation.org>
- National Eye Institute, Information Office, 31 Center Drive MSC 2510, Bethesda, MD 20892-2510, (301) 496-5248, 2020@nei.nih.gov, <http://www.nei.nih.gov>
- Prevent Blindness, 225 West Wacker Drive, Suite 400, Chicago, IL 60606, (800) 331-2020, <http://www.preventblindness.org>

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Revised by Barbara Wexler, MPH

GLB1 deficiency see **GM1-gangliosidosis**

Globoid cell leukodystrophy (GCL) see
Krabbe disease

Glucocerebrosidase deficiency see **Gaucher disease**

Glycine encephalopathy

Definition

Glycine encephalopathy is a genetic disorder that results from too much of the amino acid glycine in the body tissues, including the brain.

Description

Mutations in either of two genes can cause glycine encephalopathy. Mutations in one of the genes, known as the glycine dehydrogenase (decarboxylating) or *GLDC* gene, cause more than four-fifths of all cases. Another 10%–15% of cases result from mutations in the other gene, called the aminomethyltransferase, or *AMT* gene. The remaining 5%–10% of cases may have other causes, including mutations in a gene known as the glycine cleavage system protein H (aminomethyl carrier), or *GCSH*.

GLDC and *AMT*, the two main genes related to glycine encephalopathy, carry the instructions for making enzymes that are an important part of the mechanism involved in breaking down glycine. Glycine is an amino acid (a building block of proteins) that is also very important in the transmission of nerve impulses.

When one of these genes is defective, glycine does not break down as it should. Instead, it accumulates in tissues and organs, notably the spinal cord and brain, where it can be toxic. When this buildup occurs, the person may experience symptoms such as intellectual disability and seizures.

There are four forms of glycine encephalopathy:

- classical (or neonatal), in which symptoms appear soon after birth (the most common form of the disease)
- infantile, which usually develops when the infant is about six months old
- late onset, which may have severe and rapidly progressing symptoms
- transient glycine encephalopathy, in which glycine levels are high at birth but return to normal or near-normal later on, and which has few or no symptoms

Glycine encephalopathy is also called nonketotic hyperglycinemia (NKH).

Genetic profile

Most cases of glycine encephalopathy result from mutations in the *GLDC* or *AMT* genes, both of which lead to an overproduction of glycine. Glycine encephalopathy is an autosomal recessive disorder, which means that a child must inherit one copy of the mutated gene from each parent. The parents may not have the condition

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are needed to display the trait or disease.

Glycine—An amino acid (a building block of proteins) that is important in the transmission of nerve impulses.

Hypotonia—Low or poor muscle tone, resulting in floppy limbs.

Lethargy—Fatigue.

Neurotransmitter—Chemical in the brain that transmits information from one nerve cell to another.

Nonketotic hyperglycinemia (NKH)—Glycine encephalopathy.

Vertical gaze palsy—Uncontrolled up and down motions of the eye.

themselves but may only be carriers of the mutation. Carriers are individuals who do not develop a disorder but may pass the gene for the disorder on to their children. If both parents are carriers, each of their children has a 50% chance of being a carrier and a 25% chance of having the disorder. If both parents have glycine encephalopathy, all of their children will have the disorder.

The *GLDC* gene is located on chromosome 9, and the *AMT* gene is located on chromosome 3. The *GLDC* gene carries the instructions for making an enzyme called glycine dehydrogenase, and the *AMT* gene holds the blueprint for making an enzyme called aminomethyltransferase. These two enzymes are part of an enzyme complex known as the glycine cleavage system that works in mitochondria (the powerhouses of cells) to break down glycine. Normally, the brain has enough glycine to help transmit signals within the central nervous system. When an individual inherits a mutated *GLDC* or *AMT* gene from both parents, glycine does not break down properly. As a result, excess glycine builds up to the point that it interferes with the normal transmission of nerve signals.

Not all *GLDC* or *AMT* mutations are the same. Scientists know of more than a dozen different mutations in the *AMT* gene and more than 40 mutations in the *GLDC* gene that can lead to glycine encephalopathy. Mutations may include the following:

- substitutions of amino acids
- insertion of added genetic material into the gene
- removal of some genetic material from the gene

QUESTIONS TO ASK YOUR DOCTOR

- Based on the symptoms in the early stages of late-onset glycine encephalopathy, how can the mild episodic form be distinguished from the rapidly progressing form?
- Is it possible to increase the dosage of sodium benzoate to improve its effects?
- What are the side effects, if any, of sodium benzoate?
- What scientific evidence, if any, is available that demonstrates that sodium benzoate can help improve mental development?
- Is genetic testing available for the mutations that cause glycine encephalopathy?

Depending on the specific mutation, the glycine dehydrogenase or aminomethyltransferase may not function at all or may function in a reduced capacity.

GCSH, the gene associated with much rarer mutations related to this disorder, is located on chromosome 16 and is also part of the glycine cleavage system.

Demographics

The overall prevalence of glycine encephalopathy is unknown. Studies in Finland and in British Columbia, Canada, however, have indicated an incidence in newborns of between 1 in 55,000 and 1 in 63,000. The British Columbia study also estimated a carrier frequency of about 1 in 125.

Both male and female children are affected with the disorder at similar frequencies, but males with the classical type have milder symptoms and a higher survival rate than females with the classical type. The reason for this disparity is unknown.

Signs and symptoms

Symptoms associated with the classical type of glycine encephalopathy may include the following:

- progressive lethargy
- poor muscle tone (hypotonia)
- difficulty breathing, sometimes severe or even life-threatening
- feeding problems
- jerking of the muscles, sometimes leading to a failure of respiratory muscles and death

- severe intellectual disability
- seizures
- coma

Symptoms associated with the infantile form may include the following:

- delayed development beginning at about six months of age
- seizures
- intellectual disability that develops over time
- behavioral problems

Symptoms associated with the late-onset form may be severe and worsen rapidly. They include the following:

- spasms and weakness of the legs
- degeneration of the optic nerve that connects the eye to the brain and helps produce vision
- mild intellectual disability
- abnormal movements of the body (choreoathetosis)

Among individuals with transient glycine encephalopathy, many show no effects from the temporarily high glycine levels and go on to live normal lives. In some cases, however, patients with this form of the disease may experience seizures and some level of mental disability even after their glycine levels drop to normal or near-normal. Other symptoms that occur in some patients include the following:

- sporadic episodes of abnormal body movements
- uncontrolled up and down motions of the eye (vertical gaze palsy)

Diagnosis

Examination

A doctor may suspect glycine encephalopathy if the patient has the set of symptoms described here. To form a diagnosis, however, the doctor will order tests.

Tests

Common tests for glycine encephalopathy are urine, cerebrospinal fluid, and/or blood analyses, which can identify high levels of glycine. Genetic screening may detect mutations in the *GLDC*, *AMT*, and/or *GCSH* genes. Newborns may be screened for glycine encephalopathy.

Treatment and management

No cure exists for glycine encephalopathy. Treatments are directed at specific symptoms.

Traditional

Various treatments may be available to ease certain symptoms. For instance, physical therapy may assist with hypotonia.

Drugs

Sodium benzoate may help decrease the glycine overload. It may also help reduce convulsions and improve behavioral problems in some individuals. The doctor may prescribe anticonvulsant medications to treat seizures. Studies are continuing on the use of other drugs for the treatment of symptoms such as decreased brain activity and delayed development.

Prognosis

People with classical glycine encephalopathy often have severe breathing difficulties, among other symptoms, and frequently die soon after birth. The infants that do survive initial breathing problems and begin to breathe on their own usually have profound intellectual disability as well as repeated seizures that are hard to control even with anti-seizure drugs.

Individuals with the infantile form of glycine encephalopathy have milder, sometimes remittent symptoms, but they typically experience at least moderate intellectual disability as the years go by. This form, as well as the mild-episodic and the rapidly progressing late-onset forms of the disorder, are so rare that prognosis is given on a case-by-case basis.

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ORGANIZATIONS

- Hope for NKH, 8904 232nd Street East, Graham, WA 98338, (253) 219-7535 or (989) 845-4253, hopefornkh@gmail.com, <http://hopefornkh.org>
- NKH Crusaders Foundation, (781) 249-1835, nkhcrusaders@yahoo.com, <http://www.nkhcrusaders.com>
- NKH International Family Network, admin@nkh-network.org, <http://www.nkh-network.org>
- Office of Rare Diseases Research. National Center for Advancing Translational Sciences, National Institutes of Health, 6701 Democracy Blvd., Suite. 1001, MSC 4874, Bethesda, MD 29892, (301) 402-4336, (301) 480-9655, ordr@nih.gov, <https://rarediseases.info.nih.gov>

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Glycogen storage diseases

Definition

Glycogen is a form of stored glucose that the body uses as an energy source. Glycogen storage disease (GSD) involves defects that cause an abnormal accumulation of glycogen, usually found in the liver, muscle, or both. When accumulation occurs in the liver, glycogen storage diseases result in liver enlargement and in conditions ranging from mild hypoglycemia to liver failure. When the accumulation occurs in muscle, glycogen storage diseases result in conditions ranging from difficulty exercising to cardiac and respiratory failure.

Description

Glucose is a simple sugar that functions as a critical energy source for most bodily functions. Glucose can be acquired through the diet or formed within the bodily cells. Levels of glucose in the blood are maintained in a very narrow range before and after the ingestion of food. Eating a meal supplies a high level of dietary glucose. Hormones, such as insulin, assist in the removal of glucose from the blood and into cells to be used as energy. Excess glucose is accumulated in the form of glycogen as a type of easily mobilized energy storage for use when food is not plentiful. Even while sleeping, glycogen stores are available to maintain blood glucose levels and energy for life.

The process of the formation of glycogen sheets is termed glycogenesis and is stimulated by hormones, such as insulin. The process of the breakdown of sheets of glycogen into usable glucose is termed glycogenolysis and is also under tight control. Hormones that stimulate glycogenolysis control enzymes to remove only the necessary amount of glucose from glycogen stores. With an average

daily food intake, glycogen stores are constantly being built up and broken down based on the needs of the body. Average glycogen stores serve as a short-term supply of glucose and need to be replenished daily. Glycogen serves as energy storage in every organ, but the liver and skeletal muscles are the main sites of glycogen deposition. The brain is dependent upon glucose for energy and so requires a certain level of blood glucose to be available at all times. Because the brain has only minimal glycogen stores, it is mainly dependent on glycogen from other organs, such as the liver.

Glycogen has separate functions in liver and muscle. Muscle uses glycogen as a fuel source with which to produce energy during activity. As muscle is being used, glycogen stores are being broken down into glucose, turned into cellular energy called ATP, and depleted. In the liver, glycogen is mainly used as a maintenance energy source for the entire body and is responsible for keeping blood glucose levels in a stable range. After ingestion of dietary glucose, the liver takes up many food breakdown products from the bloodstream, converts them into glucose, and stores them as glycogen. At some point after a meal, when blood glucose levels naturally fall, the liver uses its glycogen stores to replenish the blood with glucose. Organs that cannot create enough glycogen of their own are thus supplied.

Glycogen storage diseases may involve defects in glycogen breakdown or formation in muscle, liver, or both muscle and liver. Some classic features of GSDs that primarily involve muscle are muscle cramps, exercise intolerance, and easy fatigability. Some classic features of GSDs that primarily involve the liver are liver enlargement, liver function defects, and hypoglycemia. Most GSDs can have subtypes with onset at different stages of life. There are many types of GSD that involve different defects in glycogen utilization. The types of GSD that are best described are types I through VIII, each with a distinct name and profile.

Von Gierke disease

GSD type I is also known as von Gierke disease, which has two subtypes, GSDIa and GSDIb. GSDIa is caused by a defect in the catalytic subunit of the *G6PC* gene (17q21) in the enzyme Glucose-6-Phosphatase (G6P), which is involved in the release of precursor components from liver glycogen stores. GSDIb is caused by a defect in a protein transporter, Glucose-6-Phosphatase Transporter on the *SLC37A4* gene (11q23), used to transport the necessary precursor components of the pathway to the location of the enzyme. Without dietary glucose, the body is unable to access needed energy from the liver.

In times of fasting, which is essentially any time dietary glucose is not being ingested, severe hypoglycemia can result. Normal mechanisms are in effect in the body to sense a decrease in blood sugar, and they respond by increasing rates of glycogen breakdown to maintain blood glucose. Because of the defect in glycogen breakdown, this increase does not occur, and precursor molecules from the pathway accumulate. This causes liver enlargement and the protruding abdomen that is associated with the disease. In von Gierke disease, the defects in glycogenolysis occur at a point in the pathway that causes accumulation of glucose-6-phosphate. When glucose-6-phosphate accumulates, it diverts into other metabolic pathways that form lactic acid and uric acid. The lactic acid can acidify the blood and cause a dangerous condition known as acidosis. Uric acid accumulation can cause kidney stones and kidney dysfunction. There are also alterations in blood-clotting factors that cause these individuals to bleed very easily and for prolonged periods of time. These alterations can be dangerous. Frequent nosebleeds are associated with von Gierke disease as a result. Von Gierke disease Type Ib has other defects in blood immune system components that create susceptibility to some types of bacterial infections.

Pompe disease

GSD type II is also known as Pompe disease. There are three main subtypes of Pompe disease categorized as infantile, juvenile, and adult-onset. The infantile form primarily involves defects in utilization of cardiac muscle, skeletal muscle, and respiratory muscle. This form usually presents by the age of six months and is rapidly fatal, usually due to respiratory and cardiac failure. The adult form involves muscle glycogen stores other than cardiac muscle. The adult form is a progressive disease, but there are no heart defects. However, muscle weakness often results in respiratory failure. The juvenile form includes infants and children older than six months, and involves muscle weakness without cardiac defects. In general, the older a person is at the age of onset, the lesser the likelihood of cardiac involvement. Pompe disease is caused by defects in an enzyme, acid maltase (17q25.2-q25.3), involved in a side pathway of glycogenolysis that is not critical for most glycogen degradation. The main pathway for glycogen degradation is not defective in Pompe disease, so there is no hypoglycemia. The defect does cause an accumulation of glycogen that causes enlargement and dysfunction of the organs involved. In the infantile form of Pompe disease, this is the cause of heart disease, respiratory deficiency, and overall muscle weakness.

Cori disease

GSD type III is also known as Cori disease. Cori disease is caused by a defect in a debranching enzyme, Amylo-1, 6-glucosidase (mutations in the *AGL* gene [1p21]), that is responsible for breaking down the highly branched structure of glycogen in the liver, skeletal muscle, and cardiac muscle. This defect results in hypoglycemia that occurs a relatively short time after food intake. It is unknown why the defect in Cori disease may lead to liver damage and cancers that are not seen in von Gierke disease. It is known that the hypoglycemia that develops in Cori disease is directly involved and that the liver defects improve with age. Chronic hypoglycemia also contributes to skeletal and cardiac muscle damage in Cori disease not seen in von Gierke disease. The enzymatic defect in Cori disease also contributes to an increase in fat breakdown. Excessive breakdown of fatty acids leads to higher-than-normal levels of ketone acids, fat breakdown products, in the blood. A dangerous condition known as ketoacidosis may result in organ damage. Growth retardation is associated with Cori disease.

Andersen disease

GSD type IV is also known as Andersen disease, which usually causes symptoms within the first few years of life. Andersen disease is caused by a defect in a branching enzyme, glycogen branching enzyme (3p12.2), responsible for the highly branched structure of normal glycogen. In Andersen disease, glycogen has an abnormal, unbranched structure that cannot be properly broken down into glucose molecules and so accumulates. Most forms of Andersen disease involve the liver. Multiple bodily organs or systems may be affected, including the heart, gastrointestinal tract, skin, intestine, brain, blood formation, and nervous system. Andersen disease is characterized by liver enlargement, liver-induced hypertension (portal hypertension), liver cirrhosis and failure, and often death by five years of age. Some Andersen patients have a mild disease variant with later onset associated with a non-progressive form of liver disease. This subtype may have its onset even in adulthood. Some forms of Andersen disease have primarily muscle involvement that may include cardiac muscle. The abnormal glycogen in skeletal muscle results in weakness, exercise intolerance, and muscle wasting. Abnormal glycogen in cardiac muscle can lead to cardiac failure. The abnormal glycogen formed in Andersen disease can also affect the nervous system by impairing mental function.

McArdle disease

GSD type V is also known as McArdle disease. McArdle disease is caused by a defect in an enzyme, glycogen phosphorylase of muscle or myophosphorylase

(11q12-q13.2), involved in initiating glycogen breakdown, specifically in skeletal muscle. As a result, glycogen is not broken down into glucose in skeletal muscle, which causes a deficit in cellular energy (ATP). Normal energy utilization in skeletal muscle involves breaking down glycogen fuel stores into glucose and converting glucose into ATP for energy. During exercise, the amount of ATP required for performance is greatly increased. When muscle glycogen is depleted, muscle begins to use blood glucose and fat breakdown products for energy. Individuals with McArdle disease often experience a “second wind” phenomenon in energy levels during exercise because of these secondary fuel sources. However, McArdle disease still causes muscle cramps during exercise, and exercise intolerance.

Hers disease

GSD type VI is also known as Hers disease. Similar to McArdle disease, the classic form of Hers disease is caused by a partial defect in the liver glycogen phosphorylase enzyme (*PYGL* gene [14q21-q22]). This form of Hers disease involves a partial defect in liver phosphorylase, which initiates glycogen breakdown, specifically in the liver. Other forms exist that are caused by similar defects. Hers disease includes a heterogeneous group of subtypes with mild clinical consequences. Hers disease typically involves liver enlargement, muscle weakness, growth retardation, mild fasting hypoglycemia, and mildly elevated ketone levels during childhood that resolve by puberty. Most patients have only partial impairment of glycogenolysis due to the incomplete deficiencies of the enzymes involved.

Genetic profile

The GSDs are autosomal recessive diseases, which are caused by the inheritance of two defective copies of a gene. Each parent contributes one copy of the gene for the enzymes or transporters involved in GSDs. If both copies are defective, the result is disease. If only one defective copy is present, the disease does not occur but the defective gene can still be passed on to subsequent generations. If both parents carry a defective gene, then each offspring has a 1 in 4, or 25%, chance of inheriting the disease. Populations with a high frequency of healthy individuals carrying defective genes will also have higher prevalence of offspring with the disease.

Von Gierke disease GSDIa and GSDIb are caused by mutations on chromosomes 17 and 11, respectively. GSDIa is caused by deficient activity of the enzyme glucose-6-phosphatase, both negatively impacting glycogenolysis. Pompe disease is caused by mutations on chromosome 17 that result in different types of dysfunction of the enzyme glucosidase. Mutations in Pompe disease

may cause the complete absence of the enzyme, a normal amount of enzyme with reduced activity, or a reduced amount of enzyme with normal activity. The infantile subtype usually displays an absence of enzyme activity, whereas the other forms involve enzyme levels or functionality. Cori disease may involve many different mutations in chromosome 1, and any combination of defective genes may lead to the disease. There may be a generalized debrancher enzyme deficiency in Cori disease or genetic mutations in only some of the tissue-specific enzyme types.

All forms of Andersen disease result from mutations on chromosome 3 in the genes for glycogen-branching enzymes. The branched structure of glycogen is necessary for compaction and breakdown. The mutations seen in Andersen disease cause an abnormal unbranched form of glycogen. Mutations may be generalized for all types of branching enzyme or tissue-specific. McArdle disease can be caused by multiple types of mutations on chromosome 11 for the muscle-specific form of the phosphorylase enzyme. Most cases involve the functional absence of the enzyme. Hers disease is due to mutations in multiple genes on multiple chromosomes that cause defects in liver phosphorylase enzyme pathways. Some types of the Hers form are autosomal recessive, like other GSDs. Some subtypes have been reported that display X-linked recessive inheritance. In this mode of inheritance, mothers carrying defective X-linked genes can pass one copy to each offspring. However, because female offspring also receive a normal X-linked gene from the father, female offspring do not actually develop the disease. Male offspring who receive their only X chromosome from the mother can develop the disease.

Demographics

GSDs have autosomal recessive inheritance and so occur with equal frequency in both sexes. GSDs as a group have a frequency of 1 per 20,000–25,000 births internationally. Approximately 80% of all GSD cases are a combination of von Gierke, Cori, and Hers diseases, with each contributing equally. All three subtypes of Pompe disease combined are estimated to occur at a rate of 1 per 40,000 individuals in the United States, and they account for approximately 15% of GSD cases worldwide. Cori disease is prevalent among Sephardic Jews of North African descent. In this population, the frequency is approximately 1 per 5,400 individuals. Even within the same mutation type, the physical effects of Cori disease in this population are variable. Andersen disease is uncommon and is responsible for only 3% of all GSD cases. It is prevalent among Ashkenazi Jews. McArdle disease is also rare, with only a few hundred cases reported in the United States. It may be underdiagnosed

because of its mild disease course. Only a few cases of early-onset McArdle disease have been reported. Classic McArdle disease has an adolescent onset. However, cases have been reported with onset in the sixth decade of life. Hers disease is responsible for approximately 30% of GSD cases, while approximately 75% of Hers disease is the X-linked form. Hers disease is prevalent in the Menonite population, with a frequency of 0.1%. X-linked recessive forms of Hers disease are expressed primarily in affected males. Some breakthrough expression has still been reported in carrier females with mild symptoms.

Signs and symptoms

Von Gierke disease

Infants born with von Gierke disease display initial symptoms of hypoglycemia immediately following birth. These symptoms may include tremors, cyanosis (bluish tint in the skin and mucous membranes from lack of oxygen), and seizures. Some infants are born with enlarged livers and abdomens. Onset of von Gierke disease in an older infant may also include symptoms of fatigue, difficulty waking from long periods of sleep, tremor, extreme hunger, poor growth, short stature, and a protruding abdomen with thin limbs from liver enlargement. A doll-like facial appearance is often caused by fat deposits in the cheeks. Young children with von Gierke disease may additionally have fat deposits called xanthomas on the elbows and knees, frequent nosebleeds, gingivitis (inflammation of the gums), and skin boils. Symptoms of severe hypoglycemia at all ages are likely to follow any illness or circumstance that causes a decrease in food intake. In later years, children may have rickets and anemia. Enlarged kidneys may be discovered by ultrasound imaging techniques. Complications that may arise from von Gierke disease are severe hypoglycemia, liver cancer, kidney damage, fluid retention in the brain, coma, and death. In GSDIb, severe recurrent infections from immune compromise may also be a complication.

Pompe disease

Infants born with Pompe disease display initial symptoms of protruding abdomen due to liver enlargement, muscle enlargement, muscle weakness, and respiratory and feeding difficulty. Pneumonia is a complication. A heart murmur may be audible upon physical examination. Enlargement of the left ventricle of the heart may cause obstruction of blood flow and cardiac failure. The juvenile subtype of Pompe disease displays symptoms of delayed motor development, weakness, and poor muscle tone. The adult subtype has symptoms of muscle weakness, especially when performing tasks such as climbing stairs or exercising. Approximately one-third of cases involve respiratory complications.

Cori disease

Infants born with Cori disease may be healthy for the first few months of life, then present with initial symptoms of tremors, sweating, irritability, difficulty feeding, respiratory complications, seizures, coma, and sudden death. Older infants may also present with difficulty waking from sleep, poor growth, increased appetite, and dizziness. The level of hypoglycemia associated with this disease ranges from mild to severe. An enlarged liver may or may not be present. Some patients with Cori disease have improvement in the liver complications as they get older, but others develop liver cirrhosis, liver failure, and liver cancer after puberty. Approximately 85% of patients with Cori disease have significant involvement of both the liver and skeletal muscles. During childhood, complications with muscle are often minimal, but they progressively get worse with age to the point of disability. Some patients may develop an enlarged heart, but otherwise, cardiac defects are rare. Often, Cori disease causes poor growth with a short stature in children. If blood glucose levels are appropriately maintained, the attainment of normal growth is possible.

Andersen disease

Infants born with Andersen disease usually fail to thrive during the first year of life. In some cases, liver enlargement may lead to a protruding abdomen, liver cirrhosis, jaundice, hypertension, fatigue, bruising or bleeding easily, and liver failure. In other cases, the muscles may primarily be affected, causing weakness, fatigue, and muscle wasting. Muscle complications may extend to cardiac muscle and cause defects in function. If damage to the nervous system occurs in addition to muscular deficits, there may be decreased reflexes, sensory loss, and gait disturbances. Mild mental impairment may occur.

McArdle disease

McArdle disease usually has a primary symptom of exercise intolerance with muscle weakness and fatigue. The symptoms occur during strenuous or sustained exercise and usually resolve with rest. Often there is a “second wind” of energy from glucose and fat breakdown products supplied by the blood. Symptoms may range from mild fatigue to temporarily incapacitating fatigue with muscle cramping. Late-onset cases may begin showing symptoms of progressive muscle weakness at 60–70 years of age. Other cases may present symptoms in the first year of life and become severely progressive. Even in the absence of exercise, one-third of patients experience weakness. This symptom is especially common in older age. One-half of cases filter blood in the urine after intense exercise, which may be indicative of

impending kidney failure. A small percentage of McArdle patients have seizures.

Hers disease

Hers disease usually has onset between the first and fifth year of life. Classic symptoms include a protruding abdomen due to enlarged liver, delay in growth with childhood short stature, and delayed motor development. Mild hypoglycemia may also be present, but many patients develop no other symptoms. Normal growth may be eventually achieved, along with a complete resolution in liver size to normal. Muscle strength in adults is usually normal.

Diagnosis

Von Gierke disease

Von Gierke disease is diagnosed through various types of testing. Characteristically, blood tests will reveal low blood sugar and the presence of lactic acid. Tests may also be performed to assess blood glucose levels after various challenges, such as administration of hormones that normally cause glycogen breakdown into glucose. Tests are done to assess for the presence of uric acid in the blood, kidney function, and liver function. GSDIa has a normal white blood cell (immune cells) level in the blood because the immune system is unaffected in this subtype. However, in subtype GSDIb, the immune system is impaired and has lower than normal blood levels of white blood cells. Most cases also involve a defect in blood coagulation, and tests are performed to assess bleeding times in a controlled setting. Ultrasound imaging of the abdomen is performed to assess liver and kidney size. To confirm a diagnosis, a biopsy of liver tissue is used to assess the function of the glucose-6-phosphatase enzyme that presents as defective in von Gierke disease.

Pompe disease

Blood tests are performed that can assess whether muscle disease is present by assessing for various factors, such as the enzyme creatine kinase, that are normally present inside muscle cells but not in the blood. The release of high levels of these factors into the bloodstream indicates a complication. Tests for the function of the enzyme alpha-glucosidase are performed to attain a definite diagnosis. This test may be done on white blood cells, but in infants it requires an amount of blood drawn that might not be practical. Instead, a skin biopsy is usually performed to test for the enzyme. Ultrasound imaging and tests that assess the heart's response to electrical stimulation are performed to diagnose the presence or extent of cardiac muscle defects.

Cori disease

Blood tests are done to assess blood glucose and uric acid levels. Liver function studies are performed to determine the presence or extent of liver damage. Tests may also be performed to assess blood glucose levels after various challenges, such as administration of hormones that normally cause glycogen breakdown into glucose. Both blood and urine are tested for the presence of ketone bodies, products of fat breakdown that can lead to dangerously acidic blood. Ultrasound imaging can assess for heart and liver enlargement or the presence of disease. Ultrasound imaging is also used to assess for polycystic ovaries in females, a common occurrence in Cori disease that does not seem to affect fertility. A definite diagnosis involves tests that demonstrate abnormal, unbranched glycogen along with a debrancher enzyme deficiency in liver and muscle tissues.

Andersen disease

To assess for liver complications, blood tests are performed to check for the presence of enzymes that are normally present in healthy liver cells and not in significant quantities in the blood. Distinct signs of liver cirrhosis or dysfunction may also be found in the blood. Ultrasound imaging can assess for liver enlargement, liver cirrhosis, and cardiac abnormalities. Cases in which there are primarily muscle, nervous system, or cardiac defects may have no sign of liver dysfunction. Blood glucose levels are tested to assess for hypoglycemia. To confirm a diagnosis of Andersen disease, a defect in glycogen-branching enzyme activity must be demonstrated from tissue samples. Most cases can be assessed from a variety of different tissue types. A biopsy of the liver or other affected organs, such as the heart, may be taken for microscopic examination and to assess enzyme activity. In Ashkenazi Jews, deficient glycogen-branching enzyme activity is only seen in white blood cells and nerve cells. Prenatal enzyme testing can be done from amniotic samples.

McArdle disease

Blood tests in McArdle cases show elevated levels of enzymes, such as creatine kinase, that are normally present inside muscle cells but not in the blood. The release of high levels of these factors into the bloodstream indicates a complication. Exercise does not produce an increase in blood lactic acid in McArdle disease. An electromyogram (EMG) is a graphic record of a muscle contraction in response to electrical stimulation. Half of all McArdle patients have abnormalities in EMG. A muscle tissue biopsy may be assayed for muscle glycogen phosphorylase enzyme activity.

Hers disease

The extent of abnormal blood testing results are variable and usually mild in Hers disease. There may be some hypoglycemia, ketone bodies in blood and urine, elevated blood triglycerides, or enzyme levels that indicate liver complications. Ultrasound imaging may be used to assess liver enlargement. Tests may also be performed to assess blood glucose levels after various challenges, such as administration of hormones that normally cause glycogen breakdown into glucose. To confirm a diagnosis of Hers disease, a liver biopsy is taken to assess liver glycogen phosphorylase activity.

Treatment and management

Drug therapy and enzyme supplementation are not standard parts of treatment for GSDs. Treatment focuses on maintaining blood glucose levels and treating the symptoms of complications that may arise from the disease. In most cases, this may involve frequent daytime feedings, and for infants, overnight use of a specialized nasogastric feeding tube equipped with an alarm. In most GSDs, children two years of age and older can be switched to cornstarch feeding at bedtime. Raw cornstarch, but not other types of starch, can sustain blood glucose for 4–6 hours if mixed with water at room temperature. Hot water significantly reduces the time frame in which cornstarch can sustain blood glucose levels. Any illness or condition that reduces the amount of food intake requires supplemental injections of simple sugars, such as dextrose, or intravenous administration of glucose. Caregivers need to be educated in inserting feeding tubes, dietary control, and recognizing and managing hypoglycemia.

Diet is a critical component of treatment for most GSDs and must be closely monitored by highly specialized nutritionists. Von Gierke disease requires dietary avoidance of excessive carbohydrates, fat, or calories. All contact sports should be avoided because of the potential for excessive bleeding and liver damage. Iron supplementation is advised because of liver deficiencies. In GSDIb, an immune cell booster called granulocyte colony-stimulating factor (GCSF) is administered because of the depressed immune system. Dental and oral health needs to be actively maintained in GSDIb to prevent infections. Cori disease does not involve the same carbohydrate restrictions, but avoiding excessive fat intake is advised. Cori disease is also treated with a high protein diet to supplement muscle function. Cori disease does not involve sports restrictions past the personal limits of the individual's energy and blood glucose levels. Rupture of the liver from contact sports has not been reported in Cori disease. The infantile subtype of Pompe

KEY TERMS

Amniotic sample—Sample of amniotic fluid, the protective fluid surrounding a fetus in the womb.

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Boils—Painful areas of skin inflammation caused by infection of hair follicles.

Branching enzyme—Enzyme responsible for building the branched structure of glycogen stores.

Cirrhosis—A chronic degenerative disease of the liver in which normal cells are replaced by fibrous tissue. Cirrhosis is a major risk factor for the later development of liver cancer.

Coagulation—The solidification or change from a fluid state to a semisolid mass; blood coagulation helps to close open wounds.

Cyanosis—A bluish discoloration of the skin and mucous membranes.

Debranching enzyme—Enzyme responsible for breaking down the branched structure of glycogen stores to release glucose into the bloodstream.

Gait disturbances—Disturbances that affect a person's habitual manner of walking.

Gastrointestinal tract—The food intake and waste export system that runs from the mouth through the

esophagus, stomach, and intestines to the rectum and anus.

Gingivitis—Inflammation of the gums of the mouth, characterized by redness, swelling, and a tendency to bleed.

Glycogen—The chemical substance used by muscles to store sugars and starches for later use. It is composed of repeating units of glucose.

Glycogenesis—The metabolic process responsible for the formation of glycogen from many glucose molecules.

Glycogenolysis—The metabolic process responsible for the breakdown of glycogen to mobilize glucose.

Hypoglycemia—An abnormally low glucose (blood sugar) concentration in the blood.

Jaundice—Yellowing of the skin or eyes due to excessive bilirubin in the blood.

Ketone bodies—Fat breakdown products that can make the blood acidic when present in high levels.

Left ventricle—Lower chamber of the heart from which blood is pumped into the system.

Precursor components—Components in an enzymatic pathway that are formed by previous cellular events.

Rickets—A childhood disease caused by vitamin D deficiency, resulting in soft and malformed bones.

Xanthoma—Small yellow fat deposits that appear in the skin.

disease may not improve with dietary changes and may become fatal. A high protein diet may assist with muscle functioning in people affected with McArdle disease and with adults with Pompe disease. Supplementation with B vitamins may make muscles less prone to fatigue in McArdle disease. McArdle cases are advised to avoid sustained, strenuous, or weight-bearing exercise to prevent kidney damage. While Hers disease requires avoiding long periods of fasting, most cases do not require significant dietary intervention or exercise reduction unless there is significant liver enlargement.

Blood glucose monitoring is done with specialized home kits called glucometers, which provide an exact reading of blood glucose. A test strip is used to collect a small drop of blood obtained by pricking the finger with a small needle called a lancet. The test strip is placed in the meter, and results are available within 30–45 seconds. Testing is done on a regular basis to monitor the balance

between food intake and blood sugar levels. If hypoglycemic episodes occur, drinking fruit juice or taking a few teaspoons of sugar may bring blood glucose levels back to normal. If 15 minutes have passed and blood sugar has not returned to normal, a second dose is administered.

Specialists are frequently consulted to monitor liver complications that arise in some GSDs. Andersen disease often requires liver transplantation for effective treatment. However, some cases of Andersen disease still result in a poor outcome after liver transplant. Specialists also monitor and provide symptom-specific management of cardiac and nervous system complications that arise from GSDs. Parents of children with GSDs are given genetic counseling regarding the risk of GSD to future pregnancies. There is a 25% recurrence risk for each subsequent pregnancy in most GSDs. There is a 50% chance of male offspring having X-linked forms of Hers disease.

QUESTIONS TO ASK YOUR DOCTOR

- How is a glycogen storage disease passed to my child?
- How is a glycogen storage disease diagnosed?
- How is a glycogen storage disease treated?
- Is a glycogen storage disease a life-threatening condition?

Prognosis

The prognosis of GSD is highly varied. Overall, the long-term prognosis depends on the extent, severity, and progression of the disease. GSDs are generally multisystem diseases with many potential complications. With von Gierke disease and Cori disease, many patients receiving proper treatment do not encounter life-threatening hypoglycemia and have a reasonable lifespan. However, some patients may develop liver cirrhosis, liver cancer, or liver failure. Pompe disease is also variable in prognosis. The infantile form is usually fatal within the first year of life. Death results from cardiac and respiratory failure. The juvenile (intermediate) form progresses more slowly but is generally fatal by the second or third decade of life. Most deaths are from respiratory failure. The adult form may afford survival for several decades after onset. However, muscle weakness may interfere with normal daily activities, and death may result from respiratory failure.

Andersen disease has a very poor prognosis, with the classic infantile form causing progressive liver cirrhosis and death by five years of age in the absence of a liver transplant. Liver transplantation still does not guarantee improvement. Cases involving non-progressive liver disease do not require liver transplantation but are still at increased risk of liver cancer. Cases involving cardiac complications often lead to heart failure, despite medical intervention. Andersen disease involving nervous system and skeletal muscle complications may not be life-threatening, but it may be progressive and debilitating.

The prognosis of McArdle disease is comparatively better than many other forms of GSDs. The primary complications are muscle weakness, cramping, and fatigue, which can interfere with normal daily activities. Some patients are able to adapt exercise to take advantage of the second wind phenomenon, as long as it is not too strenuous. Prognosis remains good as long as sustained, strenuous, and weight-bearing exercises are avoided, which can lead to acute renal failure. The infantile form

of McArdle disease has a poor prognosis, with death caused by severe and rapidly progressive muscle weakness that leads to respiratory failure. The best prognosis of the GSDs described is with Hers disease. Hers disease has a mild course with risk of growth retardation, mild fasting hypoglycemia, and delayed motor development in early childhood. However, these clinical features usually normalize by the time of puberty, along with liver enlargement and muscle weakness. Adult patients usually have normal stature and motor functions. Hers disease may have an excellent prognosis even without childhood dietary management.

Resources

BOOKS

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- Brunelle, Francis, Daniele Pariente, and Pierre Chaumont. *Liver Disease in Children: An Atlas of Angiography and Cholangiography*. New York: Springer, 2013.

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- Muzetti, Julio Henrique, et al. "Neurological Characteristics of Pediatric Glycogen Storage Disease." *Frontiers in Endocrinology* 12 (May 21, 2021): 685272. DOI: 10.3389/Fendo.2021.685272.

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- "Glycogen Storage Disease (GSD)." Cleveland Clinic. August 2, 2019. <https://my.clevelandclinic.org/health/diseases/15553-glycogen-storage-> (accessed June 9, 2021).
- "Glycogen storage disease type 1." MedlinePlus. August 18, 2020. <https://medlineplus.gov/genetics/condition/glycogen-storage-disease-type-i/> (accessed June 9, 2021).

ORGANIZATIONS

- Acid Maltase Deficiency Association, PO Box 700248, San Antonio, TX 78270, (210) 494-6144, (210) 490-7161, <http://www.ama-pompe.org>
- American Liver Foundation, PO Box 299, West Orange, NJ 07052, (800) 465-4837, <http://www.liverfoundation.org>
- Association for Glycogen Storage Disease, 1542 Flammang Dr., PMB 1004, Waterloo, IA 50702, info@agsdus.org, <http://www.agsdus.org>

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GM1-gangliosidosis

Definition

GM1-gangliosidosis is a lysosomal storage condition caused by a reduction in the amount of—or the absence

of—the enzyme beta-galactosidase in cells. This condition has been referred to by other names such as Norman-Landing disease, gangliosidosis-GM1 beta-galactosidase-1 deficiency, Hurler-variant, pseudo-Hurler disease, Tay-Sachs disease with visceral involvement, and *GLB1* deficiency. There are three forms of this condition, determined by the type of mutation of the associated gene and the age at which the form is diagnosed.

Description

Lysosomes are structures found inside cells that contain specific proteins and enzymes that help digest or break down many of the complex biological substances found within the cells. After the lysosomes digest these substances, the remnants are then released from the cells. The role of the lysosome is to keep the inside of a cell clean and to help the cell function normally.

One of the lysosomal enzymes, beta-galactosidase, is necessary to digest a substance called GM1-ganglioside. When there is not enough beta-galactosidase within the lysosomes, GM1-ganglioside breaks down at a slower rate or not at all. Since GM1-ganglioside is not being digested as fast as it is being produced, GM1-ganglioside accumulates within the lysosomes. When too much GM1-ganglioside accumulates, the lysosomes stop functioning effectively, thereby causing the cell not to function properly.

When enough cells in an organ or organ system stop functioning normally, the entire organ or organ system begins to experience problems. One of the first areas where GM1-ganglioside accumulates and causes problems is within the central nervous system. Other organs and systems in the body can also accumulate GM1-ganglioside; however, signs of the excessive accumulation are sometimes not immediately apparent.

There are three types of GM1-gangliosidoses; they are grouped according to the amount of beta-galactosidase detected in the individual's leukocytes (white blood cells) or skin cells, the individual's age when symptoms appear (called age of onset), and the specific symptoms that the individual exhibits. These types are labeled type I, type II, and type III.

Genetic profile

All three types of GM1-gangliosidosis are inherited in an autosomal recessive manner. Symptoms of GM1-gangliosidosis occur when the pair of genes that produce beta-galactosidase (called *GLB1*) both contain a change, causing them not to work properly. When the *GLB1* genes do not work properly, less or no beta-galactosidase is produced. Individuals with GM1-gangliosidosis inherit one of their non-working *GLB1*

genes from their mother and the other non-working *GLB1* gene from their father. These parents are called carriers of GM1-gangliosidosis. When two people are known carriers for an autosomal recessive condition, like GM1-gangliosidosis, they have a 25% chance with each pregnancy to have a child affected with the disease.

The *GLB1* gene is located on the short arm of chromosome 3, called 3p, in the region 21.33. This is written as 3p21.33. There have been over 20 mutations identified in the *GLB1* gene that can cause the gene not to work properly. The most common type of mutation detected is a missense mutation. Typically, a gene is made up of DNA that codes for specific amino acids. It is the amino acids, when combined, that make a protein. When there is a missense mutation in a gene, the DNA code for a particular amino acid has been changed, often coding for a different amino acid. Changing the amino acid often alters the protein that is made. A change in the structure or production of a protein often alters its ability to function properly.

Most individuals with GM1-gangliosidosis are compound heterozygotes. This means that an individual with GM1-gangliosidosis has one *GLB1* gene containing one mutation and his or her other *GLB1* gene has a different mutation. Researchers do not believe that there is any correlation between specific mutations in the *GLB1* gene and the severity of GM1-gangliosidosis. An exception to this is the discovery of mutations in the *GLB1* gene that instead of causing an individual to have GM1-gangliosidosis cause the individual to have another condition called Morquio syndrome type B.

Demographics

GM1-gangliosidosis is a rare condition. It is estimated that approximately 1 in 100,000–200,000 live births is affected with this condition. Type I GM1-gangliosidosis is considered to occur more often than the other two types. There has also been an increased number of individuals living in Japan, Brazil, and the Maltese Islands diagnosed with all types of GM1-gangliosidosis. However, many researchers state that this condition is not more common in individuals of certain ethnic groups, although many of the individuals with type III GM1-gangliosidosis are Japanese. Additionally, GM1-gangliosidosis occurs with equal frequency in males and females.

Signs and symptoms

The signs and symptoms of GM1-gangliosidosis largely depend on the type an individual has. As of 2014, some researches had shown these three types to be separate and distinct, while other researchers

maintained that GM1-gangliosidosis is one disorder with a spectrum of signs and symptoms.

GM1-gangliosidosis type I

Type I GM1-gangliosidosis is also called infantile GM1-gangliosidosis, or infantile type, and it is considered the most severe form of GM1-gangliosidosis. Infants with GM1-gangliosidosis type I tend to have less than 1% of the normal amount of beta-galactosidase in their cells.

Some of the symptoms seen with type I can be apparent at birth, but all infants with type I show characteristics of the condition before six months of age. All infants with type I reach a point where they fail to gain new skills and begin to regress and lose the skills they have learned.

Several of the initial symptoms seen in infants with type I are caused by the storage of GM1-ganglioside in the cells of the infant's central nervous system. One sign of a problem with the central nervous system seen in some infants with type I is their inability to eat much food or formula because of a poor appetite and/or difficulties with sucking on a bottle or nipple. As a result, they tend to gain very little weight. Another sign of GM1-ganglioside storage in the central nervous system is muscle problems. Most of these infants have low muscle tone, called hypotonia. These babies appear "floppy" or loose. As the disease progresses, the infants present with other central nervous system problems, such as an exaggerated reaction to sound and atrophy of the optic nerves. Their bodies also become rigid and stiff, and they develop tight joints (joint contractures) and experience seizures. Infants with type I can also develop brain atrophy and/or areas of decreased amount of white matter in the brain.

In GM1-gangliosidosis type I, GM1-ganglioside is also stored in the skeleton, causing visible changes on radiographs. Some of the more common bone changes are differences in the vertebrae that cause spine curvature, a thicker skull, wider bones and hands, and wide, short fingers. Also, the growth of the bones tends to slow down or stop, causing infants with GM1-gangliosidosis type I to appear smaller than expected for their age.

Additionally, infants with type I usually develop certain characteristic facial features. The facial features typically seen in infants with type I include frontal bossing, ears that are set lower on the head than normal, thicker skin, hair on the forehead and neck, an elongated space between the nose and mouth, and an enlarged tongue. Children with these facial changes are often described as appearing coarse. Coarse facial features can also be seen in infants and children who have other types of storage disorders.

Other characteristics of GM1-gangliosidosis type I include an enlarged spleen and liver (called hepatosplenomegaly), cardiomyopathy (which has only been

described in Caucasian patients), and an enlargement of the cells in the bone marrow. Additionally, infants with type I have cherry-red spots in the macula of their retinas, and several develop corneal clouding.

GM1-gangliosidosis type II

GM1-gangliosidosis type II is also referred to as the juvenile or intermediate type. In children with type II, the amount of beta-galactosidase in the cells is approximately 1%–5% of normal.

Type II GM1-gangliosidosis is characterized by a slower progression of symptoms and a shortened life expectancy of early adulthood. Signs of type II often appear late in infancy or in early childhood around 18 months to five years of age. Although each individual with type II may present differently, several children with type II have been reported to have difficulty walking and to have developed seizures and/or developmental regression. The bone changes seen in type I may or may not occur in children with type II. Furthermore, children with type II do not have macular cherry-red spots, enlarged spleen or liver, or the facial changes associated with type I.

GM1-gangliosidosis type III

Individuals with GM1-gangliosidosis type III are labeled as having the adult or chronic type of this condition. Individuals with type III tend to have approximately 10% of the normal amount of beta-galactosidase in their cells. The age when symptoms begin to appear in individuals with type III is extremely variable. There have been reports of individuals with type III exhibiting symptoms as early as 3 years of age to as late as 30 years old. The symptoms slowly worsen over many years.

Individuals with GM1-gangliosidosis type III tend to experience some symptoms related to the storage of GM1-ganglioside in their central nervous system; however, these symptoms are not as severe as those seen in infants with type I. The signs of GM1-ganglioside storage can be different in each person affected with GM1-gangliosidosis type III, but many individuals with type III have been reported to have signs of dystonia. Other neurological symptoms in type III can include difficulty or unusual methods of walking (ataxia), mild mental delays, and slurred speech. Often the ataxia and slurred speech are some of the first symptoms to appear.

Individuals with type III also have GM1-ganglioside storage in bone cells, but bone changes are considered milder than those seen in type I. Often the vertebrae of individuals with type III tend to have a flattened appearance and/or the presence of other mild vertebral changes. On CT or MRI examinations, mild brain atrophy with

KEY TERMS

Amino acids—Organic compounds that form the building blocks of protein. There are 20 types of amino acids (8 are essential amino acids that the body cannot make and must therefore obtain from food).

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Atrophy—Wasting away of normal tissue or an organ due to degeneration of the cells.

Basal ganglia—A section of the brain responsible for smooth muscular movement.

Cardiomyopathy—A thickening of the heart muscle.

Cytoplasm—The substance within a cell, including the organelles and the fluid surrounding the nucleus.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Dystonia—Painful involuntary muscle cramps or spasms.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Frontal bossing—A term used to describe a rounded forehead with a receding hairline.

Gray matter—Areas of the brain and spinal cord that are made up mostly of unmyelinated nerves.

Lysosome—A membrane-enclosed compartment in cells that contains many hydrolytic enzymes; where large molecules and cellular components are broken down.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and that can be transmitted to offspring.

Myelin—A fatty sheath surrounding nerves in the peripheral nervous system that helps them conduct impulses more quickly.

Organelles—Small subcellular structures that carry out different functions necessary for cellular survival and proper cellular functioning.

White matter—A substance found in the brain and nervous system that protects nerves and allows messages to be sent to and from the brain to the various parts of the body.

signs of storage in the basal ganglia can be present in some individuals with type III. Also, some individuals with type III have experienced corneal clouding. However, the macular cherry-red spots, facial changes, and differences in the bones are not seen in individuals with GM1-gangliosidosis type III.

Diagnosis

The diagnosis of GM1-gangliosidosis in an individual can be made by measuring the amount of beta-galactosidase in either skin cells or in leukocytes. Additionally, prenatal testing to determine whether a fetus is affected with GM1-gangliosidosis prior to its delivery can be accomplished by measuring the amount of beta-galactosidase on cultured cells from an amniocentesis or chorionic villus sampling (CVS). Amniocentesis is a procedure used to remove some of the fluid, which contains fetal cells, from around the fetus. CVS is used to obtain cells from the placenta. With both of these procedures, the cells collected are stimulated to multiply so that there are enough cells to perform certain analyses, in this case measuring the amount of beta-galactosidase. Both of these procedures have their own risks, benefits, and limitations.

X-rays can detect bone changes and organ enlargement. However, in early stages of the condition, bone differences may not have developed or the organs may not yet be enlarged. A CT scan and/or MRI can identify brain changes, such as cerebral atrophy or a loss of myelin in the white matter of the brain. An eye examination can detect any macular cherry-red spots or other changes.

Analysis of the amount of beta-galactosidase in an individual's cells cannot be used to determine whether the person is a carrier of GM1-gangliosidosis. This is because the range for the amount of beta-galactosidase seen in carriers of this condition overlaps with the range of the amount of beta-galactosidase seen in individuals who are not carriers.

As of 2021, molecular genetic testing of the *GLB1* gene is available from the Centogene AG laboratory in Germany. The test can be performed on amniotic fluid, fetal blood, bone marrow, a buccal swab, fresh or frozen tissue, and isolated DNA.

Treatment and management

There is no cure for GM1-gangliosidosis. Most of the treatments revolve around trying to alleviate some of the

QUESTIONS TO ASK YOUR DOCTOR

- What type of gangliosidosis does my child have, and what is his or her life expectancy?
- What will daily life be like while taking care of a child with gangliosidosis?
- Are there at-home care services we could utilize for physical and occupational therapy, if needed?
- How should my child be monitored for changes in other organs or organ systems?
- How far into my next pregnancy should I be tested for carrying a child with this disorder?
- Are there any organizations for emotional and/or financial support established to help us take care of a child with this syndrome?

symptoms, such as helping infants with type I to eat, and providing devices that can help with problems walking in individuals with type III. Physical therapy, occupational therapy, and early intervention for education and social outcomes are also important for the daily and overall life activities of an individual. Management often includes routine monitoring of growth and neurological function as well as nutritional assessment, cardiac examination, and assessment of the stability of the spine. Additionally, there is ongoing research into gene therapy for GM1-gangliosidosis to infuse genes that produce beta-galactosidase into the body.

Prognosis

In type I GM1-gangliosidosis, the child dies within a few years after the symptoms begin, typically by age two. In type II GM1-gangliosidosis, the prognosis is variable. Some individuals have died during childhood or early adulthood, and others have lived many years after symptoms began. In type III GM1-gangliosidosis, no decrease in lifespan has been reported.

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ORGANIZATIONS

- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>
- Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476(202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

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Goiter-sensorineural deafness syndrome see
Pendred syndrome

Golabi-Rosen syndrome see
Simpson-Golabi-Behmel syndrome

Greig cephalopolysyndactyly

Definition

Greig cephalopolysyndactyly (GCPS) is a very rare autosomal dominant disorder. The syndrome is characterized by physical abnormalities of the head, face, fingers, and toes. Distinct features include extra fingers and/or toes; a large and unusual shape of the skull; a high, prominent forehead; and widely spaced eyes. The range and severity of symptoms may vary greatly between individuals. Some individuals with Greig cephalopolysyndactyly require medical or surgical intervention to manage these problems. The syndrome is familial and in most cases is transmitted as an autosomal dominant trait.

Description

The disorder is named for D. M. Greig (pronounced Gregg), a Scottish physician, who first described the features of this syndrome in 1928. He saw a mother and her daughter who had a peculiar shape of the skull (cephalus) and polysyndactyly of the hands and feet. Polysyndactyly means that the patient has both extra digits (toes, fingers) as well as webbing (syndactyly) between the digits. Dr. Greig described them as having a high forehead and widely spaced eyes. Thus, the syndrome was termed Greig cephalopolysyndactyly.

Genetic profile

Greig cephalopolysyndactyly can be found in several generations of a family. It is an autosomal dominant disorder and can be inherited and passed on by men as well as women. Almost all genes come in pairs. Cells work best when both copies of the gene pairs are intact and do not have mutations. One copy of each pair of genes is inherited from the father, and the other copy of each pair of genes is inherited from the mother. Therefore, if a parent carries a gene mutation for GCPS, each of his/her children has a 50% chance of inheriting the gene mutation. Each child also has a 50% chance of inheriting the working copy of the gene, in which case they would not have GCPS.

The search to find the causative gene took a number of years. The first clue came in 1989, when an 11-month-old infant was found to have a deletion of genetic material on chromosome 7. The infant had a large head and polysyndactyly of the hands and feet. Other reports soon followed, with small deletions and translocations of chromosome 7. Then, in 1991, investigators began to study a gene called *GLI3* as the candidate gene. This gene was found in the region of chromosome 7p13, which was missing in these individuals. The *GLI3* gene was also suspect because of previous studies done in mice.

The mouse gene *GLI3* normally functions in the design of the skeleton and limbs in the embryo. The *GLI3* gene also works in the developing brain. Mice lacking both copies of the gene die before birth. Many have severe birth defects of the brain, skeleton, and central nervous system. However, mice with just one non-working copy of the *GLI3* gene do not die. They have minor birth defects, most notably extra digits, often of the hind feet. The mice also have a duplicated bone in their front feet, and an enlarged bone in the front portion of the skull. This combination of birth defects is unusual, but common to both Xt mice and individuals with Greig cephalopolysyndactyly.

With this in mind, the *GLI3* gene was scanned for alterations (mutations) in individuals with GCPS. Of interest, both small and large mutations were found throughout the coding regions of the gene. As none of these mutations were found in unaffected individuals, this proved that the *GLI3* gene was the cause of the condition.

In addition to GSPC, Pallister-Hall syndrome and post-axial polydactyly type A (PAP-A), two other disorders of human development, are caused by alterations in the *GLI3* gene. The common feature of each disorder is polydactyly of the hands and feet. However, individuals with Pallister-Hall syndrome have additional growth problems and severe intellectual disability. Extra fingers and

toes are the primary feature of PAP-A, and thus, the most mild in expression of the three conditions.

Scientists have used animal models and the fruit fly *Drosophila* to study the function of the *GLI3* gene. The normal function of the GLI3 protein is to bind to the DNA helix at specific places. By doing so, it helps to regulate which genes are activated or “turned on.” Many of the mutations identified so far seem to interfere with the protein binding function. In effect, other genes that would normally be activated during development of the embryo may in fact not be turned on.

It is known that the limbs (arms, legs, fingers, toes) develop between the fourth and eighth week of pregnancy. The limb defects seen in GCPS must occur during this crucial period of development.

Demographics

Greig cephalopolysyndactyly affects both males and females equally. It most likely occurs in every race and ethnic group. In all, about 200 individuals have been described worldwide, but it is possible that the disorder is underdiagnosed because some affected persons may have only mild symptoms. Therefore, it is a rare condition.

Signs and symptoms

Most individuals with Greig cephalopolysyndactyly have a large head circumference (the distance as measured around the cranium). The forehead is high and wide, and slightly rounded in front (frontal bossing). This is due to the cranial sutures closing later than normal, causing the bones of the forehead to remain apart. The widening of the forehead appears to dip down into the space between the eyes, setting the eyes farther apart than normal. The bridge of the nose is broad and flat. This adds to the impression of distance between the eyes. Many times, the rest of the face will also look broad, almost box-like. The chin is small in comparison. The mouth is wide, and the corners of the mouth may be turned downward. The ears are usually normal. Individuals with GCPS can have a short neck, making it look as if the head rests on the shoulders. Intelligence is usually normal, although a few individuals have had mild learning disabilities.

The hands are quite distinctive in appearance. Most individuals with GCPS have extra fingers on each hand. The extra finger is rarely on the thumb side (pre-axial polydactyly). It is most often on the pinky finger side (post-axial polydactyly). Some individuals have an extra finger on each side of the hand, and thus, the possibility of 14 fingers. However, the extra finger may or may not include bone, and could just be a skin tag. The thumbs are frequently quite wide in appearance. Sometimes the bones of the thumb are

KEY TERMS

Abdominal hernia—Bulging of an organ or tissue through the muscle of the stomach wall.

Chromosome deletion—A missing sequence of DNA or part of a chromosome.

Chromosome translocation—The exchange of genetic material between chromosomes, which can lead to extra or missing genetic material.

Hypospadias—An abnormality of the penis in which the urethral opening is located on the underside of the penis rather than at its tip.

Polysyndactyly—Having both extra digits (toes, fingers) as well as webbing (syndactyly) between the digits.

Post-axial polydactyly—An extra finger or toe on the outside of the hand or foot.

Pre-axial polydactyly—An extra finger or toe on the inside of the hand or foot.

Syndactyly—Webbing or fusion between the fingers or toes.

duplicated or split at the tip. There may also be duplication or fusion in some of the bones that make up the hand, which can be seen on x-ray. Their hands are still quite functional, although surgery may be necessary.

Many of these patients have extra toes. What is unusual is that the extra toe is most often on the great toe side, opposite to what is found in the hands. The toes may also be short. Syndactyly (extensive webbing of the skin) is a constant finding in these patients. The webbing is usually between the toes, but may involve the hands. The webbing can vary from being mild, to complete joining of the digits, with skin up to the nail. Sometimes, just a few of the digits are fused together; in others, all of the toes are webbed. The webbing may be present alone without extra toes, although this is uncommon. The syndactyly may also occur on just one foot, and can be quite variable. Foot mobility and walking is usually not a problem.

There are other occasional problems seen in GCPS. These include craniosynostosis (premature fusion of the skull bones), mild intellectual disability, hernia of the abdominal (stomach) muscles, and lesser birth defects of the urinary tract system, such as hypospadias in males.

Diagnosis

Each individual with Greig cephalopolysyndactyly is affected somewhat differently. The features are usually

quite variable, even within the same family. The facial features can be mild with most individuals only having a high and broad forehead.

Polysyndactyly of the hands and feet remains the most distinctive feature of the syndrome. With the use of x-rays, changes in the bones of the hands and feet can be seen. The diagnosis of GCPS is suspected when the physician identifies the extra digits on the outside of the hands and on the inside of the foot, along with the broad forehead. This is usually seen at birth.

The availability of direct gene testing allows for a definitive diagnosis for these patients. Using a blood sample, a direct gene test looking for alterations (mutations) in the *GLI3* gene can be done. An identifiable gene mutation would confirm the diagnosis in sporadic (non-inherited) patients as well.

Treatment and management

Very often, the physical characteristics of the face do not require surgical treatment. Sometimes, the facial appearance even improves as the child grows. However, if the cranial sutures in the forehead close either very early or very late, there may be fairly severe disfigurement to the face. This would require surgery from a specialized craniofacial medical team. Craniofacial surgery rearranges or reconstructs the bones of the face to correct the abnormal fusion of the cranial bones.

Some degree of surgery is needed for the polydactyly of the hands and feet. The extra digits that are just skin tags (no bone within) are tied off at the base and allowed to self-amputate. This is usually done at birth. For those digits that include bone, most surgeons would save the digit that would have the best use. The other digit (or digits) would then be surgically removed, usually around one year of age. Surgery is often done to release the webbing of the fingers and toes, and can be quite extensive.

Prognosis

Most individuals with Greig cephalopolysyndactyly appear to have a normal life span.

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ORGANIZATIONS

AboutFace International, 51 Wolseley St., Toronto, ON M5T 1A4, Canada (416) 597-2229 or (800) 665-3223, (416) 597-8494, info@aboutface.ca, <http://www.aboutface.ca>

FACES: The National Craniofacial Association, PO Box 11082, Chattanooga, TN 37401, (423) 266-1632 or (800) 332-2373, faces@faces-cranio.org, <http://www.faces-cranio.org>

Genetic Alliance, 26400 Woodfield Road #189, Damascus, MD 20872, (202) 966-5557, info@geneticalliance.org, <http://www.geneticalliance.org>

Kevin M. Sweet, MS, CGC

Griscelli syndrome

Definition

Griscelli syndrome is a rare, sometimes fatal disorder that includes symptoms of partial albinism, neurological impairment, and immunodeficiency. There are three types of Griscelli syndrome, characterized by varying degrees of albinism; a partial lack of melanin, the pigment that gives color to the eyes, hair, and skin; immune system abnormalities; and intellectual and developmental delay.

Description

There are three types of Griscelli syndrome. They are diagnosed based on their symptoms and the genetic mutations that cause them. All three types involve partial albinism—hypopigmented or unusually pale skin and light silver to gray hair even in infancy.

The three types of Griscelli syndrome are the following:

- Griscelli syndrome type 1 (GST1): This type is characterized by partial albinism and neurological impairment caused by abnormalities of the brain. Individuals with GST1 experience developmental and

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are needed to display the trait or disease.

Melanin—A broad term for a group of pigments normally produced by the body that give color to the skin and hair.

Melanocytes—Cells that can produce melanin.

Melanosomes—Granules of pigment within melanocytes that synthesize melanin.

Natural killer cells (NK cells)—White blood cells that fight virally infected cells and tumor cells within the body.

T cells—White blood cells that fight both virally and bacterially infected cells within the body.

intellectual delays, seizures, hypotonia (muscle weakness), and eye anomalies that affect vision.

- Griscelli syndrome type 2 (GST2): This type of Griscelli syndrome does not involve neurological impairment. It is characterized by hypopigmentation of the skin and hair and immune system disorders. Individuals with GST2 suffer from frequent infections and an immune system disorder called hemophagocytic lymphohistiocytosis (HLH). HLH is a serious, sometimes life threatening condition in which the immune system produces abnormal white blood cells—specifically T cells and NK cells. Under normal circumstances, these cells destroy infected cells and protect the body; however, in those with HLH, these cells become over active and begin to attack healthy tissues and organs throughout the body, including the brain, liver, bone marrow, and others.
- Griscelli syndrome type 3 (GST3): This type of Griscelli syndrome is a less severe form of the syndrome in which the only symptoms are unusually light skin and hair color.

Genetic profile

Griscelli syndrome is caused by mutations in three genes: *MYO5A*, *RAB27A*, and *MLPH*. These genes carry the information necessary to produce proteins found in cells called melanocytes. These proteins work within cells to transport structures called melanosomes, which produce melanin, the pigment that gives eyes, skin, and hair their color. The melanosomes are created near the cell's center and must travel to the cell membrane and move into other types of cells so that normal

QUESTIONS TO ASK YOUR DOCTOR

- What are the most serious symptoms of Griscelli syndrome?
- At what age can Griscelli syndrome be diagnosed, and on what is a diagnosis based?
- Is Griscelli syndrome confused with other genetic disorders and, if so, which ones?
- What medications or procedures are available for the cure or treatment of Griscelli syndrome?

pigmentation can occur. If the *MYO5A*, *RAB27A*, and *MLPH* genes are mutated, the melanosomes cannot travel within the cell and begin to form clumps. These clumps prevent melanosomes from traveling and prevent melanin from being delivered to other cells to spread pigmentation. These clumps, visible in the shafts of hair when examined under a microscope, are a key feature of Griscelli syndrome.

The three genetic mutations each cause one type of Griscelli syndrome: GST1 is caused by mutations in the *MYO5A* gene on chromosome 15, GST2 is caused by mutations in the *RAB27A* gene on chromosome 15, and GST3 is caused by mutations in the *MLPH* gene on chromosome 2. All three mutations are inherited in an autosomal recessive pattern, which means both copies of the gene in each cell must have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition or syndrome.

Demographics

Both males and females are born with Griscelli syndrome. In general, Griscelli syndrome is an extremely rare condition. Of the three types, GST2 is the most common. There are fewer than ten known cases of Griscelli syndrome in the United States, and most known cases have been reported in Mediterranean populations.

Signs and symptoms

Griscelli syndrome causes pigmentary dilution of the skin and hair, and clumps of pigment in hair shafts. Griscelli syndrome also causes an accumulation of melanosomes in melanocytes.

People with Griscelli syndrome may have frequent infections in which pus is present, fever, an abnormal

decrease in the number of white blood cells, and a reduction in the number of platelets in the blood.

Diagnosis

Griscelli syndrome is generally diagnosed based on the signs and symptoms, or by microscopically examining the hair shaft. Genetic testing may be done to identify mutations in the *MYO5A*, *RAB27A*, and *MLPH* genes.

Treatment and management

Treatment options for individuals with Griscelli syndrome are limited and will depend on which type of Griscelli syndrome the patient has and how severe the symptoms.

Treatment for GST1 involves educational intervention for intellectual and developmental delays, neurological care for associated seizure disorders, and ophthalmological care for the associated eye and vision anomalies.

Treatment for GST2 is especially important because of the significant risks of repeated infections and the life-threatening risks associated with HLH. In patients with HLH, the main treatment options are stem cell transplantation and bone marrow transplantation. Both stem cell and bone marrow transplantation involve injecting the patient with stem cells and/or bone marrow from a donor who has been carefully matched to his or her blood type and human leukocyte antigen (HLA) type. HLA helps the body identify blood that belongs and other substances that must be destroyed such as infections. Siblings generally have similar HLA and often make the most compatible donors.

Generally, no treatment is required for GST3, since there are no neurological or immunological symptoms associated with this type.

Prognosis

The prognosis for individuals with Griscelli syndrome varies depending on which type they have. Those with GST1 will experience lifelong neurological impairment. Prognosis for those with GST2 is poor without bone marrow/stem cell transplantation; individuals with GST3 generally have a normal life expectancy.

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ORGANIZATIONS

Genetic Alliance, 26400 Woodfield Road #189, Damascus, MD 20872, (202) 966-5557, (202) 966-8553,

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Genetic Disease Foundation, Mount Sinai School of Medicine, One Gustavo L. Levy Place, Box 1497, New York, NY 10029, (212) 659-6704, <http://www.geneticdiseasefoundation.org>
Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476/(202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

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Gronblad-Strandberg-Touraine syndrome
see **Pseudoxanthoma elasticum**



Haim-Munk syndrome

Definition

Haim-Munk syndrome is an extremely rare genetic disorder similar to Papillon-Lefèvre syndrome. Features include callous patches of skin on the palms of the hands and the soles of the feet, long pointy fingers, and degeneration of the tissues that surround and support the teeth.

Description

Haim-Munk syndrome is characterized by red, scaly thick patches of skin on the palms of the hands and soles of the feet (palmoplantar hyperkeratosis) that are apparent at birth, along with frequent pus-producing (pyogenic) skin infections, overgrowth of the fingernails and toenails (onychogryphosis), and degeneration of the gums and bone surrounding the teeth (periodontitis) beginning in childhood. The severe and ongoing periodontitis usually causes the baby teeth to fall out prematurely and often results in the loss of the permanent adult teeth as well.

In 1965, researchers Haim and Munk reported findings similar to Papillon-Lefèvre syndrome in four siblings from an inbred Jewish family that originated from Cochin, India, on the Malabar Coast, and later migrated to Israel. Features that are present in both Papillon-Lefèvre syndrome and Haim-Munk syndrome include skin abnormalities and severe periodontitis. These disorders are considered alternate forms of the same genetic mutation. There are a number of additional features reported in Haim-Munk syndrome that include long, thin, pointed fingers (arachnodactyly), bone loss in the fingers or toes (acroosteolysis), abnormal changes of the nails, and a claw-like deformity of the hands.

Haim-Munk syndrome is also known as Cochin Jewish disorder or congenital keratosis palmoplantaris.

Genetic profile

Haim-Munk syndrome is a homozygous expression of an autosomal recessive trait. Among palmoplantar

keratoderma disorders, only Papillon-Lefèvre syndrome and Haim-Munk syndrome are associated with the premature loss of teeth. It is suspected that Haim-Munk syndrome could be genetically different from common forms of palmoplantar keratoderma that are linked to the cyto-keratin gene families.

Preliminary findings suggest that DNA markers other than keratin genes are responsible for the Haim-Munk syndrome. In 1997, genotype data in affected individuals found that the gene mutations in Haim-Munk syndrome were not due to a gene defect in either type I or type II keratin gene clusters on chromosomes 12 and 17, markers common to other palmoplantar keratoderma conditions.

Because Papillon-Lefèvre syndrome and Haim-Munk syndrome present different symptoms than palmoplantar keratoderma disorders, both genetic syndromes are thought to be related to specific bacterial infections in those with palmoplantar keratoderma.

The cause of Papillon-Lefèvre syndrome is a mutation in the cathepsin C gene resulting in periodontal disease and palmoplantar keratosis. Haim-Munk syndrome is thought to be a variant clinical expression of Papillon-Lefèvre syndrome that is caused by defects in the cathepsin C gene as well.

A study in 2000 reported a mutation of cathepsin C (exon 6, 2127A→G) that changes a highly conserved amino acid in the cathepsin C peptide. This suggests that Haim-Munk syndrome and Papillon-Lefèvre syndrome are alternate forms of defects in the cathepsin C gene. The study also notes that the basis for the difference in clinical expression (symptoms) of these two syndromes caused by the mutated cathepsin C gene is not known.

Demographics

The estimated occurrence of Papillon-Lefèvre syndrome, of which Haim-Munk is an extremely rare variant, is considered one to two persons per million. There appears to be no variance by gender. While Papillon-

KEY TERMS

Acroosteolysis—Loss of bone tissue at the ends of the fingers and/or toes.

Arachnodactyly—A condition characterized by abnormally long and slender fingers and toes.

Atrophy—Wasting-away of normal tissue or an organ due to degeneration of the cells.

Onychogryphosis—Overgrowth of the fingernails and toenails.

Palmoplantar keratoderma—Group of mostly hereditary disorders characterized by thickening of the corneous layer of skin (hyperkeratosis) on the palms and soles as a result of excessive keratin formation (protein in the skin, hair, and nails).

Palmoplantar keratosis—A raised thickening of the outer horny layer of the skin on the palms of the hands and the soles of the feet.

Periodontitis—Inflammatory reaction of the tissues surrounding and supporting the teeth that can progress to bone destruction, abscess formation, and eventual tooth loss.

Pes planus—Flat feet.

Pyogenic—Pus-forming.

Lefèvre syndrome cases have been identified throughout the world. Haim-Munk syndrome has only been described among descendants of an inbred Jewish family originally from Cochin, India, who migrated to Israel.

Signs and symptoms

The two major manifestations of Haim-Munk syndrome are dermatological abnormalities and juvenile periodontitis.

Individuals identified with Haim-Munk syndrome show more severe skin abnormalities than groups with Papillon-Lefèvre syndrome. Extensive palmoplantar hyperkeratosis typically begins within the first two to three years of life. At birth, the palms and soles are bright red in color and then progress to a callused and scaly appearance. As the patient gets older, the disease often involves thick, scaly patches on the entire front and back area of the hands and feet, as well as the elbows and knees.

A typical pattern of periodontitis with Haim-Munk syndrome is as follows: Initially, the deciduous (baby) teeth appear at the normal time, but the gums proceed to swell and bleed. Usually, all the deciduous teeth fall out

by age four; the mouth then heals and the secondary teeth begin to appear. Severe gingival inflammation develops, and the majority, or all, of the permanent teeth often fall out by age 15.

Individuals with Haim-Munk syndrome may also have some of the following signs and symptoms:

- wasting (atrophy) or thickening of the nails
- a deformity of the fingers called arachnodactyly—abnormally long, thin, tapered fingers and toes
- lack of normal blood flow to the extremities that results in numbness and tingling in the fingers and/or toes; it also can cause loss of bone tissue at the ends of the fingers and/or toes (acroosteolysis)
- a curve of the bones in the hands causing claw-like features
- flat feet (pes planus)
- recurrent pus-forming (pyogenic) skin infections

Diagnosis

There are no published diagnostic criteria for Haim-Munk syndrome. Researchers use clinical examination of inbred Jewish Cochin descendants to confirm the presence of Haim-Munk. Diagnosis of Papillon-Lefèvre syndrome is confirmed by red, thick, callused skin on the palms and soles at birth and dental problems that are usually present by age five.

Affected individuals are diagnosed with Haim-Munk syndrome when all of the following features are present:

- palmoplantar keratoderma
- thick, rough, and scaly patches of skin on the forearms and legs
- severe early-onset periodontitis
- arachnodactyly
- abnormal changes of the nails

Radiology is used to view the thin and tapering bone deformities in the fingers and dental problems associated with Haim-Munk syndrome.

Genetic testing can confirm the mutation of the cathepsin C gene. Genotyping for polymorphic DNA markers (D11S1887, D11S1367, and D11S1780) is used to identify the presence of the cathepsin C gene mutations associated with Haim-Munk syndrome.

Treatment and management

Treatments include extraction of the teeth and use of dental prosthesis, or dentures. Medications are also used to treat skin lesions associated with this disorder.

QUESTIONS TO ASK YOUR DOCTOR

- What is the prevalence of Haim-Munk syndrome in the general population and in any specialized population at risk for the disorder?
- What are the first symptoms of Haim-Munk syndrome to occur in a young child?
- What forms of treatment are available for controlling or curing the symptoms of Haim-Munk syndrome?
- Is there any reason for parents outside of the special group at risk for Haim-Munk syndrome to be concerned about the disease?

Prognosis

A normal lifespan has been reported for individuals with Haim-Munk syndrome. Loss of the baby teeth may occur by age six and loss of the permanent teeth by age 15; however, general health is not impaired and dentures are well tolerated.

Resources

BOOKS

- Griffiths, Anthony J. F., et al., eds. *Introduction to Genetic Analysis*. 12th ed. New York: Macmillan, 2020.
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PERIODICALS

- Pap, É. M., et al. "Identification of Putative Genetic Modifying Factors that Influence the Development of Papillon-Lefèvre or Haim-Munk Syndrome Phenotypes." *Clinical and Experimental Dermatology* 45, no. 5 (July 2020): 555–559. DOI: 10.1111/Ced.14171.

WEBSITES

- "Haim-Munk Syndrome." GARD. <https://rarediseases.info.nih.gov/diseases/44/haim-munk-syndrome> (accessed June 9, 2021).
- "Haim-Munk Syndrome." NORD. <https://rarediseases.org/rare-diseases/haim-munk-syndrome/> (accessed June 9, 2021).

ORGANIZATIONS

- Genetic Alliance, 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008-2369, (202) 966-5557, (202) 966-8553, info@geneticalliance.org, <http://www.geneticalliance.org>

Genetic Disease Foundation, 1425 Madison Ave., Box 1498, New York, NY 10029, (212) 659-6704, <http://www.geneticdiseasefoundation.org>

Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

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Hair loss syndromes

Definition

Hair loss syndromes are a varied group of disorders and conditions characterized by the gradual or sudden loss of large amounts of hair—most often from the scalp, but sometimes from other areas of the body. Hair loss (or baldness) is sometimes referred to as alopecia. Madarosis is the medical term for the loss of eyelashes (ciliary madarosis) or eyebrows (superciliary madarosis).

Genetic factors are the most common cause of alopecia. Studies have shown that 80% of hair loss cases are indeed due to genetic factors. Although hair loss, unlike some genetic disorders, is not a life threatening or disabling condition, it often has painful psychological consequences. Good grooming and an attractive appearance are important factors in the contemporary job market as well as interpersonal relationships, and a full head of hair is considered a positive feature. Historically, men have tended to put less weight on their external appearance than women have, but this pattern has changed in the last two decades. Present evidence indicates that men are now as vulnerable to pressures to "look good" as women are and that hair loss is a frequent focus of men's concerns about their looks.

Description

Hair loss syndromes can be divided into two major categories: those caused by some type of inflammation, and those caused by genetic factors, aging, or medication side effects. The noninflammatory syndromes are subdivided into two groups according to the pattern of hair loss. The inflammatory syndromes are also subdivided into two groups according to the presence or absence of tissue destruction.

Noninflammatory patterned hair loss

ANDROGENETIC ALOPECIA. Androgenetic alopecia is the most common hair loss syndrome, accounting for about 95% of cases of hair loss. It is also referred to as androgen-dependent or genetic hair loss. In order to understand this form of alopecia, it is useful to begin with



Alopecia, an inherited hair loss syndrome, results in balding. (Fresnell/Shutterstock)

some basic facts about the structure and growth cycle of human hair. Hair is composed primarily of keratin, a tough protein that is also found in the fingernails, toenails, and the outermost layer of skin. Each individual hair consists of a hair follicle, which is a small sac that produces the hair shaft, and the hair shaft itself. The average adult scalp contains about 100,000 hair follicles, the number depending on the natural color of the hair. Brunettes have the highest number of scalp follicles (about 155,000), followed by blondes (140,000) and redheads (85,000). The average adult loses between 70 and 100 scalp hairs per day from ordinary combing, brushing, or shampooing. A loss of more than 150 hairs per day is abnormal.

Human hair differs from the hair of other animals in that its growth cycle is not synchronized; an examination of a group of scalp hairs from the same part of the scalp will show that they are in different phases of growth. There are three phases in the human hair growth cycle. Hairs in the anagen, or growth, stage remain in the follicle during an average period of two to eight years, and grow between a quarter-inch and a half-inch per month. About 90% of scalp hairs are in the anagen phase at any one time. At the end of the anagen phase, the hair enters a

brief catagen phase lasting between two and four weeks. During this phase the follicle begins to break down. The catagen phase is followed by a telogen, or resting, phase that lasts between two and four months. Hairs in the telogen phase are shed when the growth phase of the next cycle begins and the new hair shaft pushes out the old hair. About 10% of the hairs on the scalp are normally in the telogen phase. These hairs will regrow about six months after they have been shed.

In androgenetic baldness, the hair growth cycle is affected by the rise in the level of androgens (male sex hormones) in the body that occurs at puberty. Women as well as men produce androgens, although in much smaller amounts. The amount of these hormones does not need to be abnormally high for androgenetic hair loss to occur. Males who have a normal level of androgens and a gene for baldness will develop male pattern hair loss, or MPHL. There are two androgens that contribute to MPHL, dihydrotestosterone (DHT) and testosterone.

Testosterone is converted to DHT by an enzyme called 5-alpha-reductase. In men with genes for baldness, the hair follicles in the scalp remove testosterone from circulation and convert it to DHT. The action of DHT over time shortens the duration of the anagen phase of the hair growth cycle and decreases the proportion of the hairs in the anagen phase. As the anagen phase decreases, the hairs produced are shorter in length and thinner in diameter. As a larger percentage of the hairs are in the resting or telogen phase, more are lost during normal grooming. This process of the shortening and thinning of each hair shaft is called miniaturization. Miniaturization is accompanied by the loss of hair pigment production, so the miniaturized hairs are also lighter in color. The light-colored fine hairs that are left at the end of the miniaturization process are called vellus hairs.

In MPHL, hair loss tends to occur in certain areas rather than being distributed evenly over the head. One common pattern is recession of the hair at the temples, with the man's hairline moving backward over time in an "M" pattern. The hair at the crown of the head also begins to thin, and may meet the receding hairline so that the remaining hair forms the rough outline of a horseshoe.

In female pattern hair loss, or FPHL, there is an overall thinning of the hair as well as more pronounced hair loss in certain areas of the scalp, usually the crown. Women with FPHL may find that their hairlines recede a little, but rarely to the same extent as happens in men. Androgens play the same role in hair loss in women that they do in men, since the adrenal glands and ovaries secrete small amounts of androgens.

There are other important differences between FPHL and MPHL:

- FPHL generally appears at later ages—in the woman's late 20s or early 30s—whereas MPHL can affect boys as young as 15.
- FPHL is frequently associated with hormonal changes in women, such as those that occur after childbirth, with the use of birth control pills, or after menopause.
- Women very rarely experience complete loss of hair from a specific area of their scalp due to FPHL. The process of miniaturization in FPHL affects the hair follicles at random, so some hairs are unaffected. These normal, thick hairs are interspersed among thinner, miniaturized hairs.

TRACTION ALOPECIA. Traction alopecia is a non-inflammatory patterned hair loss syndrome in which the pattern of loss is related to pulling or friction on specific areas of the scalp. It is usually caused either by hair styles in which the hair is pulled into tight braids or held too tightly by rubber bands or by frequent use of electronic headsets for long periods of time. The tension or rubbing damages the hair shafts and hinders the growth of new hair. In some cases the use of tight hair rollers at night or frequent use of blow dryers on high settings contributes to hair loss from traction alopecia.

TRICHOTILLOMANIA. Trichotillomania is a psychiatric disorder that results in patterned hair loss. It is characterized by recurrent episodes of pulling or tugging at the hair in order to relieve stress or tension. The most commonly affected areas are the scalp, the eyebrows, and the eyelashes, although some patients with the disorder pull at hair elsewhere on the body. Trichotillomania can usually be differentiated from other hair loss syndromes by laboratory study of a hair sample.

Noninflammatory diffuse hair loss

TELOGEN EFFLUVIUM. Telogen effluvium is a common cause of diffuse hair loss, which means that hairs are shed from all parts of the scalp, not just certain patterned areas. “Effluvium” is a Latin word that means “outflow” and refers to the large amounts of hair that may be lost. Persons affected by telogen effluvium may lose as much as 30%–40% of their hair in a short period of time.

Telogen effluvium results from an abnormal alteration of the hair growth cycle in which large numbers of hairs in the anagen phase suddenly switch into the telogen phase. Within six weeks to four months after this switch, these hairs begin to shed.

There are a number of possible causes for telogen effluvium, including the following:

- major surgery
- pregnancy and childbirth

- crash dieting
- nutritional deficiencies, including iron deficiency
- malabsorption syndrome
- infectious diseases accompanied by high fever, such as scarlet fever, early syphilis, or typhoid
- hypothyroidism medications

A number of medications are known to cause telogen effluvium, including beta blockers, oral contraceptives, retinoids, nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin (Indocin) and ibuprofen (Advil), aspirin and other salicylates, lithium, anticoagulants (blood thinners), and anticonvulsants (medications for seizures).

Telogen effluvium usually stops after a few months and new hair grows in. The first regrowth may be finer than usual, but the follicles eventually produce hair of normal thickness.

ANAGEN EFFLUVIUM. Anagen effluvium is a type of diffuse hair loss resulting from a sudden interruption of the growth phase. Unlike the time lag that characterizes telogen effluvium, hair loss in anagen effluvium occurs all at once. The most common cause of anagen effluvium is chemotherapy, including treatment with methotrexate, bleomycin, vinblastine, vincristine, cyclophosphamide, doxorubicin, daunorubicin, and cytarabine. This form of hair loss can also be caused by poisoning with arsenic, thallium, bismuth, or borax.

Anagen effluvium usually stops as soon as the chemical cause is removed, but it may take several months for hair to regrow completely.

Inflammatory nonscarring hair loss

ALOPECIA AREATA. Alopecia areata is a nonscarring recurrent form of hair loss characterized by smooth, round, or oval patches of bare skin. There may be some mild itching but no visible skin eruptions. Alopecia areata is usually considered an idiopathic disorder, which means its cause is unknown. Some researchers, however, consider it an autoimmune disorder. It is often triggered by stress or anxiety. Alopecia areata usually affects only the scalp, the eyebrows, and (in men) the beard, but it may cause hair loss over the entire scalp (alopecia totalis) or even the entire body (alopecia universalis). The loss of hairs from the eyebrows and eyelashes that may be associated with alopecia totalis is called madarosis.

PSORIASIS. Psoriasis is a chronic inflammatory skin disease that frequently affects the elbows and knees as well as the scalp. On the scalp, psoriasis is marked by the appearance of red plaques or patches with silvery scales. These patches may also be found behind the ears. Psoriasis can cause massive but temporary hair loss.

Inflammatory scarring hair loss

In hair loss syndromes marked by tissue scarring, the hair loss is permanent and irreversible. These syndromes should be diagnosed as quickly as possible to minimize the extent of damaged tissue.

LUPUS ERYTHEMATOSUS. Lupus erythematosus is an autoimmune disorder that can affect a number of different organ systems. About 85% of lupus patients are women between 20 and 40 years of age. More than 10% of women with lupus develop a form of the disorder known as chronic discoid or chronic cutaneous lupus erythematosus. Chronic discoid lupus can occur on the scalp as well as the face, and it is marked by dark red patches or plaques between 0.5 in. (1.3 cm) and 0.75 in. (1.9 cm) in diameter. The plaques are covered by dry, horny scales that plug the hair follicles and cause permanent hair loss.

LICHEN PLANOPILARIS. Lichen planopilaris is a form of lichen planus, an idiopathic recurrent skin disorder that usually affects the wrists, legs, and mucous membranes. It is characterized by itching pinkish-red or purplish patches or pimples on the scalp. Like lupus, lichen planopilaris can cause lasting hair loss.

BACTERIAL OR FUNGAL INFECTIONS. Scarring alopecia can be caused by dermatophytes, which are fungi that live on the skin and hair. These fungi include *Trichophyton rubrum*, *Trichophyton tonsurans*, and *Microsporum audouinii*. The dermatophytes infect the skin of the scalp and move down the hair shaft into the follicle, which may be permanently destroyed.

SCLERODERMA. Scleroderma is a chronic disorder in which the patient's skin and connective tissue become progressively thicker and more rigid. Its cause is not known. As the patient's scalp thickens, the hair is gradually but permanently lost.

INJURIES. Scarring alopecia can also result from burns, trauma to the scalp, or radiation treatment.

Genetic profile

Male pattern hair loss (MPHL)

MPHL is a polygenic disorder, which means that its appearance is directed by more than one gene. It may be inherited from either the father's or mother's side. The belief that MPHL is inherited only through the mother is a myth. Genes for baldness are, however, dominant, which means that 50% of the children of a balding parent of either sex will inherit the baldness genes. Studies have shown a link between MPHL and neighboring genes on the X chromosome, including *androgen receptor (AR)* and *ectodysplasin A2 receptor (EDA2R)*, all of which are involved in male pattern baldness. Genetic factors appear

to influence the age of onset of MPHL, the extent and speed of hair loss, and the pattern of hair loss. MPHL may begin at any time after the levels of androgens in a boy's blood begin to rise during puberty.

It is important to note that genes for baldness depend on normal levels of androgen in the body to produce androgenetic hair loss. Men who were castrated prior to puberty or have abnormally low levels of androgen for other reasons do not go bald, even if they have a gene for baldness.

Female pattern hair loss (FPHL)

Female pattern hair loss, or FPHL, is also a dominant disorder. Studies suggest that there is a genetic factor involved, although a genetic mutation has yet to be determined. Studies have also determined a likely correlation between anemia and sex hormones as triggering factors, although they do not indicate a direct relation in terms of severity of the condition.

Alopecia areata

About 20% of cases of alopecia areata are thought to have a genetic component.

Demographics

Androgenetic alopecia

Androgenetic alopecia is quite widespread in the general U.S. population. It is estimated that 35 million American men are affected by this hair loss syndrome. About 25% of Caucasian men begin to show signs of baldness by the time they are 30, and 67% are either bald or developing a balding pattern by age 60. The first evidence of hair loss, namely a receding hairline at the temples, can be found in 96% of Caucasian males over age 15, including those who will not lose any more hair.

There is less agreement on the incidence of androgenetic alopecia among women in the United States: estimates range from 8% to 87%. A commonly accepted figure is that 21 million women are affected. About 80% of girls begin to show some loss of hair at the hairline during puberty, including some who will not develop FPHL.

Alopecia areata

About 2.5 million people in the United States have alopecia areata. It appears to affect men and women equally.

Trichotillomania

Trichotillomania was once thought to be an uncommon disorder, but more recent research suggests that it

occurs fairly frequently among adolescents and young adults. Surveys of college students indicate that 1%–2% are or have been affected by trichotillomania. The male/female ratio is 1:1 in children, but it is about 1:4 in college students. The disorder may be underdiagnosed in males because their hair loss is attributed to MPHL.

Signs and symptoms

The signs and symptoms of each hair loss syndrome are included in its description.

Diagnosis

The differential diagnosis of hair loss is usually made on the basis of the patient's history, visual examination of the scalp, and the results of laboratory tests. The more common forms of alopecia can be diagnosed by a family physician, but those that are related to skin disorders may require referral to a dermatologist. There are four key questions that the doctor will ask in evaluating hair loss:

- How long has the patient been losing hair?
- Is there a pattern to the remaining hair?
- Is the hair loss associated with redness, itching, or pain?
- Are there any patches of broken skin, pimples, plaques, or other signs of infection in the affected areas?

Patient history

The patient's medical history may contain information about previous episodes of hair loss; eating and nutritional habits; use of prescription medications; surgery or chemotherapy; occupational exposure to arsenic, thallium, or bismuth; recent illnesses with high fevers; recent periods of severe emotional stress or anxiety; or other factors that may influence hair loss. In addition, the doctor will ask about grooming habits, including the use of dyes, home permanents, hair straighteners, hair sprays, and similar products, as well as blow dryers, rollers, and other hair styling equipment.

Laboratory tests

Laboratory tests are performed on samples of the hair itself as part of the differential diagnosis. Microscopic study of a hair sample will indicate, for example, damage to the hair shaft, broken hairs, and changes in the shape of the hair. For example, broken hairs may suggest traction alopecia or trichotillomania. In trichotillomania, there will also be an unusually high number of hairs in the catagen phase. Anagen effluvium produces hairs with tapered or pointed ends, sometimes called "pencil-point" hairs. In telogen effluvium, the hairs have white bulbs at the end and can often be removed from the head by very gentle

pulling. In alopecia areata, the area of hair loss is bordered by telltale "exclamation point" hairs.

Hair samples can also be subjected to chemical analysis if heavy metal poisoning is suspected. Arsenic and thallium are absorbed by the hair shaft and can be detected by appropriate tests.

Skin biopsies are most useful in diagnosis when an infection or other inflammatory condition is suspected as the cause of the hair loss. While scarring can often be seen during a visual examination of the scalp, a biopsy may be the only way to tell if the hair follicles have been destroyed, as well as to differentiate among lupus, dermatophyte infection, alopecia areata, and scleroderma. Biopsies may also be useful in determining the presence of traction alopecia or trichotillomania. In these conditions, pieces of hair shaft are sometimes found in the surrounding skin. Some hair follicles may show signs of injury and are interspersed among normal follicles.

Treatment and management

The treatment of hair loss syndromes is determined by their causes.

Medications

TOPICAL APPLICATIONS. Topical applications for hair loss syndromes fall into two major categories—those that stimulate the growth of new hair and those that reduce inflammation. The most frequently prescribed topical medication for male pattern hair loss is minoxidil, which was originally developed to lower high blood pressure. It was approved by the FDA for the treatment of androgenetic hair loss in 1988. Minoxidil, sold under the trade name Rogaine, is applied twice a day as a 2% or 5% solution. It is also sometimes prescribed for female pattern hair loss and alopecia areata. Its chief drawback is its high cost: it costs between \$650 and \$700 a year to use twice a day.

Alopecia areata may be treated with topical corticosteroids or with injections of triamcinolone acetonide (Kenalog) in the affected areas every three or four weeks. Topical corticosteroids are also used to treat chronic discoid lupus, lichen planopilaris, and psoriasis. Tar shampoos are frequently recommended along with topical steroids to treat psoriasis of the scalp.

ORAL MEDICATIONS. One oral medication, finasteride, has been approved by the FDA for the treatment of male pattern hair loss. Finasteride, sold under the trade names Propecia or Proscar, works by interfering with the body's production of 5-alpha-reductase, the enzyme that converts testosterone to DHT. It is considered the most effective nonsurgical treatment of MPHL. The usual daily dose of finasteride is 1 mg. Unlike minoxidil, finasteride does not appear to be effective in postmenopausal

KEY TERMS

Alopecia—Loss of hair or baldness.

Alopecia areata—A nonscarring hair loss syndrome characterized by smooth, round, or oval hairless areas on the scalp.

Anagen—The growth phase of the human hair growth cycle.

Androgens—A group of steroid hormones that stimulate the development of male sex organs and male secondary sexual characteristics.

Catagen—The breakdown phase of the hair growth cycle.

Dihydrotestosterone (DHT)—A male sex hormone formed from testosterone by the enzyme 5-alpha-reductase. DHT causes hair follicles to shut down, shortening the growth phase of the hair growth cycle and leading to miniaturization.

Effluvium—The medical term for massive hair loss or shedding.

Finasteride—An oral medication used to treat male pattern hair loss. Finasteride, sold under the trade names Proscar and Propecia, is an androgen inhibitor.

Keratin—A tough, non-water-soluble protein found in the nails, hair, and outermost layer of skin. Human hair is made up largely of keratin.

Madarosis—The medical term for loss of hair from the eyebrows or eyelashes. Madarosis may be associated with a form of alopecia areata called alopecia totalis. It may also result from such diseases as leprosy and syphilis, or from trauma.

Miniaturization—The process of shortening and thinning of the hair shafts that is found in androgenetic alopecia. It is caused by the effects of DHT on the hair follicle.

Minoxidil—A topical medication sold under the trade name Rogaine for the treatment of male pattern hair loss. It is applied to the scalp as a 2% or 5% solution.

Telogen—The resting phase of the hair growth cycle.

Traction alopecia—Hair loss caused by pressure or tension on the scalp related to certain types of hair styles or equipment worn on the head.

Trichotillomania—A psychiatric disorder characterized by hair loss resulting from compulsive pulling or tugging on one's hair.

Vellus hairs—The fine lighter-colored hairs that result from miniaturization.

women. It has not been tested on women of childbearing age because its androgen content could cause birth defects in male children.

Oral antifungal medications are considered better than topical preparations for treating dermatophyte infections of the scalp because topical products do not penetrate around the hair follicle. The mostly commonly prescribed oral antifungal drugs are griseofulvin (Grisactin, Fulvicin), ketoconazole (Nizoral), and fluconazole (Diflucan).

Clomipramine (Anafranil), which is a tricyclic antidepressant, and fluoxetine (Prozac), a selective serotonin reuptake inhibitor (SSRI), have been used in the treatment of trichotillomania.

Surgery

Surgical transplantation is considered the most effective treatment of MPHL, but it is not recommended for alopecia areata. Punch grafts or larger skin flaps bearing the patient's own hair are transferred from areas of the head with normal hair growth to the balding areas. Hair transplantation is expensive but is usually permanent. It appears to work best on patients with dark or curly hair.

Scalp reduction, in which bald areas at the top of the scalp are removed, is another surgical technique used in treating MPHL. It works best for patients with relatively little hair loss.

Nonsurgical hair additions

These devices consist of human hair, synthetic fibers, or combinations of both. They are added to existing hair or attached to the scalp with adhesives to cover areas of hair loss. They include hair weaves, hair pieces, hair extensions, toupees, partial hair prostheses, and similar devices. Nonsurgical hair additions are less expensive than surgery but still cost between \$750 and \$2,500, depending on materials and design. They can be used in combination with hair replacement surgery.

Psychotherapy

Cognitive-behavioral therapy is considered the most effective form of psychotherapy in treating trichotillomania. Individual psychodynamic psychotherapy is often helpful for persons who are emotionally upset by hair loss, particularly those whose employment depends on their appearance.

QUESTIONS TO ASK YOUR DOCTOR

- Is the hair loss I am experiencing likely to continue, or is it only a temporary problem that will eventually go away?
- Is there any reason to suspect that my hair loss is related to genetic factors? How can I find out one way or another?
- What procedures are available to reduce or reverse the hair loss I have been experiencing?
- Is hair transplantation likely to be an effective method for dealing with my hair loss?

Prognosis

The prognoses of hair loss syndromes vary according to their causes. Hair loss caused by inflammatory scarring has the worst prognosis because syndromes or injuries that form scar tissue destroy the hair follicles, preventing regrowth. The prognosis for alopecia areata is less favorable if the disorder affects large areas of the scalp, begins in adolescence, or has existed for a year or longer before the patient seeks treatment. Alopecia areata that begins in adult life and is limited to a few small areas of the scalp often goes away by itself in a few months, although the condition can recur. Diffuse hair loss related to anagen or telogen effluvium has a good prognosis. Although complete regrowth may take some months, the hair does come back once the cause is identified and removed.

The prognosis for androgenetic alopecia varies. Rogaine does not work equally well for all men with MPHL. Those who benefit most from treatment with Rogaine have been bald for less than ten years, have a bald spot on the crown of the head that is smaller than 4 in. (8cm) across, and still have vellus hairs in their balding areas. Hair that grows in as a result of Rogaine will fall out once the patient stops using the medication. Finasteride is becoming the first-line nonsurgical treatment for MPHL because it prevents hair loss as well as aids regrowth; one study indicates that finasteride prevents further loss of hair in 90% of men even five years after they take it, and it assists regrowth in 65% of men even two years later.

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ORGANIZATIONS

American Academy of Dermatology, PO Box 4014, Schaumburg, IL 60168, (866) 503-7546, (847) 240-1859, info@ahlc.org, <http://www.aad.org>
 American Hair Loss Council, 30 South Main, Shenandoah, PA 17976, <http://www.ahlc.org>
 American Society for Dermatologic Surgery, 5550 Meadowbrook Dr., Suite 120, Rolling Meadows, IL 60008, (847) 956-0900, <https://www.asds.net>
 National Alopecia Areata Foundation (NAAF), 65 Mitchell Blvd., Suite 200-B, San Rafael, CA 94903, (415) 472-3780, (415) 480-1800, info@naaf.org, <https://www.naaf.org>

Nina B. Sherak, MS, CHES

Hallermann-Streiff syndrome

Definition

Hallermann-Streiff syndrome is a rare genetic condition that causes characteristic facial features, visual abnormalities, tooth problems, short stature, and, occasionally, mental impairment.

Description

Hallermann-Streiff syndrome is also known as François dyscephaly syndrome, Hallermann-Streiff-François syndrome, oculomandibulodyscephaly with hypotrichosis, and oculomandibulofacial syndrome. The distinctive facial features of Hallermann-Streiff syndrome include a very small head that is unusually wide; a prominent forehead; a small, underdeveloped jaw; an unusually small mouth; and a characteristic beak-shaped nose. Small eyes, clouding of the lens of the eyes (cataracts), and other eye problems often leading to blindness are common. Problems with the teeth, skin, hair, and short stature are also common. Most individuals are of normal intelligence, but mental impairment has been reported in some. Most cases of Hallermann-Streiff syndrome occur randomly for unknown reasons and may be the result of mutations, or changes to the genetic material.

Genetic profile

Hallermann-Streiff syndrome is a genetic condition. Genes are units of hereditary material passed to a child

by his or her parents. The information contained in genes is responsible for the growth and development of all the cells and tissues of the body. Most genes occur in pairs: one copy of each pair is inherited from the mother through the egg cell and one copy of each pair is inherited from the father through the sperm cell. If there is a gene alteration (mutation), this may interfere with normal growth and development. The specific gene responsible for Hallermann-Streiff syndrome has not yet been identified.

Most cases of Hallermann-Streiff syndrome occur randomly in families with no other affected individuals. In this situation, the gene alteration is a spontaneous mutation. This means that some unknown event has caused the gene (which functions normally in the parent) to change in either the father's sperm or the mother's egg from which the affected individual was conceived. A person who has Hallermann-Streiff syndrome due to a spontaneous mutation can pass on this mutated gene to offspring who will also be affected. The chance for someone with Hallermann-Streiff syndrome to have a child with the same condition is 50% in each pregnancy. There is also a 50% chance to have a child who is not affected with Hallermann-Streiff syndrome.

There are some reports in the literature that indicate that Hallermann-Streiff syndrome is inherited as a recessive condition. Recessive conditions occur when both copies of a gene pair are changed. The affected individual inherits one mutated gene from each parent. The parents of the affected individual are carriers for one changed copy of the gene pair but are not affected themselves. Carrier couples have a 25% chance in each pregnancy to have a child affected with the condition. Diagnosed individuals are at risk to have an affected child only if their partner is also affected or is a carrier. There is no clear agreement on whether Hallermann-Streiff syndrome can be inherited as a recessive condition. Some have argued that the families reported to have recessive Hallermann-Streiff syndrome in fact do not have this condition but some other condition with features very similar to Hallermann-Streiff syndrome.

Demographics

Hallermann-Streiff syndrome affects both males and females in all ethnic groups. There have been over 150 cases reported in the literature.

Signs and symptoms

Hallermann-Streiff syndrome affects the face, skull, hair, skin, eyes, teeth, and overall growth and development.

Face and skull

The facial features of individuals with Hallermann-Streiff syndrome are distinctive. The face is small with a thin, tapering, pinched nose and small chin. The head is small and unusually wide with a prominent forehead; a small, underdeveloped jaw; and a small mouth. Characteristic changes in the bones of the skull and the long bones of the arms and legs can usually be seen on x-ray. The hair is usually sparse, particularly that of the scalp, brows, and lashes. Often there is no hair around the front and sides of the head. The skin of the scalp is thin and taut, and scalp veins are prominent.

Potential complications in Hallermann-Streiff syndrome are related to the narrow upper airway associated with the shape of the skull, particularly the small chin, mouth, and nose. The narrow air passages may result in feeding difficulties and mild aspiration of food. This can lead to severe complications including early lung infection and breathing difficulties. The lung infection can be life threatening. Some individuals may experience a temporary stop in breathing during sleep because of an obstruction caused by the shape of the skull (obstructive sleep apnea). Individuals with Hallermann-Streiff syndrome are also at increased risk of breathing difficulties when given a general anesthetic before surgery.

Eyes

Individuals with Hallermann-Streiff syndrome may be born with clouding of the lenses of the eyes (congenital cataracts). Congenital cataracts are the most common eye disorder and are usually the reason for a visit to the eye specialist in early life. The cataracts have been reported to spontaneously disappear in some cases. The second most common eye problem is that the eyes are unusually small. Other eye problems may include rapid, involuntary eye movements; crossing of the eyes and/or decreased visual clarity; and, in some cases, blindness.

Teeth

Dental problems are very common. They may include the presence of teeth at birth and the presence of extra teeth. Underdevelopment of tooth enamel and cavities are also common. There may also be absence, malformation, and/or improper alignment of certain teeth.

Growth and development

Most individuals with Hallermann-Streiff syndrome are born at term, but about one-third are born premature and/or have a low birth weight. Short stature is seen in about half of the individuals with Hallermann-Streiff syndrome. The average final height is about 60 in. (152 cm) for females and 61 in. (155 cm) for males.

KEY TERMS

Anesthetic—Drug used to temporarily cause loss of sensation in an area of the body. An anesthetic may either be general, associated with a loss of consciousness, or local, affecting one area only without loss of consciousness. Anesthetics are administered either via inhalation or needle injection.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual or manifest as disease and can be transmitted to offspring.

Trachea—Long tube extending from the larynx down into the lungs, responsible for passing air.

Tracheostomy—An opening surgically created in the trachea (windpipe) through the neck to improve breathing.

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.

Most individuals are of normal intelligence; however, it is estimated that 15%–30% of individuals with Hallermann-Streiff syndrome show some degree of mental impairment or slow development. Hyperactivity and seizures have been reported in a small number of individuals.

Other

A small number of individuals with Hallermann-Streiff syndrome have heart defects (such as a hole in the heart). There has also been a report of an individual with a weakened immune system.

Diagnosis

The diagnosis of Hallermann-Streiff syndrome is based on the presence of certain features including the characteristic facial, eye, dental, hair, and skin findings. The main features indicative of Hallermann-Streiff syndrome include a small, wide head with a prominent forehead; the characteristic small jaw and mouth with a pinched nose; cataracts; small eyes; dental abnormalities; sparse or absent hair; thin skin; and short stature. X-rays of the bones of the body may be helpful in establishing a diagnosis of Hallermann-Streiff syndrome because there are characteristic changes evident in the bones of individuals with this condition. There is no laboratory test that can be done to confirm the diagnosis. Genetic testing

to identify the specific genetic alteration causing the condition is not available since the gene for Hallermann-Streiff syndrome has not been identified. Testing for Hallermann-Streiff syndrome in an unborn baby has not been done. It may be possible to detect the abnormal head shape and small chin on an ultrasound of the developing baby, but this has not been documented in the literature.

Treatment and management

There is no cure for Hallermann-Streiff syndrome. In general, an individual with Hallermann-Streiff syndrome requires a team of specialized doctors for treating the various problems that can occur. Assessments by a dentist, dental surgeon, and oral-facial surgeon may also be necessary to evaluate the teeth and difficulties caused by the small chin and mouth. An assessment for possible airway problems is essential. Any individual with Hallermann-Streiff syndrome who shows signs of daytime sleepiness or snoring should be referred to a sleep center for proper diagnosis and treatment of possible obstructive sleep apnea. Treatment for this condition may include surgical procedures, such as making a hole in the trachea through the neck to relieve whatever is obstructing the breathing (tracheotomy). Other surgical treatments may include advancing the chin, reducing the size of the tongue, and/or removing the tonsils. Nonsurgical treatments may include medications, providing the individual with an oxygen mask, and modifying his or her sleeping position.

An individual with Hallermann-Streiff syndrome should be examined by an eye specialist (ophthalmologist) for signs and symptoms of eye problems. Surgery for some types of eye problems (cataracts, crossed eyes) may be necessary. Individuals who are blind or at risk of losing their eyesight may benefit from being referred to an association for the blind for guidance and counseling.

An examination by a heart specialist (cardiologist) for possible heart problems and by an immune specialist (immunologist) for possible decreased immune function is also recommended. Some types of heart problems may be treated with medications or may require surgical correction.

For individuals with developmental delay or mental impairment, treatment may include special education, speech therapy, occupational therapy, and physical therapy. Drugs may be used to treat hyperactivity, seizures, and other problems.

Some individuals with Hallermann-Streiff syndrome may seek cosmetic surgery for the various effects the syndrome has on the face and skull. Counseling by psychologists may also help individuals with Hallermann-Streiff

QUESTIONS TO ASK YOUR DOCTOR

- How is it possible to predict the possible occurrence of Hallermann-Streiff syndrome in a family?
- What are the physical characteristics on which a diagnosis of Hallermann-Streiff syndrome is based in a young child?
- What types of treatment are available for the disorder, and how effective are those treatments?
- What patient-support organizations are available for families with a Hallermann-Streiff child?

syndrome cope with the psychological impact of having a facial difference.

Individuals with Hallermann-Streiff syndrome and their families may also benefit from genetic counseling for information on the condition and recurrence risks for future pregnancies.

Prognosis

Individuals diagnosed with Hallermann-Streiff syndrome typically have normal intelligence and life-spans when complications of this disorder are properly managed. A major difficulty for individuals with Hallermann-Streiff syndrome is that the visual problems can often lead to blindness, despite surgery. Lung infections can be life threatening to these patients and must be treated immediately. Breathing problems are another serious complication resulting from the abnormal skull formation that narrows the upper airway. Although uncommon, developmental delay and mental impairment have been reported in a minority of individuals affected with Hallermann-Streiff syndrome. These individuals with significant mental impairment may require lifelong supervision.

Resources

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ORGANIZATIONS

- FACES: The National Craniofacial Association, PO Box 11082, Chattanooga, TN 37401, (423) 266-1632 or (800) 332-2373, faces@faces-cranio.org, <http://www.faces-cranio.org>
- National Eye Institute (NEI), 31 Center Dr., MSC 2510, Bethesda, MD 20892, (301) 496-5248, 2020@nei.nih.gov, <http://www.nei.nih.gov>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Nada Quercia, MSc, CGC

Hand-foot-genital syndrome

Definition

Hand-foot-genital (HFG) syndrome is a very rare genetic disorder that affects the development of the hands, feet, urinary tract, and reproductive tract.

Description

The hallmarks of HFG include incurving of the fingers (clinodactyly) and shortened and relocated thumbs. There are also wrist- and ankle-bone fusions, very small feet, short great toes, urinary-tract abnormalities, duplications of the reproductive tract in women, and urethral openings on the underside of the penis and a curved penis in men. HFG was first described in 1970 as hand-foot-uterus (HFU) syndrome. Based on the findings of genital abnormalities in affected males, a 1975 study suggested that HFG was the more accurate name. Although people with HFG are usually fertile, because of problems with early uterine development, some women are at increased risk for pregnancy loss, premature labor, and stillbirth.

Genetic profile

HFG is caused by autosomal dominant mutations in the *HOXA13* gene, which stands for "homeobox A13." Autosomal dominant means that only one altered *HOXA13* gene—inherited from one parent—is required for HFG to develop, even in the presence of a normal

KEY TERMS

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a nonsex chromosome is required for a disease or inherited trait to develop in an individual.

Clinodactyly—An abnormal inward curving of the fingers or toes.

HOXA13 gene inherited from the other parent. In some cases, rather than being inherited from a parent, HFG is caused by *de novo* (new or sporadic) *HOXA13* mutations that occur in the sperm or egg or during early embryonic or fetal development. In such cases, there is no family history of the disorder.

HOXA13 is located on the short arm (p) of chromosome 7 at position 15.2 (7p15.2). *HOXA13* is a member of a gene family known as *homeobox* genes. It produces a protein called a transcription factor that binds to specific regions of DNA to regulate the activity of other genes. *HOXA13* is critical during embryonic development, especially for the formation of the hands and feet and the urinary tract and reproductive system.

Different mutations in the *HOXA13* gene result in different signs and symptoms or phenotypes of varying severity. The *HOXA13* gene contains three regions that code for strings of the amino acid alanine in the protein. Many of the HFG-causing mutations add extra alanines to these strings, making them abnormally long and unstable. *HOXA13* proteins with these extra alanines are degraded by the cell and are not available for developmental functions. Other identified mutations in *HOXA13* include “nonsense” mutations that result in a shortened nonfunctional *HOXA13* protein. Some mutations change single amino acids within the *HOXA13* protein, resulting in an abnormal protein that interferes with normal functioning within the cells of the developing fetus. These mutations that lead to an altered protein appear to cause more severe signs and symptoms than mutations that lead to a nonfunctional protein.

Demographics

HFG syndrome is extremely rare. Worldwide, there are only a few families who have been identified with HFG.

Signs and symptoms

HFG affects the hands, feet, and urinary and reproductive tracts, although the abnormalities and their severity

vary, even in individuals in the same family. HFG causes abnormal thumbs and small feet with short big toes. Females have duplications within the genital tract. Many affected individuals have defects in the ureters, which transport urine from the kidneys to the bladder; others have defects in the urethra, through which urine exits the body. These abnormalities can result in frequent urinary tract infections or urinary incontinence (inability to control urination). About half of affected males have the urethra opening on the underside of the penis.

Diagnosis

Diagnosis of HFG is usually made with a physical examination by a medical geneticist and x-rays or other imaging of the hands, feet, and reproductive and urinary tracts. Genetic testing for HFG may be available by sequencing the entire coding region of the *HOXA13* gene or deletion/duplication analysis of the gene.

Treatment and management

There is no specific therapy that can repair all of the effects of HFG syndrome, but surgery can alleviate some abnormalities. Management focuses on treating specific effects of the disorder.

Prognosis

Because the signs and symptoms of HFG vary considerably, the prognosis for affected individuals varies. Most people with mild or moderate hand, foot, and/or genital abnormalities lead relatively normal lives. Severe urinary- and/or reproductive-tract abnormalities may require multiple surgeries with prognoses depending on the severity of the abnormalities and success of the surgeries. Some people with severe reproductive-tract abnormalities may have difficulty having children.

Resources

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- Kliegman, Robert M., et al., eds. *Nelson Textbook of Pediatrics*. 21st ed. Amsterdam: Elsevier, 2019.
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QUESTIONS TO ASK YOUR DOCTOR

- Why do you think my child has hand-foot-genital syndrome?
- Did my child inherit hand-foot-genital syndrome, or is it a result of a *de novo* or sporadic mutation?
- Is genetic testing available for hand-foot-genital syndrome, and what information could genetic testing provide?
- What treatments are available for my child?
- Will my child be able to have children?

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 "Hand foot uterus syndrome." GARD. <https://rarediseases.info.nih.gov/diseases/2594/hand-foot-uterus-syndrome> (accessed June 10, 2021).

ORGANIZATIONS

March of Dimes, 1275 Mamaroneck Ave., White Plains, NY 10605, (914) 997-4488, <http://www.marchofdimes.org>
 Reach: The Association for Children with Upper Limb Deficiency, Pearl Assurance House, Brook Street, Tavistock, Devon UK PL19 0BN, 0845 1306 225, <http://www.reach.org.uk>

Dawn A. Jacob, MS, CGC
 and Margaret Alic, PhD

Harlequin ichthyosis

Definition

Harlequin ichthyosis (HI) is a very severe skin disorder in which infants are born with thick, plate-like scales all over their bodies. HI can result in facial disfigurement and limited movement of the arms, legs, fingers, and toes. In the past, affected infants died during the first weeks of life, but improved treatments have significantly increased survival rates.

Description

HI represents the most severe presentation of congenital ichthyosis. It is also known as autosomal recessive

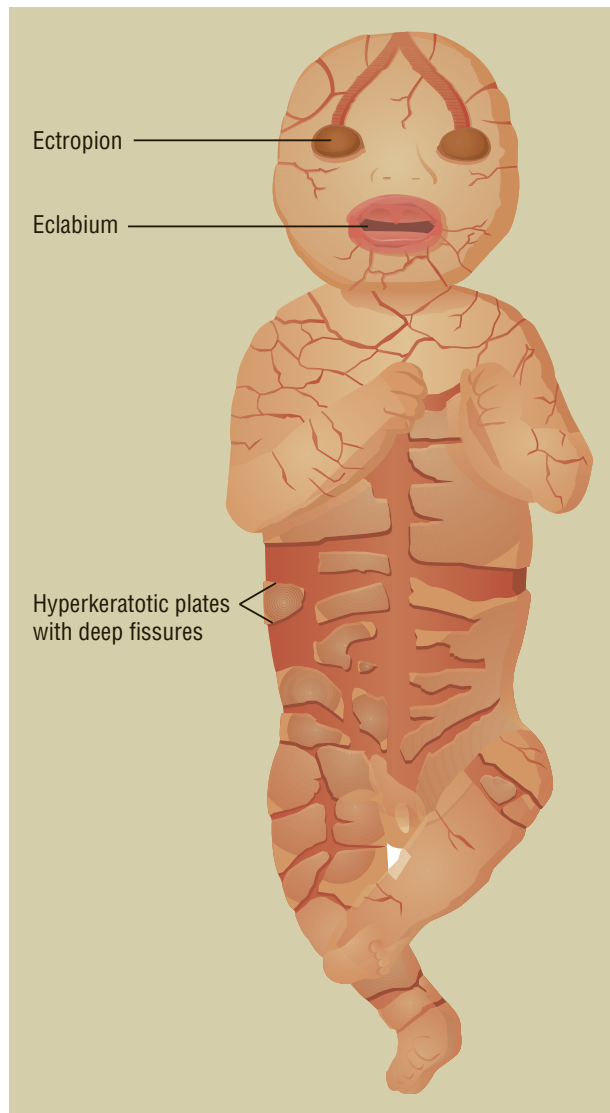
congenital ichthyosis 4B (harlequin) or ARCI4B. The term "ichthyosis" is derived from the Greek word for "fish." Ichthyoses are a family of more than 25 types of skin disorders characterized by markedly thickened, ridged, and cracked skin. They are caused by various underlying genetic abnormalities of metabolism that result in defective keratinization, which is the process in which new epidermal cells of the outermost layer of skin are gradually changed into the stratum corneum. The layers of dead cells of the stratum corneum are filled with keratin protein and act as a protective barrier over the surface of the body. This process is controlled by a number of different metabolic pathways, and an abnormality at any point can theoretically lead to conditions such as ichthyosis or other serious skin abnormalities.

The types of ichthyoses are defined by their clinical features, the age at which symptoms appear, and their underlying genetic cause. Ichthyosis of the newborn is present at birth or shortly thereafter and can be caused by several different genetic abnormalities, even when there is some similarity in the clinical features. HI, however, is such a distinct and striking disorder that it is rarely confused with other types of ichthyosis. HI was previously known as harlequin fetus. Affected infants have thick, armor-like skin with deep cracks running in different directions all over their bodies. This gives the appearance of diamond-shaped plaques; thus, the descriptive term "harlequin." This severe skin abnormality leads to an open, "fish-mouthed" appearance and a turning outward of the eyelids. Abnormalities of the internal organs are uncommon but have been reported. Early death from severe skin infection is common because the abnormal skin does not form a proper barrier between the body and the environment.

Genetic profile

HI is inherited as an autosomal recessive condition. This means that an affected child has inherited two copies of a defective gene—one from each parent. In most cases, the parents are carriers with one defective and one normal gene and no symptoms of the disorder. If each parent is a carrier, there is a one in four chance that each of their children will have HI and an additional 50% risk that each child will inherit one gene for HI and be a carrier.

HI is caused by mutations in the *ABCA12* gene located on the long arm (q) of chromosome 2 at position 2q35. *ABCA12* stands for "ATP-binding cassette subfamily A member 12." The HI mutation inherited from each parent may be the same or different changes within the *ABCA12* gene. *ABCA12* is believed to produce a protein that plays a major role in the transport of lipids (fats) across cell membranes in the epidermis and is essential for the normal development of skin cells. *ABCA12*



Harlequin fetus is a severe and usually fatal form of ichthyosis. This rare skin disorder results in thick, scaly skin; turning out of the eyelids (ectropion) and the lips (eclabium); and deep skin fissures. (Gale)

mutations can lead to no protein at all or to a shortened protein that cannot properly transport lipids. This prevents normal skin development and results in hard, thick, scaly epidermis—hyperkeratosis.

More than 55 different *ABCA12* gene mutations that cause HI have been identified. These include different-sized deletions within the *ABCA12* gene. All of the HI-causing mutations prevent production or functioning of the transporter protein. If the *ABCA12* gene mutations in an affected family have been identified, prenatal testing and carrier testing of at-risk relatives are available. Other mutations in *ABCA12* can cause a different form of ichthyosis called lamellar ichthyosis.

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are needed to display the trait or disease.

Carrier—An individual who possesses an unexpressed abnormal gene of a recessive genetic disorder.

Eclabium—Outward turning of the lip.

Ectropion—An abnormal turning out, as of the eyelid.

Epidermis—The outermost layer of the skin.

Hyperkeratosis—Abnormal thickening of the outermost layer of the skin, the stratum corneum.

Keratinization—The conversion of the epidermis into the stratum corneum.

Pathogenic variant—A mutation or variation in a gene that causes a genetic disorder.

Stratum corneum—The outer portion of the epidermis made up primarily of dead, flattened cells filled with the protein keratin.

Demographics

HI is a very rare form of congenital ichthyosis. It is estimated to affect about 1 in every 200,000 births in the United States or about 19 newborns per year. Like other autosomal recessive conditions, HI is more common among the children of consanguineous (related) couples, such as first cousins. Biologically related individuals are much more likely to carry the same recessive gene and, hence, have offspring with autosomal recessive disorders.

Signs and symptoms

Infants affected with HI have a unique and striking appearance at birth. Their skin is unusually thick, off-white in color, and resembling “armored” scales separated by deep, moist cracks running in different directions. The facial appearance is distorted with marked ectropion or turning outward (eversion) of the eyelids. The lips also turn outward (eclabium). The external ears are absent or flattened against the side of the head, and the nose is flattened. The hands and feet are grayish-white in color. The fingers and toes appear malformed due to impeded blood circulation from the constrictions that can cause tissue death (necrosis). Nails and body hair may be missing. There is limited mobility of the arms and legs due to the scaly plates and constrictions. Abnormalities of the central nervous system, kidneys, and lungs

QUESTIONS TO ASK YOUR DOCTOR

- What treatments are available for harlequin ichthyosis?
- What is the prognosis for my child with harlequin ichthyosis?
- Can my partner and I have genetic testing for the gene that causes harlequin ichthyosis?
- What are the chances that we will have a second child with harlequin ichthyosis?
- Is preimplantation or prenatal testing available for harlequin ichthyosis?

have been described in some affected individuals. Short stature has been observed in survivors. However, because the protective barrier of the skin is severely compromised, newborns are at serious risk for systemic infection (sepsis), dehydration, and poor temperature regulation.

Diagnosis

HI may be diagnosed by clinical examination after birth; however, a skin biopsy may be necessary to confirm a diagnosis of this particular type of ichthyosis. A sample of skin is examined under an electron microscope for the characteristic changes of hyperkeratosis (overgrowth of the stratum corneum). Prenatal diagnosis of HI can be performed by genetic testing for *ABCA12* gene mutations, microscopic analysis of cells from a sample of amniotic fluid, or biopsy of the fetal skin. This is usually accomplished by a combination of fetoscopy and amniocentesis. The cellular changes associated with hyperkeratosis begin during the latter part of the second trimester of pregnancy—21–23 weeks gestation, possibly earlier. Prenatal ultrasound alone will not detect many of the features associated with HI, particularly in a low-risk patient population.

Treatment and management

Infants with HI tend to be born prematurely. Thus, if HI has been diagnosed prenatally and the pregnancy is continued, the mother should undergo close monitoring for the remainder of her pregnancy. Most deaths from HI occur in the first few days after birth. Immediate care of a newborn with HI focuses on control of body temperature and prevention of dehydration, malnutrition, and infection. Infants who are born prematurely may require a breathing tube, as well as intravenous fluids, nutrients, and antibiotics. Medication for pain management should

be provided as needed. Sponge baths or tub soaking and the application of skin moisturizers with antibiotics should be performed twice daily to soften the skin, reduce scaliness, and prevent infection. The oral retinoids isotretinoin or etretinate also loosen and help shed the scales. Artificial tear treatments may be required for infants with severe ectropion.

Prognosis

In the past, most infants with HI died within a few days of birth. However, advances in neonatal care, and perhaps etretinate treatments, have increased survival rates. Common causes of death include respiratory complications due to prematurity or constriction by the thick scales that causes dehydration or skin infection. Among survivors, the ichthyosis does not go away, but large, thin scales covering dry, reddish skin gradually replace the cracked, thick skin. Hair may be sparse. The eversion of the eyelids and lips gradually resolves. Physical development may be slow due to the enormous caloric requirement for skin functioning. An extensive skincare program must be maintained to keep the skin pliable and moist and prevent fissuring and cracking that can lead to infection. Mental development is usually normal. However, sudden death may occur even with attentive medical care. As of 2015, several individuals with HI had survived into their teens and 20s. In 2013, a young woman with HI gave birth to a healthy baby.

Resources

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ORGANIZATIONS

American Academy of Dermatology, PO Box 4014, Schaumburg, IL 60168, (866) 503-7546, (847) 240-1859, <https://www.aad.org>

Foundation for Ichthyosis & Related Skin Types (FIRST), 2616 N. Broad St., Colmar, PA 18915, (215) 997-9400, info@firstskinfoundation.org, <http://www.firstskinfoundation.org>

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HeLa cells

Definitions

HeLa cells refer to the oldest and best-known immortal cell line used in biomedical research. An immortal cell line is a population of cells that has evaded normal cellular senescence (the ending of cellular replication) and can continue to reproduce indefinitely, usually as the result of a mutation. The name *HeLa* (pronounced HEE-la) was formed from the first two letters of the first and last names of Henrietta Lacks, the terminally ill patient who provided the cervical tissue used to start the cell line during her treatment for cancer in 1951.

Description

The patient

Henrietta Lacks (1920–1951) was a 31-year-old African American woman living in Baltimore, Maryland, who noticed unexplained vaginal bleeding shortly after the birth of her fifth child. She went to Johns Hopkins Hospital in January 1951 for examination, as it was the only hospital in the area that treated Black patients. Her surgeon biopsied a mass that he found on her cervix; it was an adenocarcinoma of the cervix, a particularly aggressive form of cervical cancer.

There were very few treatments for cervical cancer in the early 1950s. Lacks was initially treated with brachytherapy, a type of cancer treatment in which a sealed source of radiation is placed in or near the area to be treated. While she was an inpatient, two samples of her cervical tissue, one healthy and one cancerous, were removed without her knowledge or consent. This taking of tissue samples from hospital patients was standard practice in the 1950s, however, and was done without regard to the

patient's age, sex, race, or income level. Lacks' samples were given to the cell biologist George Otto Gey (1899–1970; name is pronounced *guy*), the director of the Tissue Culture Laboratory at Johns Hopkins Hospital.

After several months of outpatient X-ray therapy, Lacks returned to the hospital in early August 1951 with severe abdominal pain; she remained there until her death on October 4, 1951. Her autopsy showed that the cancer had spread throughout her body. A detailed description of her autopsy published in 2009 indicated that her chest and abdominal cavities were filled with cancerous tumors, and her ovaries and fallopian tubes had been completely destroyed by the cancer.

The laboratory

Gey's Tissue Culture Laboratory at Johns Hopkins Hospital was small and underfunded compared to today's large and well-furnished biomedical laboratories. The laboratory was given about \$5,000 per year in 1951, a sum equivalent to \$51,770 in 2021. Gey, who was particularly interested in cancer research, had only two assistants: his wife Margaret, a registered nurse; and Mary Kubicek, a recent college graduate with a degree in physiology. Kubicek used Gey's roller-tube technique to incubate the cells from Lacks' cancerous biopsy specimen. Unlike previous attempts to culture cervical cancer cells in the laboratory, Lacks' cells grew vigorously, dividing every 20 to 24 hours, and showed no signs of cellular senescence. The cells, named HeLa (for Henrietta Lacks), were incubated in a mixture of chicken plasma, bovine embryo extract, and human placental cord serum, according to an article published in *Cancer Research* by Gey and Kubicek in 1952.

Neither Gey nor Johns Hopkins Hospital was interested in profiting from the sale of the HeLa cells. As the founder of the Tissue Culture Association (now the Society for In Vitro Biology), Gey donated the cells freely to other researchers for what he considered their benefit to science. Later, however, a number of scientists and laboratories did make money from the sale of HeLa cells—which prompted a controversy that continues to the present day and will be discussed below.

Distinctive features of HeLa cells

Advances in both technology and laboratory technique enabled researchers in the early 2000s to discover several features of HeLa cells that explain their immortality as well as their distinctive genome. In 2007, a team of researchers found that HeLa cells express telomerase, an enzyme that prevents telomere shortening during the process of cell division. Telomeres are repeated DNA sequences that cap the ends of chromosomes and protect

chromosomal stability. In normal cells, the telomeres are shortened each time the cell divides until they reach a critical length known as the Hayflick limit. At that point (between 40 and 60 cell divisions) the cell stops dividing and enters senescence. In contrast, the telomeres of HeLa cells are not shortened during cell division, and consequently the cells evade the Hayflick limit.

The HeLa genome is unusual in several respects. It resulted from horizontal gene transfer from human papillomavirus (HPV) 18 to the original cervical cancer cells, leading to an uncommonly high total number of chromosomes. Present cytogeneticists define the HeLa chromosome number as hypertriploid, meaning that each HeLa cell contains more than three times the normal haploid number of human chromosomes, which is 23. Some HeLa cells contain as many as 76 to 80 chromosomes. Repeated karyotyping has shown that this unusual genome has remained stable even after years of cell culture.

Purpose

The HeLa cells are considered a landmark contribution to biomedical research and have led to numerous discoveries; over 110,000 articles that involved the use of HeLa cells were published in medical journals between 1952 and 2018. Immortal cell lines are important in medical research because they guarantee that the cells from a given line are homogeneous (identifiably the same throughout a specific experiment), and that a given experiment can be replicated (reproduced) by other scientists using the same cell line to verify the accuracy of the first group's results.

A lasting problem with the HeLa cells that could not have been foreseen in 1951, however, was that their immortality turned out to include the colonization and contamination of other cell lines. The cells' invasiveness led to a major scientific crisis in the late 1960s and early 1970s. A cell biologist named Stanley Gartler (1923–), then at the University of Washington, published an article in *Nature* in 1968 showing that 19 other cell lines thought to be unique had in fact been cross-contaminated by HeLa cells, most likely as a result of poor laboratory storage and handling techniques.

Gartler's work, which used enzyme biomarkers, was followed up by Walter Nelson-Rees (1929–2009), a cytogeneticist who worked in what was then the Naval Biosciences Laboratory (NBL) in Oakland, California. The cell culture laboratory within the NBL was funded by the National Cancer Institute (NCI) to establish, store, and distribute cell lines to researchers around the world. Nelson-Rees used Giemsa staining to mark the banding patterns on chromosomes rather than Gartler's enzyme

profiles; this change in method enabled him to uncover a much larger number of supposedly independent cancer cell lines that had been contaminated by HeLa cells during their use as model systems for studies on breast, prostate, ovarian, and various other cancers. Nelson-Rees' findings meant that any organ- or tissue-specific studies based on the contaminated cell lines were useless. One writer estimated that at least 500 publications had been invalidated and over \$20 million in research funding had been wasted between 1975 and 1981. Nelson-Rees retired in 1981 before the application of molecular methods to cell line verification, but the newer technique of forensic DNA fingerprinting has confirmed the accuracy of his work.

Early HeLa research

HeLa cells played an important part in the following discoveries:

- 1953: Jonas Salk (1914–1995) begins clinical trials of his killed-virus polio vaccine. George Gey notes in the same year that HeLa cells are useful in testing a polio vaccine because the cells are easily infected and killed by the poliovirus. To obtain enough cells for testing Salk's vaccine, a cell culture "factory" is opened at Tuskegee University in Alabama for mass production of HeLa cell lines. At its peak, the Tuskegee team is shipping 20,000 tubes of HeLa cells per week to various laboratories.
- 1953: Theodore Puck (1916–2005) and Philip Marcus (1927–2013) successfully clone HeLa cells, making them the first human cells to be cloned.
- 1955: Joe Hin Tjio (1919–2001; pronounced CHEE-oh) makes use of a laboratory error in which HeLa cells were mixed with the wrong liquid to make an accurate count of the normal number of chromosomes in humans. Scientists had thought that there are 24 pairs of chromosomes in human cells since 1921, when the first attempt was made to count them; Tjio showed that there are only 23 pairs.
- 1964: HeLa cells are sent into space on satellites and manned space missions to evaluate the long-term effects of space flight on living tissues. It is found that HeLa cells divide even more rapidly than usual in zero gravity.

HeLa research after 1968

Gartler's and Nelson-Rees' discovery of HeLa cells' cross-contamination of other cell lines did not hinder ongoing work with the cells:

- 1983: Harald zur Hausen (1936–), a German cancer researcher, identifies the DNA of human papillomavirus 16 in human cervical cancer tumors, followed by identification of HPV 18 in these cancers a year later—the first time that a researcher shows that a viral

- infection can cause cancer. Zur Hausen also demonstrates that HPV 18 infection caused the aggressive cancer that killed Henrietta Lacks. A vaccine effective against HPV was developed in 2006.
- 1988: Researchers discover that HeLa cells are not easily infected by HIV; this discovery in turn leads them to gain a better understanding of how HIV infection actually proceeds.
- 2001: Researchers in the field of veterinary medicine use HeLa cells to study how parvoviruses, which cause severe infections in cats and dogs, gain entrance to and replicate in animal cells.
- 2009: Elizabeth Blackburn, Carol Greider, and Jack Szostak receive the 2009 Nobel Prize in Physiology or Medicine for their discovery of the enzyme telomerase in HeLa cells and its role in their immortality.
- 2019: A team of researchers at the University of Texas Medical Branch at Galveston shows that the Zika virus will not multiply in HeLa cells.

Controversies

HeLa cells have been at the center of several major controversies about the doctor/patient relationship, equal access to health care, patient privacy, and the use of patient samples in for-profit medical research. These controversies have arisen as a result of technological, social, communications, and legislative changes in the 70 years since Henrietta Lacks' death in 1951. Some key dates that provide a historical perspective on these changes include the following:

- Passage of the Civil Rights Act of 1964, which prohibits unequal application of voter registration requirements, racial segregation in schools and public accommodations, and employment discrimination.
- 1969: The first computers are connected to ARPANET, the forerunner of the Internet.
- 1973: Introduction of the first handheld cellular phone.
- 1974: Introduction of the first true personal computer.
- 1985: First use of DNA profiling to identify an individual to solve a murder case in the United Kingdom.
- 1990: In *Moore v. Regents of the University of California*, the Supreme Court of California rules that a patient's discarded blood and tissue samples are not the patient's personal property, and that individuals cannot claim a share of the profits earned by commercialization of their cells.
- 1997: SixDegrees is launched as the first social media platform; Facebook follows in 2004.
- 2003: The work of the Human Genome Project is declared complete.

- 2013: German researchers at the University of Heidelberg publish the HeLa genome.
- 2021: The Henrietta Lacks Enhancing Cancer Research Act of 2019 is signed into law as Public Law 116-291.

Ownership of human tissue samples

The case of *Moore v. Regents of the University of California* set an important precedent for patients seeking financial compensation for researchers' or pharmaceutical companies' commercialization of their biospecimens. John Moore was a California man whose leukemia cells were later developed into a cell line by his physician and by UCLA. Since this 1990 case, most courts in the United States have ruled against family members who sue researchers and universities over the improper commercialization of a dead relative's biospecimens.

A major reason for rising discontent with the 1990 California decision is the vast sums of money involved in contemporary biomedical research compared with funding in the 1950s. One illustrative example is the difference between the \$5,000 that George Gey was given to work with at Johns Hopkins in 1951 and the \$6.9 billion budget of the National Cancer Institute in 2020. To quote the author of an article published in *Johns Hopkins Magazine*, Henrietta Lacks' family came to believe that "someone somewhere is making a lot of money off of drugs and biological products that were developed using pieces of tissue from people who now are entitled to a piece of the profits." One of the tragic aspects of the family's story is that Lacks' descendants had difficulty affording even basic health care until the publication of Rebecca Skloot's 2011 book about the HeLa cells, *The Immortal Life of Henrietta Lacks*.

Informed consent

Informed consent refers to a process in which a health care provider obtains a patient's permission before performing a medical or surgical intervention, before enrolling a person in a clinical trial or other form of research, or before disclosing personal health information (PHI). The health-care provider must make sure that the patient understands the nature of the procedure or research, including its risks as well as possible benefits; and that he or she is not intoxicated or suffering from a mental disorder or disability. This safeguard did not exist in the 1950s, as medical research did not then involve shared decision-making between practitioner and patient.

In 1981, the Common Rule was instituted in the United States as a federal code of ethics governing the protection of human subjects in medical research. The rule stipulates the importance of obtaining subjects' informed consent; specifies the provision of institutional

review boards (IRBs) in all institutions conducting research with human subjects; and requires additional protections for such vulnerable subjects as pregnant women, fetuses, children, and prisoners. At present, Johns Hopkins and other university-related medical centers ask patients to sign a consent form giving the institution permission to use tissue samples provided that the school “may only use or disclose tissues or parts that identify [the patient] for research with [his or her] permission or with approval of a review board governed by federal laws protecting these activities. If the tissues or parts do not identify [the patient], Johns Hopkins may use them for scientific (research) purposes without [his or her] permission or action by a review board.”

A major complication with informed consent in 2021, however, is the rapid growth in genomics as well as other technological changes speeding up biomedical research. One consequence is that neither patients nor researchers can foresee how biospecimens donated in 2021 might be used in research in 2031. Henrietta Lacks’ physicians could not possibly have anticipated the many uses to which the HeLa cells have been put since 1951. An ongoing ethical issue with informed consent is how much flexibility researchers should be given in using previously donated biospecimens, or whether there should be tighter regulation of future research.

Patient privacy

George Gey never disclosed Henrietta Lacks’ identity; to protect her, he named her cell line according to the convention common in the 1950s, of using the first two letters of her first and last names. Until the 1970s, researchers using the HeLa cells assumed that the donor’s name was either Helen Lane or Helen Larson. Lacks’ privacy was breached, however, in 1976, when a team of Johns Hopkins geneticists contacted the Lacks family in order to obtain blood samples from Henrietta’s widower and children. The reason for the blood draws was to obtain DNA markers that could identify HeLa cells in any laboratory sample. Then Victor McKusick (1921–2008), the leader of the Hopkins team, published an article in *Science* in January 1976, in which he not only described the genetic characteristics of HeLa cells but identified Lacks and referred to her other family members as “Husband,” “Child 1,” and “Child 2.” No reputable geneticist would use such identifiers in 2021; in addition, biospecimens are now identified only by code numbers rather than letters or initials.

Another violation of privacy occurred in 1985, when someone at Johns Hopkins gave copies of Lacks’ medical records to Michael Gold, a journalist who published a book in 1986 about Walter Nelson-Rees’ investigation of cell lines that had been cross-contaminated by HeLa

cells. Gold included a detailed description of Lacks’ autopsy in his book.

The turning point occurred in 2013, when a group of geneticists at the University of Heidelberg in Germany published the complete genome of a HeLa cell in the journal *G3* without the knowledge of the Lacks family. When the Lacks family objected, the German scientists voluntarily withheld access to the sequence data. Francis Collins, the director of the NIH, then worked with the family to arrive at an agreement announced in August 2013. Access to the HeLa genome is as of 2021 controlled by a committee that includes two members of the Lacks family as well as four scientists and ethicists. Researchers seeking access to the genome must demonstrate to the committee’s satisfaction that the proposed study is for medical research and that the users will abide by the terms of the HeLa Genome Data Use Agreement.

Underserved populations

Given the social and political changes that have taken place since 1951 in the United States in regard to race relations, Henrietta Lacks’ situation as an African American woman in a city that still practiced racial segregation in 1951 has attracted the attention of current historians as well as medical researchers. Jonas Salk’s decision to secure HeLa cells for testing his polio vaccine from Tuskegee University, a historically Black institution, was an early step toward progress.

In 2010, Johns Hopkins began to host two annual symposia in honor of Henrietta Lacks, one focusing on medical ethics and the other on research using HeLa cells. In 2011, the university established a four-year scholarship in Lacks’ name for a graduate of a local high school pursuing a career in the health sciences. In May 2014, the Brooklyn Public Library in New York held a special event for students and educators titled “We Speak Your Name: Exploring the Life of Henrietta Lacks,” sponsored by the Smithsonian’s National Museum of African American History and Culture and the NHGRI. The Brooklyn event led to the development of four high school–level lesson plans exploring the ongoing significance of Lacks’ life and experiences for understanding health disparities in the present-day American population.

The publication of Rebecca Skloot’s book on Henrietta Lacks’ cell line reopened a nationwide conversation on the relationship between biomedical research, the American health care system, and the need to improve health care for historically underserved groups. The definition of such groups, however, is changing as more and more Americans identify as multiethnic or multiracial rather than as members of only one racial or ethnic group. It is now also increasingly recognized that age,

KEY TERMS

Adenocarcinoma—A general term for a type of cancer that originates in glandular tissue or behaves like glandular tissue. About 10% to 15% of cancers of the cervix are adenocarcinomas.

Cell line—A defined population of cells that can be maintained in culture for an extended period of time while retaining stable phenotypes and functions. Cell lines can be either finite (lasting for a limited period of time due to cellular senescence) or immortal (able to divide and reproduce indefinitely in a suitable culture medium as a result of mutations).

Cellular senescence—The point at which cell division stops in an average cell, usually around 50 successive divisions. This stopping point is called the Hayflick limit.

Common Rule—A federal policy for the protection of human research subjects in any study funded by the U.S. government; it was first defined in 1981 and amended in 2018. Formally stated in the Code of Federal Regulations, Title 45, Part 46, the Common Rule requires informed consent from all research subjects and the oversight of every study by an institutional review board (IRB).

Cytogenetics—The branch of genetics that studies the components of a cell associated with heredity, particularly the chromosomes.

DNA fingerprinting—A laboratory technique used to identify individuals by extracting and identifying base-pair patterns in a person's DNA. Originally developed to solve crimes or identify human remains, DNA fingerprinting has been used to detect cross-contamination in cell lines since the early 1990s.

Ethics—The branch of philosophy dealing with questions of good and evil, and with moral duties and obligations in human society.

Genome—The total amount of genetic information within an organism's chromosomes, including its genes and DNA sequences.

Giemsa stain—A nucleic acid stain used to band chromosomes and to make a karyogram or map of

chromosomes. The stain is named for Gustav Giemsa (1867–1948), the German pharmacist and bacteriologist who devised the stain in 1904.

Haploid—Referring to cells that have only one chromosome of each type, and therefore have only one complete set of genes.

Hayflick limit—The number of times (usually around 50) that a normal differentiated human cell will divide before its telomeres shorten to a critical length and cell division stops. The limit is named for Leonard Hayflick, an American professor of anatomy who first described it in 1961.

Informed consent—The process in which health-care professionals explain the purpose, risks, benefits, and alternatives of a proposed test or treatment to a patient, and make sure that the patient understands the explanation.

Karyotype—The complete set of chromosomes in a species or individual organism. The term can also refer to the laboratory technique used to produce an image of an individual's chromosomes.

Phenotype—The set of observable characteristics or traits of an organism. It includes physical form and structure, development, metabolic processes, movement, and behavior.

Reproducibility—A major principle of the scientific method, used to confirm the validity of a new discovery by repeating the research that produced it.

Roller-tube technique—A technique used in tissue culture in which test tubes containing tissue or cell samples are held in a wheel-shaped instrument at a 15° angle from the horizontal, and the wheel is rotated vertically every 2 minutes. George Gey developed this technique in 1933.

Telomere—A region of repeated DNA sequences at each end of a chromosome that serves to stabilize the chromosome. Telomeres are progressively shortened each time the cell divides until cell division stops, usually around 50 divisions. HeLa cells are distinctive in that their telomeres are copied repeatedly during cell division, so that they are never shortened.

geographic location, and economic status are also important determinants of a person's access to health care alongside race or ethnicity.

Named in Lacks' honor, the Henrietta Lacks Enhancing Cancer Research Act of 2019 was passed by both houses of Congress in December 2020 and signed into

law as Public Law 116-291 by the President on January 5, 2021. The Act directs the Government Accountability Office to examine barriers to participation in clinical cancer trials by underrepresented groups—which the Act defines as “racial and ethnic minorities and older, rural, and lower-income individuals.” The Act notes that as of

QUESTIONS TO ASK YOUR DOCTOR

- Did you learn about the use of HeLa cells in research when you were in medical school?
- If so, were you aware of the controversies that had developed around the cells?
- In your opinion, why has research funding and the commercialization of biospecimens increased so dramatically since the 1950s?
- What do you think can be done at present to improve health care for underserved patient groups?

2021, about 1 in every 5 clinical trials for cancer therapy fail because of inadequate subject enrollment. It would be a fitting tribute to Henrietta Lacks if her life as well as her cell line led a new generation of clinical trial participants and scientists to a cure for a disease that had so few treatments in 1951.

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ORGANIZATIONS

- American College of Medical Genetics and Genomics (ACMG), 7101 Wisconsin Ave, Suite 1101, Bethesda, MD 20814, (301) 718-9603, (301) 718-9604, acmg@acmg.net, <https://www.acmg.net/>
- American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA 20110, (800) 638-6597, (703) 365-2700, <https://www.atcc.org/en/support/contact-us>, <https://www.atcc.org/en>
- Henrietta Lacks Commission, 1100 Confroy Drive, South Boston, VA 24592, [no telephone number given], <https://henrietalackscommission.com/the-commission/>, <https://henrietalackscommission.com/>
- Johns Hopkins University, 3400 N. Charles Street, Baltimore, MD 21218, (410) 516-8000, <https://www.jhu.edu/>
- National Cancer Institute (NCI), 9609 Medical Center Drive, Rockville, MD 20850, (800) 422-6237, (301) 435-3848, NCInfo@nih.gov, <https://www.cancer.gov/>
- National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, <https://www.genome.gov/about-nhgri/Contact>, <https://www.genome.gov/>
- Society for In Vitro Biology, 514 Daniels St., Suite 411, Raleigh, NC 27605, (910) 755-5431, (910) 755-5432, <https://sivb.org/contactus.html>, <https://sivb.org/>

Rebecca J. Frey, PhD

Hemihypertrophy (Hemihyperplasia)

Definition

Hemihypertrophy, more correctly termed hemihyperplasia, is defined as the enlargement of one side of the body or part of the body.

Description

Hemihypertrophy is characterized by unequal (asymmetric) growth of the cranium, face, trunk, limbs, and/or digits. Hemihypertrophy can be an isolated finding, or it can be associated with certain malformation syndromes. Isolated hemihypertrophy refers to hemihypertrophy for which no cause can be found. The degree of asymmetry is variable, and very mild cases can go undiagnosed. There are three categories of hemihypertrophy, depending on the body parts involved. The size difference can involve only a specific part of the body such as a finger (called simple hemihypertrophy) or an entire half of the body (called total or complex hemihypertrophy). It usually involves only one side of the body, but it can involve both sides (called crossed). There is also hemifacial hyperplasia, which involves one side of the face. Usually multiple organ systems are involved (i.e., the skin, vascular system, internal organs, or bones). In complex hemihypertrophy, the right side is more often involved than the left.

Hemihypertrophy may involve not only the part of the body that is visible but also the underlying internal organs. Enlargement of one kidney, adrenal gland, testis, or ovary has been reported. The enlarged area usually also has thickened skin, more sebaceous (sweat) glands, and more hair. It may have pigmentary abnormalities, and the bones may be larger or may be deformed. In persons with facial involvement, the asymmetry can include the cheek, lip, nose, ear, eye, tongue, jaw, roof of the mouth, or teeth.

The nervous system may also be affected, causing unilateral nerve enlargement or sciatic nerve inflammation. Occasionally, a part of the brain is affected, causing intellectual disability (15% to 20% of cases). Many cases of hemihypertrophy have hamartomatous lesions (birthmarks that involve blood vessels) or abnormalities of the genito-urinary system.

As with other overgrowth syndromes, there is an increased risk for childhood cancers in people with isolated hemihypertrophy (about 6%), particularly cancers of the kidney (Wilms tumor, 3% of individuals), adrenals, and liver.

Genetic profile

The cause and exact mechanism of isolated hemihypertrophy is not known. The asymmetry occurs most likely as a result of an increase in the rate of cell growth or unregulated cell growth. Most cases of hemihypertrophy are not inherited, but there have been seven familial cases reported in which two or more persons were affected. These cases are not well documented, and it is possible that the families actually had another genetic syndrome. Males and females are equally affected with this condition.

It is clear that there is not a single gene responsible for hemihypertrophy, but the exact number of genes and their locations and functions are not known. It has been suggested that isolated hemihypertrophy may be related to another condition, called Beckwith-Wiedemann syndrome, a genetic overgrowth syndrome that can include both hemihypertrophy and Wilms tumor. Beckwith-Wiedemann syndrome has been associated with abnormalities on chromosome 11, which contains genes involved with growth, development, and cancer.

Good data do not exist for recurrence risk for siblings of patients or for children of affected persons. Case reports suggest a slightly increased risk for siblings and for offspring of affected mothers.

Demographics

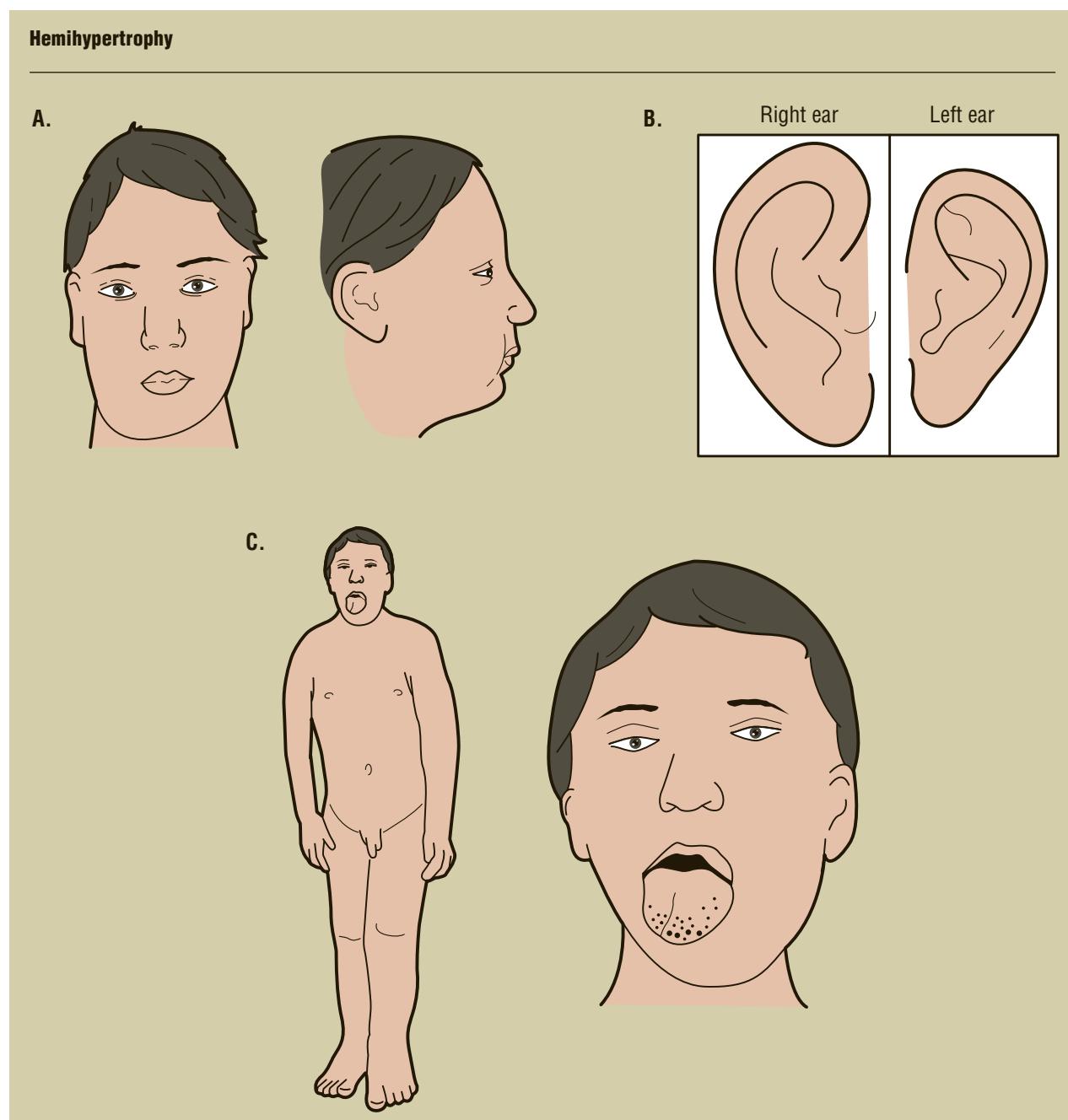
Hemihypertrophy occurs in about 1 in 15,000 live births. Isolated hemihypertrophy occurs in about 1 in 86,000 live births. There are approximately 200 cases reported. Females and males are affected equally.

Signs and symptoms

Hemihypertrophy is usually recognized at birth by physical examination. It can become more serious over time, especially during puberty, when growth is more rapid. Very mild forms of this condition often go unnoticed and are very common.

Diagnosis

The diagnosis is made by clinical examination of body asymmetry. There are no laboratory tests available for this condition. Diagnostic imaging may show advanced bone age or larger bones in the hypertrophied limbs, supporting a diagnosis of hemihypertrophy, or characteristic bone changes supporting another diagnosis. Other genetic syndromes associated with asymmetry must be excluded, as must other causes of asymmetry, such as atrophy of one side of the body due to neurological disorder or skeletal abnormalities that cause asymmetric hand or limb enlargement.



The enlarged growth of only one side of the body is characteristic of hemihypertrophy. The asymmetric development may be isolated to one organ or limb or may occur to the entire body. (Gale)

Prenatal diagnosis is theoretically possible by ultrasound, provided that the difference in size is large enough to be detected or if an embryonic tumor is present, although a confirmed diagnosis is not possible until after birth.

Treatment and management

The treatment for hemihypertrophy is different for each individual and depends on the specific symptoms. If

leg-length differences are present, corrective shoes can increase the sole for the unaffected leg to prevent scoliosis and walking difficulties. Orthopedic devices such as braces or, more rarely, surgery to lengthen the normal leg may be indicated. Surgery to retard growth of the overgrown leg is controversial and not recommended. Surgery for congenital defects or laser surgery for birthmarks may be indicated. Plastic surgery may be considered to correct very discrepant facial features.

KEY TERMS

Hemi—One-sided.

Hypertrophy—Excessive development of an organ or part.

A protocol to screen for childhood cancers has been proposed, which includes abdominal ultrasound every three months until age six, every six months until puberty, and careful medical follow-up of patients into adulthood. Management of childhood hemihypertrophy includes occupational therapy and physical therapy as well. Surgical intervention is appropriate if cancers are detected. Monitoring of serum alpha fetoprotein levels may also be useful as a marker of hepatic tumors.

Appropriate special education services are necessary for those with intellectual disability. Counseling related to social stigmatism may be necessary if severe disfigurement is an issue.

Prognosis

Hemihypertrophy does not alter lifespan, although complications from associated abnormalities such as childhood cancer and intellectual disability can cause problems. Asymmetry of the limbs can interfere with their proper function and cause pain. Insecurities due to disfigurement are possible and can be addressed through support groups or therapy.

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"Hemihypertrophy in Children." Children's Hospital Colorado. <https://www.childrenscolorado.org/conditions-and-advice>

QUESTIONS TO ASK YOUR DOCTOR

- Are my reproductive organs affected by this syndrome and, if so, what can I do to increase fertility?
- How often should I be monitored for a change in my condition or for prevention of associated issues?
- What other signs/symptoms should I watch for to recognize any other changes in my body?
- What are the chances of developing something more serious with this condition such as cancer?
- Should I be screened for any other congenital anomalies or genetic disorders and, if so, how?

/conditions-and-symptoms/conditions/hemihypertrophy/ (accessed June 10, 2021).

ORGANIZATIONS

Genetic Alliance, 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008-2369, (202) 966-5557, (202) 966-8553, info@geneticalliance.org, <http://www.geneticalliance.org>

Genetic Disease Foundation, 1425 Madison Ave., Box 1498, New York, NY 10029, (212) 659-6704, <http://www.geneticdiseasefoundation.org>

Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

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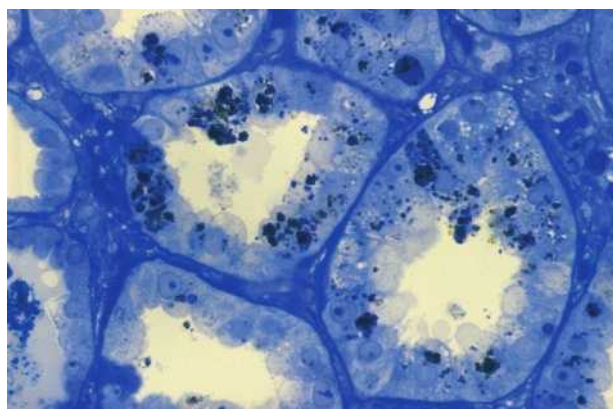
Hemochromatosis

Definition

Hemochromatosis is a blood disorder that results from an overload of iron in the body that can affect multiple organs, including the liver, pancreas, heart, thyroid, joints, skin, reproductive organs, and pituitary. Hemochromatosis is usually caused by a genetic condition that causes the body to retain excessive amounts of iron.

Description

Hemochromatosis is also known as iron overload, bronze diabetes, hereditary hemochromatosis, and familial hemochromatosis. It is most commonly caused by a



Light micrograph of a kidney in early hemochromatosis showing iron deposits in the tubules. Hemochromatosis results from an inherited defect in iron metabolism.
(Biophoto Associates/Science Source)

genetic condition that is also called primary or hereditary hemochromatosis. All other cases are called secondary hemochromatosis and are usually caused by either eating or drinking too much iron or having too many blood transfusions or by a condition where the body is producing too many red blood cells. Hereditary hemochromatosis causes increased absorption of intestinal iron, well beyond that needed to replace the body's loss of iron.

There are four types of hereditary hemochromatosis:

1. Type 1: Caused by mutations in the HFE gene.
2. Type 2a: Caused by mutations in the hemojuvelin gene and 2b caused by mutations in the hepcidin gene. Age of onset is usually 15 to 20 years. It is autosomal recessive, meaning that an affected individual has two pathogenic variants (mutations). They are both seen in Caucasians and non-Caucasians.
3. Type 3: Caused by mutations in the transferrin receptor-2 gene. It is autosomal recessive and seen in Caucasians and non-Caucasians. Age of onset is usually 30 to 40 years.
4. Type 4: Caused by mutations in the ferroportin gene. It is autosomal dominant, meaning that you need to only inherit one pathogenic variant of the ferroportin gene to get hemochromatosis. It is seen in Caucasians and non-Caucasians and has an age of onset of 10 to 80 years. HFE-related hemochromatosis is responsible for 90% of the cases of hereditary hemochromatosis and will be the focus of this entry.

Hemochromatosis causes excess iron storage in several organs of the body, including the liver, pancreas, endocrine glands, heart, skin, joints, and intestinal lining. The buildup of iron in these organs can lead to serious complications, including heart failure, liver cancer, and

cirrhosis of the liver. It is estimated that about 5% of cirrhosis cases are caused by hereditary hemochromatosis.

Genetic profile

Pathogenic variants (mutations) in the *HFE* gene causes HFE-related hemochromatosis. The *HFE* gene is located on chromosome 6. The *HFE* gene contains the instructions to produce the HFE protein, which appears to control the amount of iron taken up by the cells by interacting with the transferrin receptor. Transferrin binds and transports iron in the blood.

Hereditary hemochromatosis is an autosomal recessive condition, which means that an individual with hemochromatosis has pathogenic variants (mutations) in both of their *HFE* genes, which they inherited from their parents. Carriers have one *HFE* gene variant and one normal *HFE* gene. They do not typically have symptoms of hemochromatosis, as their normal gene is usually able to compensate for their gene with the pathogenic variant.

Children of two carrier parents have a 25% chance of inheriting two *HFE* gene variants and having hemochromatosis. Since hemochromatosis is so common in the United States, it is possible for both parents to have hemochromatosis or for one parent to be a carrier, and one parent to have hemochromatosis. If both parents have hemochromatosis, then all of their children will have it as well. If one is a carrier and the other has hemochromatosis, then there is a 50% chance that each child will have hemochromatosis. Because it is so common, there are families with multiple generations of family members with hemochromatosis, which is unusual for an autosomal recessive condition.

The likelihood that an individual will develop symptoms depends on which gene mutation he or she has as well as environmental factors. The age at which symptoms begin is variable, even within the same family. The two most common variants in the *HFE* gene are C282Y and H63D. Untreated individuals with two C282Y variations are more likely to have iron overload than are those with two H63D variants. However, some research suggests that H63D variants may be more associated with joint abnormalities and neurodegenerative diseases like dementia and ALS than C282Y variants.

Demographics

Hemochromatosis affects as many as 1.5 million persons in the United States. It is one of the most common genetic disorders in the United States. Between one in 200 and one in 400 people in the United States are affected



The hands of a healthy patient (far left and right) and a patient suffering from hemochromatosis, or iron overload (center). Hemochromatosis is the accumulation of iron in the body. Iron is stored in the liver, heart, and pancreas, and if untreated, the overabsorption can lead to organ failure. The most important causes are hereditary hemochromatosis (HHC), a genetic disorder, and transfusional iron overload, which can result from repeated blood transfusions. (Clinical Photography, Central Manchester University Hospitals NHS Foundation Trust, UK/Science Source)

with hereditary hemochromatosis. Approximately one in nine individuals (11%) is a carrier for hemochromatosis.

Men and women are equally affected by hemochromatosis, but women are diagnosed later in life because of blood loss from menstruation and childbirth. It most commonly appears in patients between the ages of 40 and 60, since it takes many years for the body to accumulate excessive iron. Symptoms in females usually occur after menopause.

Signs and symptoms

The symptoms of hemochromatosis include fatigue, weight loss, weakness, shortness of breath, heart palpitations, chronic abdominal pain, and impaired sexual performance. The patient may also show symptoms commonly connected with heart failure, diabetes, or cirrhosis of the liver. Changes in the pigment of the skin may appear, such as grayness in certain areas or a tanned or yellow (jaundice) appearance. The ages of onset and initial symptoms vary.

Diagnosis

The most common diagnostic methods for hemochromatosis are blood studies of iron, genetic testing, magnetic resonance imaging (MRI), and liver biopsy.

Blood studies of transferrin-iron saturation and ferritin concentration are often used to screen for iron overload. Ferritin is a protein that transports iron and liver enzymes. Additional studies are performed to confirm the diagnosis.

Studies that are used to confirm the diagnosis include additional iron studies and/or genetic testing. Genetic testing, which is a reliable method of diagnosis, became available in the late 1990s. Most individuals who are affected with hemochromatosis (90%) have two identifiable gene variants, so genetic testing will confirm the diagnosis. Genetic studies are also used to determine whether the affected person's family members are at risk for hemochromatosis. It is important to remember that not all people who inherit gene variants associated with hemochromatosis will have symptoms.

MRI scans and/or liver biopsy may be necessary to confirm the diagnosis. MRI studies of the liver, or other iron-absorbing organs, with quantitative assessment of iron concentration, may reveal abnormal iron deposits. For the liver biopsy, a thin needle is inserted into the liver while the patient is under local anesthesia. The needle will extract a small amount of liver tissue, which can be analyzed microscopically to measure its iron content and other signs of hemochromatosis.

KEY TERMS

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Cirrhosis—A chronic degenerative disease of the liver, in which normal cells are replaced by fibrous tissue. Cirrhosis is a major risk factor for the later development of liver cancer.

Diabetes mellitus—The clinical name for common diabetes. It is a chronic disease characterized by inadequate production or use of insulin.

Phlebotomy—The taking of blood from the body through an incision in the vein, usually in the treatment of disease.

Treatment and management

Patients who show signs of iron overload will often be treated with phlebotomy, a procedure that involves drawing blood from the patient, just like blood donation. Its purpose is to rid the body of excess iron. Patients may need these procedures once or twice per week for a year or more. Less-frequent phlebotomy may be continued in subsequent years to keep excess iron from accumulating. Patients who cannot tolerate phlebotomy can be treated with iron-chelating drugs like Desferal (desferrioxamine). Iron-chelators help the body excrete iron through urine or feces. Complications from hemochromatosis, such as cirrhosis or diabetes, may also require treatment.

Diet restrictions may help lower the amount of iron in the body, but they do not prevent or treat hemochromatosis. Individuals who have symptoms or who have variants in both copies of their *HFE* gene may reduce iron intake by avoiding iron and mineral supplements, excess vitamin C, and uncooked seafood. If a patient is symptomatic, he or she may be advised to abstain from drinking alcohol.

New treatments for hemochromatosis are being developed. For example, a drug called ebselen is being developed to prevent heart failure in hemochromatosis patients. Early research suggests that this drug may block the channels that allow iron to enter the heart. This, in turn, could help prevent heart failure.

Prognosis

With early detection and treatment, the prognosis is usually good. Most symptoms are prevented if iron levels

are kept within the normal range. This is easier if the diagnosis is made before an individual is symptomatic. If a patient is symptomatic but treated successfully before he or she develops liver cirrhosis, the patient's life expectancy is near normal. However, if left untreated, complications may arise that can be fatal. These include liver cancer, liver cirrhosis, diabetes mellitus, congestive heart failure, and difficulty depleting iron overload through phlebotomy. Liver biopsy can be helpful in determining prognosis of more severely affected individuals. Genetic testing may also help assess prognosis. Men are two times more likely than women to develop severe complications, since women have natural phlebotomy through menstruation.

Prevention

Screening for hemochromatosis can be cost-effective, especially for those of European ancestry. Relatives of patients with hemochromatosis—including children, siblings, and parents—should be tested. If genetic testing has not been done in the family, then the best testing method may be iron and ferritin studies. If the affected family member's diagnosis has been confirmed by genetic testing, then genetic testing of at-risk relatives would be recommended. Relatives who have hemochromatosis, but do not yet have symptoms, can reduce their risks by reducing their iron intake and beginning phlebotomy.

Population screening for hereditary hemochromatosis is widely debated. Many doctors and scientists want population screening because hemochromatosis is easily and cheaply treated, and quite common. Arguments against screening are that it may pick up individuals who will never have symptoms and may result in health and life insurance discrimination. The publicity around screening has been beneficial as it has increased awareness and testing for hemochromatosis in at-risk individuals.

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ORGANIZATIONS

- American Hemochromatosis Society, Inc., P.O. Box 950871, Lake Mary, FL 32795, (407) 829-4488, mail@americanhs.org, <http://www.americanhs.org>
- American Liver Foundation, 39 Broadway, Suite 2700, New York, NY 10006, (211) 668-1000, <http://www.liverfoundation.org>
- Iron Disorders Institute, Inc., P.O. Box 4891, Greenville, SC 29608, info@irondisorders.org, <http://www.irondisorders.org>

Michelle Q. Bosworth, MS, CGC
Revised by Lisa L. Andres, MS, CGC

Hemoglobin-beta locus see **Beta thalassemia**

Hemolytic-uremic syndrome

Definition

Hemolytic-uremic syndrome (HUS) is a syndrome defined by the presence of acute hemolytic anemia (low red blood cell count caused by the breakup of red cells within the bloodstream by a person's own immune system), thrombocytopenia (a low number of platelets), and kidney failure. Having these three symptoms all at once

can be caused by a number of problems—infections, genes, or a still-unknown cause.

Description

About 90% of HUS cases occur in children less than five years of age. In most cases, there is an early phase of diarrhea, followed by the lowered blood counts and the renal failure. Most patients get better after HUS, a few die during the worst stage of the illness, others go on to have life-long kidney disease, and some will progress to having a form of HUS that comes and goes over the rest of their lives. Which patients will have which outcome is not known during the illness.

Many infectious organisms have been thought to play a role as things that may cause HUS outbreaks, such as one *E. coli* serotype and one *Shigella dysenteriae* serotype. About 40% of patients who ingest *E. coli* 0157:H7 (the implicated serotype) will go on to get some form of diarrhea. Of those that develop diarrhea, about 5% will progress to some form of HUS (ranging in strength from mild to fatal). The bacteria linked to HUS have been shown to produce a toxin that gets released into the bloodstream after the organisms invade the colon's mucosal lining. The toxin, once inside of cells, disrupts protein synthesis. The spreading of organisms that make toxins tends to occur through food products.

Many outbreaks of HUS in the United States have occurred over the last several decades. These outbreaks have been linked to various food sources such as hamburger meat that is not cooked enough, apple juice and apple cider that has not been pasteurized, water, fruits, vegetables, and unpasteurized milk. Hamburger meat is the most common way that *E. coli* spreads. This bacterium is part of the normal flora of cow intestines, and it is thought that it gets into the meat during the process of killing and cutting up the cow. When this beef is then not cooked enough to kill the organism, it is able to travel into the human GI (gastro-intestinal) system with ease. The spreading of this disease can also occur with person-to-person contact through a fecal–oral route. Support for this theory includes data from daycare centers that had outbreaks of HUS.

About 10% of cases in children and 50% of cases in adults are a type of HUS that occurs without diarrhea. Of these cases, some can be linked with other infections, but other cases have no clear cause. Out of these unclear cases, some are a form of HUS that runs in families. There have been many research studies into families that have many members who have a form of HUS that keeps coming back over the patient's lifetime. Genetic tests of these families have found what may be a gene that can cause some cases of HUS.

KEY TERMS

Alternate complement pathway—A cascade of enzymatic reactions that produce antibacterial proteins. This pathway helps to ward off infections.

Idiopathic—Of unknown origin.

Serotype—One form of a bacteria that has unique surface proteins. Each serotype causes a unique antibody response from a person's immune system.

Patients with HUS all show signs of making thrombi (blood clots) in small vessels. These thrombi form in kidney blood vessels as well as small arteries all over the body. Thus, clots can cause infarcts (starvation and death) of kidney tissue, brain tissue, the bowel, and other organs.

Genetic profile

While most families have a form of HUS that passes on the disease in an autosomal recessive pathway, there have been some families with signs of autosomal dominant transmission. Genetic tests have found that a region on chromosome 1q can play a role in the forms of HUS that run in families. The gene for factor H (a protein regulator of the alternate complement pathway) is the leading gene candidate. Molecular proof linking factor H to cases of HUS that occur without diarrhea was first produced in 1998. Since then, screening of patients and families of patients with HUS not linked to a preceding episode of diarrhea have found a subset of patients who have mutated copies of the factor H gene.

Tests that look at different families with an inherited form of HUS have shown that there are many different point mutations within the factor H gene. All of these mutations led to some reduced level of factor H. With this lower level, many researchers have noticed that patients also have reduced levels of a protein called C3. This protein is part of the complement cascade that is supposed to attack bacteria within the body. Patients with low levels of C3 may be at more risk of having very bad problems arise from infections than patients with normal immune systems. Also, the familial form of HUS is most likely a multifactorial disease (i.e., no one gene mutation causes it by itself) that occurs in certain patients who are predisposed to the disorder.

Demographics

The largest number of cases occurs in children between the ages of six months and five years of age. The mean age of children who get HUS is four. Within

the United States, this disease most often occurs in epidemics, versus an endemic form that is found in other parts of the world. For example, Argentina has a much higher incidence of HUS than the United States. Interestingly, the prevalence of *E. coli* that make the toxins that cause infections is greater in Argentina.

Signs and symptoms

The clinical history most often seen in patients with HUS is of a diarrheal illness that comes before the anemia and renal disease by five to seven days. Some children have symptoms other than diarrhea. These include belly pain, nausea, and throwing up.

When HUS occurs, patients can have many different types of symptoms. Patients tend to have pallor (pale skin), decreased urine output, and fatigue. Even though they tend to have low platelet (the cells that cause blood to clot) counts, they seldom have too much bleeding. About one-quarter of patients have neurologic signs and symptoms that present as seizures, drowsiness, coma, and personality changes. Most of the patients that have HUS with diarrhea also have hypertension (high blood pressure). Almost one-fifth of patients with HUS have some form of pancreatic problems that can lead to the body not making enough insulin and causing diabetes. In some cases, the diabetes may last for the rest of the patient's life.

Kidney problems vary from patient to patient in how severe they may be. Some patients only have lower urine output, but others progress to full kidney failure. In some patients who develop HUS without diarrhea, the onset of renal failure is more subtle such that they present with symptoms of volume overload (too much retained fluid).

Diagnosis

The diagnosis of HUS should be considered in patients who present with symptoms of anemia or renal failure who either give a history of diarrhea before it or have certain problems that show up in their lab tests. Patients will always have low red blood cell counts (anemia) with signs of the ongoing breakdown of red blood cells. On peripheral smear (blood looked at through a microscope), Burr cells can be seen. These are red blood cells with bumps sticking out of the surface of the cell. Schistocytes (pieces of red blood cells that have been destroyed) can be seen under a microscope, which provide clues of the ongoing breakdown of red blood cells (hemolysis).

Diagnosis of familial HUS depends on the presence of many cases within one family that are not linked to an outside epidemic. Often, the cases occur over a stretch of many years. As of yet, there is no genetic or lab test

QUESTIONS TO ASK YOUR DOCTOR

- At what age is hemolytic uremic syndrome most commonly diagnosed, and how is that diagnosis made?
- If one child in a family has been diagnosed with hemolytic uremic syndrome, what are the chances that a second child will have the same disorder?
- What kinds of medications and other procedures are recommended for the ongoing treatment of hemolytic uremic syndrome?
- What support groups and organizations are there for parents of a child with hemolytic uremic syndrome?

that can tell which people will get familial HUS. Prenatal testing is not yet available either.

Treatment and management

There is no certain treatment for patients with HUS other than supportive care. Many types of treatments have been tried in attempts to reduce the amount of clotting that occurs in small vessels, but with little or no success. Antibiotic treatment for children with diarrhea caused by *E. coli* tended to raise, instead of lower, the rate of transformation into HUS. Thus, antibiotics tend not to be used for children with diarrhea. They are of little benefit and may be harmful. Treatment of diarrhea in children should consist of supportive care with ample fluids in order to prevent dehydration.

Careful notice must be paid to fluid intake. It is very easy for kidney failure patients to build up too much volume and have problems with their electrolyte levels. Patients with really low red blood cell counts can be given blood transfusions. Those who get severe renal failure may need dialysis treatment to rid their blood of toxins that would have been cleared by the kidneys. These treatments apply to all forms of HUS including HUS with diarrhea, HUS without diarrhea, and familial HUS. In some patients with recurring familial disease, kidney transplants have been tried, but the disease did recur in many patients.

Prognosis

As many as 25% of children die during the acute phase of the illness or are left with chronic renal or brain damage. Most of the deaths during the acute phase occur

in children where organs other than the kidneys are also involved (i.e., brain thrombi formation). Long-term effects also include diabetes, rectal stricture (narrowing of the rectum caused by fibrous tissue formation), and neurologic deficits (related to strokes). Of children who have HUS with diarrhea (most of the cases), about 1% will have the illness return.

In adults, the death rate is much higher, at 15%–30%. Thirty percent of those who do not die from HUS will have chronic kidney damage, and 25% may go on to have the disease recur. This difference in age-related recurrence rates and outcomes may be due to the fact that a higher number of adults get the form of HUS that begins without diarrhea.

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Benjamin Morris Greenberg

Hemophilia

Definition

Hemophilia is a genetic disorder—usually inherited—of the mechanism of blood clotting. Depending on the degree of the disorder present in an individual, excess bleeding may occur only after specific, predictable events (such as surgery, dental procedures, or injury) or occur spontaneously, with no known initiating event.

Description

The normal mechanism for blood clotting is a complex series of events involving the interaction of the injured blood vessel, blood cells (called platelets), and over 20 different proteins that circulate in the blood.



Frontal X-ray showing the damaged knee joints of a hemophiliac. While hemophilia is often associated with external bleeding, it can also result in internal bleeding, which can damage and weaken the joints. (Mike Devlin/ Science Source)

When a blood vessel is injured in a way that causes bleeding, platelets collect over the injured area and form a temporary plug to prevent further bleeding. This temporary plug, however, is too disorganized to serve as a long-term solution, so a series of chemical events occur, resulting in the formation of a more reliable plug. The final plug involves tightly woven fibers of a material called fibrin. The production of fibrin requires the interaction of several chemicals, in particular a series of proteins called clotting factors. At least 13 different clotting factors have been identified.

The clotting cascade, as it is usually called, is the series of events required to form the final fibrin clot. The cascade uses a technique called amplification to rapidly produce the proper-sized fibrin clot from the small number of molecules initially activated by the injury.

In hemophilia, certain clotting factors are either decreased in quantity, absent, or improperly formed. Because the clotting cascade uses amplification to rapidly plug up a bleeding area, absence or inactivity of just one clotting factor can greatly increase bleeding time.

Hemophilia A is the most common type of bleeding disorder and involves decreased activity of factor VIII due to IgG antibodies attaching themselves to the domains of the factor that give it its function, therefore decreasing or obliterating its function. There are three levels of factor VIII deficiency: severe, moderate, and mild. This classification is based on the percentage of normal factor VIII activity present:

- Individuals with less than 1% of normal factor VIII activity level have severe hemophilia. Half of all people

with hemophilia A fall into this category. Such individuals frequently experience spontaneous bleeding, most frequently into their joints, skin, and muscles. Surgery or trauma can result in life-threatening hemorrhage and must be carefully managed.

- Individuals with 1%–5% of normal factor VIII activity level have moderate hemophilia and are at risk for heavy bleeding after seemingly minor traumatic injury.
- Individuals with 5%–40% of normal factor VIII activity level have mild hemophilia and must prepare carefully for any surgery or dental procedures.

Individuals with hemophilia B have symptoms very similar to those of hemophilia A, but the deficient factor is factor IX. This type of hemophilia is also known as Christmas disease.

Hemophilia C is very rare and much milder than hemophilia A or B; it involves factor XI.

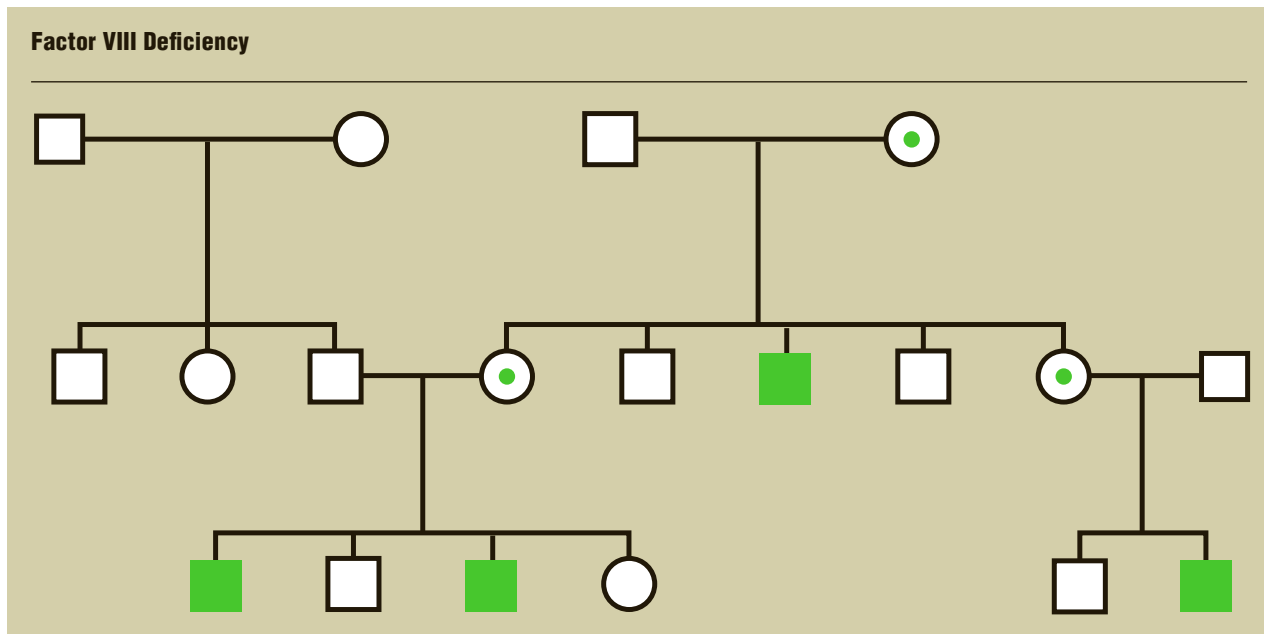
Genetic profile

Hemophilia A and B are both caused by a genetic defect present on the X chromosome. (Hemophilia C is inherited in a different fashion.) About 70% of all people with hemophilia A or B inherited the disease. The other 30% develop the disorder from a spontaneous genetic mutation.

The following concepts are important to understanding the inheritance of these diseases. All humans have two chromosomes determining their gender: females have XX, and males have XY. Because the trait is carried only on the X chromosome, it is called “sex-linked.” The chromosome’s flawed unit is referred to as the gene.

Both factors VIII and IX are produced by a genetic defect of the X chromosome, so hemophilia A and B are both sex-linked diseases. Because a female child always receives two X chromosomes, she nearly always will receive at least one normal X chromosome. Therefore, even if she receives one flawed X chromosome, she is still capable of producing a sufficient quantity of factors VIII and IX to avoid the symptoms of hemophilia. Such a person who has one flawed chromosome but does not actually have the disease is called a carrier. She carries the flaw that causes hemophilia and can pass it on to her offspring. If, however, she has a son who receives her flawed X chromosome, he will be unable to produce the right quantity of factors VIII or IX, and he will suffer some degree of hemophilia. (Males inherit one X and one Y chromosome and, therefore, have only one X chromosome.)

In rare cases, a hemophiliac father and a carrier mother can pass on the right combination of parental chromosomes to result in a hemophiliac female child.



Hemophilia: pedigree analysis chart. (Gale)

This situation, however, is rare. The vast majority of people with either hemophilia A or B are male.

About 30% of all people with hemophilia A or B are the first member of their family to ever have the disease. These individuals have had the unfortunate occurrence of a spontaneous mutation, meaning that in their early development, some random genetic accident befell their X chromosome, resulting in the defect causing hemophilia A or B. Once such a spontaneous genetic mutation takes place, offspring of the affected person can inherit the newly created, flawed chromosome.

Demographics

Hemophilia affects all races and populations equally. As of 2015, there was an estimated worldwide rate of 3–20 cases per 100,000 people. Also, as of 2015, hemophilia was the most common coagulation factor deficiency and also had the highest associated treatment cost for a disorder.

Signs and symptoms

In the case of severe hemophilia, the first bleeding event usually occurs prior to 18 months of age. In some babies, hemophilia is suspected immediately, when a routine circumcision (removal of the foreskin of the penis) results in unusually heavy bleeding. Toddlers are at particular risk because they fall frequently and may bleed into the soft tissue of their arms and legs. These small bleeds result in bruising and noticeable lumps but don't usually need treatment. As a child becomes more active,

bleeding may occur into the muscles, a much more painful and debilitating problem. These muscle bleeds result in pain and pressure on the nerves in the area of the bleed. Damage to nerves can cause numbness and decreased ability to use the injured limb.

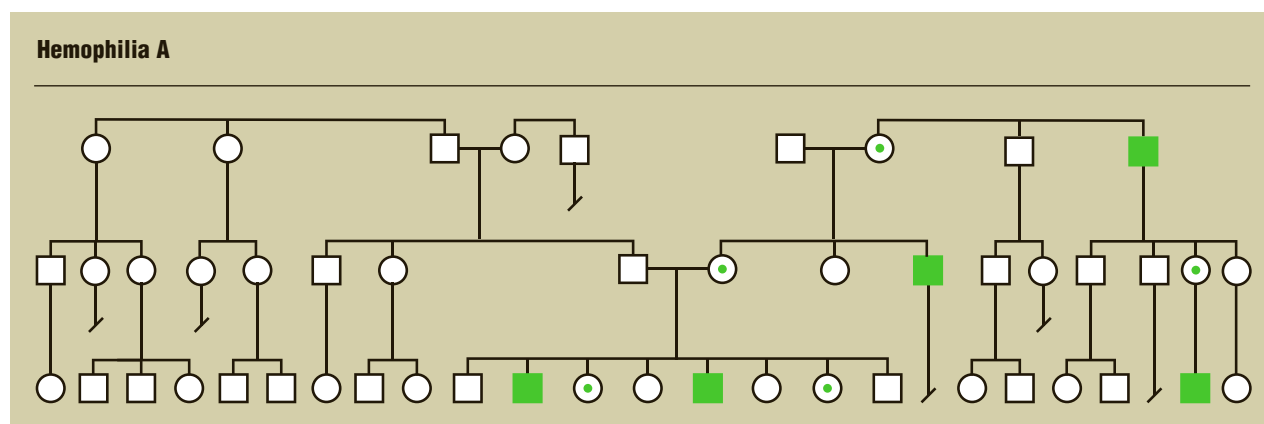
Some of the most problematic and frequent bleeds occur into the joints, particularly into the knees and elbows. Repeated bleeding into joints can result in scarring within the joints and permanent deformities. Individuals may develop arthritis in joints that have suffered continued irritation from the presence of blood. Mouth injuries can result in compression of the airway, and, therefore, can be life threatening. A blow to the head, which might be insignificant in a normal individual, can result in bleeding into the skull and brain. Because the skull has no room for expansion, the hemophiliac individual is at risk for brain damage due to blood taking up space and exerting pressure on the delicate brain tissue.

People with hemophilia are at very high risk of hemorrhage (severe, heavy, uncontrollable bleeding) from injuries such as motor vehicle accidents and also from surgery.

Some other rare clotting disorders such as Von Willebrand disease present similar symptoms but are not usually called hemophilia.

Diagnosis

Various tests are available to measure, under very carefully controlled conditions, the length of time it takes



Hemophilia: pedigree analysis chart. (Gale)

to produce certain components of the final fibrin clot. Tests called assays can determine the percentage of factors VIII and IX present compared to normal percentages. This information can help in demonstrating the type of hemophilia present, as well as the severity.

Individuals with a family history of hemophilia may benefit from genetic counseling before deciding to have a baby. Families with a positive history of hemophilia can have tests done during a pregnancy to determine whether the fetus is a hemophiliac. The test, called chorionic villus sampling, examines proteins for the defects that lead to hemophilia. This test, which is associated with a 1% risk of miscarriage, can be performed at 10–12 weeks. Another test, amniocentesis, examines the DNA of fetal cells shed into the amniotic fluid for genetic mutations. Amniocentesis, which is associated with a 1 in 200 risk of miscarriage, is performed at 16–18 weeks gestation.

Treatment and management

The most important thing that individuals with hemophilia can do to prevent complications of the disorder is to avoid injury. Those individuals who require dental work or any surgery may need to be pretreated with an infusion of factor VIII to avoid hemorrhage. Also, hemophiliacs should be vaccinated against hepatitis. Medications or drugs that promote thinning of the blood or bleeding, such as aspirin, should be avoided.

Various types of factors VIII and IX are available to replace a patient's missing factors. These are administered intravenously (directly into the patient's veins by needle). These factor preparations may be obtained from a single donor, by pooling the donations of as many as thousands of donors or by laboratory creation through highly advanced genetic techniques.

The frequency of treatment with factors depends on the severity of the individual patient's disease. Patients with relatively mild disease require treatment only in the event of injury or to prepare for scheduled surgical or dental procedures. Patients with more severe disease require regular treatment to avoid spontaneous bleeding. If bleeding does occur, antihemorrhagic drugs are usually administered.

While appropriate treatment of hemophilia can both decrease suffering and be life-saving, complications associated with treatment can be quite serious. About 20% of all patients with hemophilia A begin to produce chemicals in their bodies that rapidly destroy infused factor VIII. The presence of such a chemical may greatly hamper efforts to prevent or stop a major hemorrhage.

Individuals who receive factor prepared from pooled donor blood are at risk for serious infections that may be passed through blood. Hepatitis, a severe and potentially fatal viral liver infection, may be contracted from pooled factor preparations. A good deal of concern has been raised about the possibility of hemophiliacs contracting a fatal slow virus infection of the brain (Creutzfeldt-Jakob disease) from blood products. Unfortunately, pooled factor preparations in the early 1980s were contaminated with human immunodeficiency virus (HIV), the virus that causes AIDS. A large number of hemophiliacs were infected with HIV, and some statistics show that HIV is still the leading cause of death among hemophiliacs. Careful methods of donor testing, as well as methods of inactivating viruses present in donated blood, have greatly lowered this risk.

New treatments currently being researched involve efforts to transfer new genes to hemophiliacs. These new genes would have the ability to produce the missing factors. As yet, these techniques are not being performed

KEY TERMS

Amplification—A process by which something is made larger. In clotting, only a very few chemicals are released by the initial injury; they result in a cascade of chemical reactions that produces increasingly larger quantities of different chemicals, resulting in an appropriately sized, strong fibrin clot.

Factors—Substances in the blood, such as proteins and minerals, that are necessary for clotting. Each clotting substance is designated with roman numerals I through XIII.

Fibrin—The final substance created through the clotting cascade, which provides a strong, reliable plug to prevent further bleeding from the initial injury.

Hemorrhage—Very severe, massive bleeding that is difficult to control. Hemorrhage can occur in hemophiliacs after what would be a relatively minor injury to a person with normal clotting factors.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease and can be transmitted to offspring.

Platelets—Small disc-shaped structures that circulate in the bloodstream and participate in blood clotting.

Trauma—Injury.

on humans, but there is a possibility that eventually this type of gene therapy will be available.

As of 2015, bypassing agents and other homeostatic therapies had also been studied for the treatment of hemophilia A. Although these are emerging treatment options that need more conclusive studies, there is already evidence of their efficacy for treating patients with severe hemophilia A.

Management of hemophilia may also include surveillance by diagnostic imaging to closely monitor any resulting bone and joint disease. Support from a physiotherapist may also be recommended for exercise supervision.

Prognosis

Prognosis is very difficult to generalize. Because there are so many variations in the severity of hemophilia,

QUESTIONS TO ASK YOUR DOCTOR

- What is the best treatment option for me?
- Are there any activities or sports I should avoid?
- Which type of hemophilia do I have, and how severe is it?

and because much of what befalls a hemophiliac patient depends on issues such as physical activity level and accidental injuries, statistics on prognosis are not generally available.

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ORGANIZATIONS

Hemophilia Federation of America, 820 First St. NE, Suite 720, Washington, DC 20002, (202) 675-6984 or (800) 230-9797, (972) 616-6211, <http://www.hemophiliafed.org>

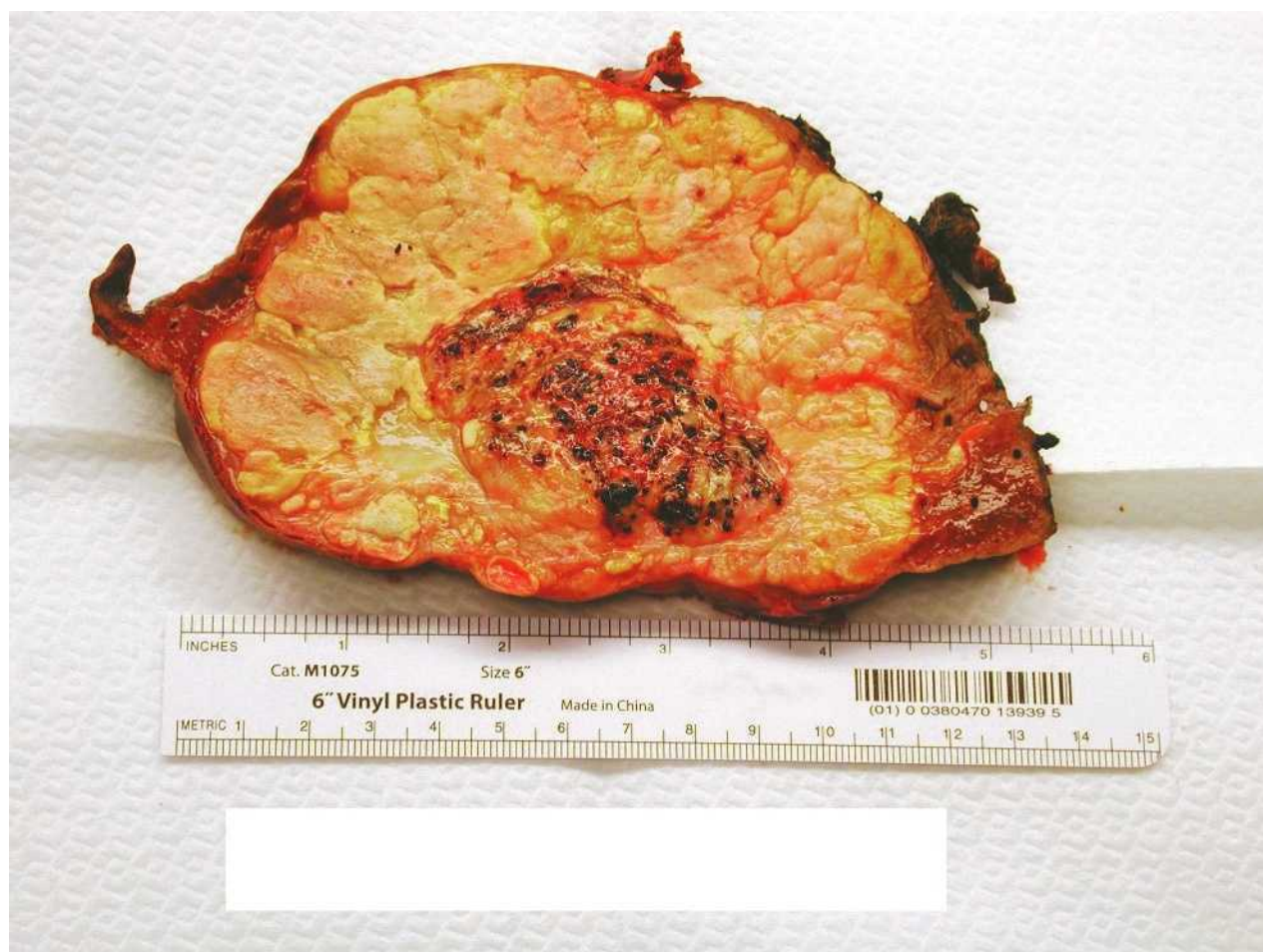
National Hemophilia Foundation, 7 Penn Plaza, Suite 1204, New York, NY 10001, (212) 328-3700, (212) 328-3777, handi@hemophilia.org, <http://www.hemophilia.org>

Jennifer F. Wilson, MS
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Hepatocellular carcinoma

Definition

Hepatocellular carcinoma (HCC), or liver cancer, is a form of cancer with a high mortality rate. It is also called malignant hepatoma. Liver cancers in general can be



Left lobe of a liver with hepatocellular carcinoma (HCC or malignant hepatoma). (Boilershot Photo/Science Source)

classified into two types. They are either primary, when the cancer starts in the liver itself; or metastatic, when the cancer has spread to the liver from some other part of the body.

Description

Primary liver cancer

Primary liver cancer is the sixth most commonly diagnosed cancer in the world. About 80% of all primary liver cancers are hepatocellular carcinomas. Primary liver cancer is, however, a relatively rare disease in the United States, representing about 2% of all malignancies. It is much more common in other parts of the world, representing from 10% to 50% of malignancies in Africa and parts of Asia.

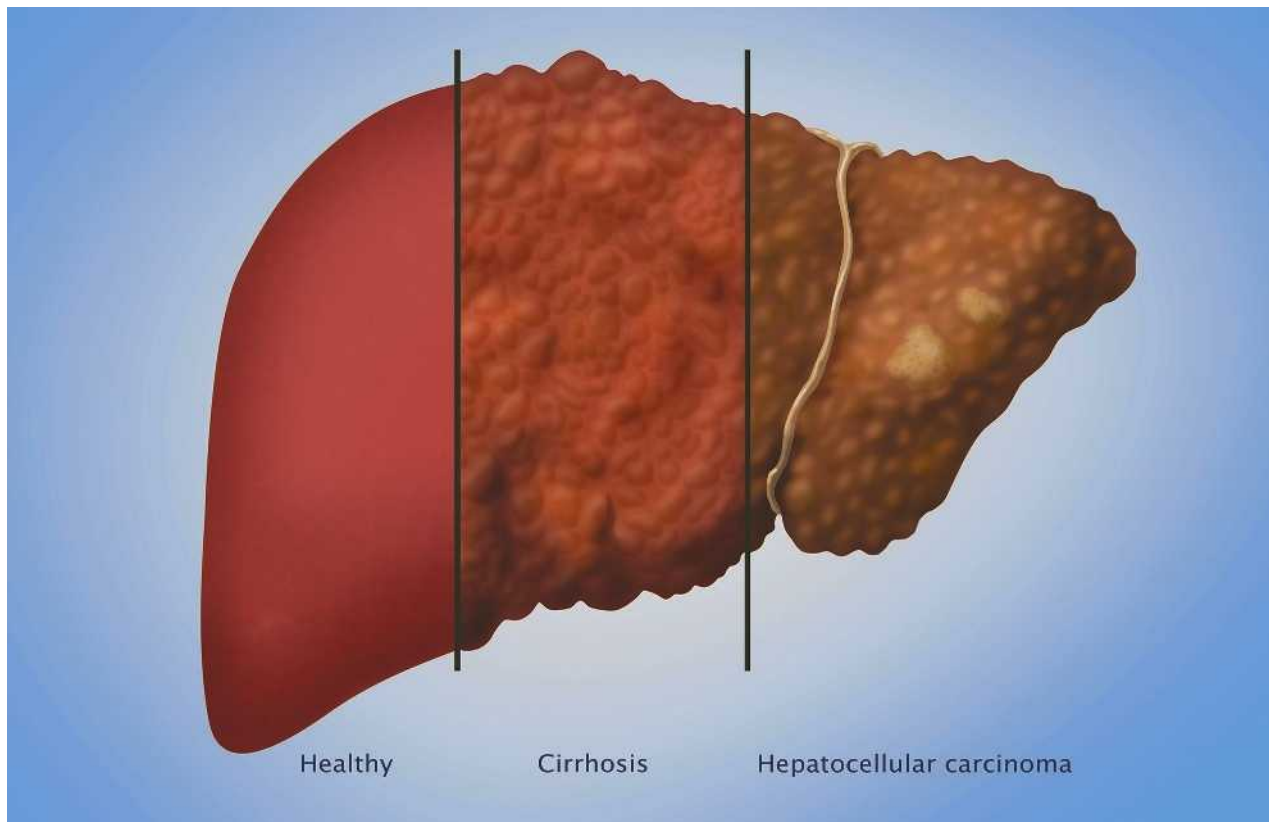
In adults, most primary liver cancers belong to one of two types: hepatomas, or hepatocellular carcinomas, which start in the liver tissue itself; and cholangiomas, or cholangiocarcinomas, which are cancers that develop

in the bile ducts inside the liver. About 80% of primary liver cancers are hepatomas. The American Cancer Society estimated that in the United States, at least 42,230 new cases of liver and bile duct cancers would be diagnosed in the United States in 2021 (28,980 in men, and 12,340 in women), and roughly 30,230 deaths from these cancers in the same year. The rate of primary liver cancer has been slowly rising in North America since the 1980s.

There is one type of primary liver cancer that usually occurs in children younger than four years of age and between the ages of 12 and 15, called a hepatoblastoma. Unlike liver cancers in adults, hepatoblastomas have a good chance of being treated successfully. Approximately 70% of children with hepatoblastomas experience complete cures. If the tumor is detected early, the survival rate is over 90%.

Metastatic liver cancer

The second major category of liver cancer, metastatic liver cancer, is about 20 times as common in the United



Comparing the appearance of a healthy liver (left) with its appearance in cirrhosis and hepatocellular carcinoma (liver cancer). Cirrhosis is a consequence of chronic liver disease characterized by replacement of liver tissue with fibrosis, scar tissue, and regenerative nodules (lumps that occur as a result of damaged tissue being regenerated), leading to loss of liver function. Liver cancer is often secondary to cirrhosis. (Monica Schroeder/Science Source)

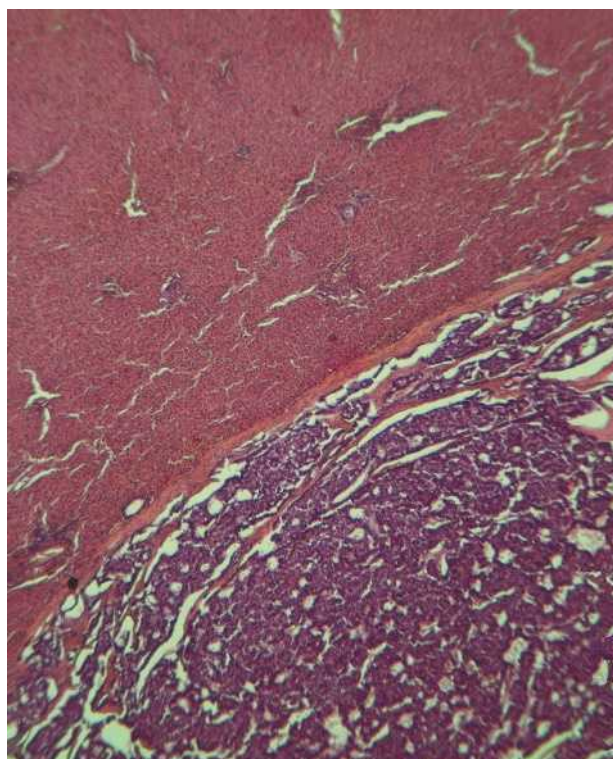
States as primary liver cancer. Because blood from all parts of the body must pass through the liver for filtration, cancer cells from other organs and tissues easily reach the liver, where they can lodge and grow into secondary tumors. Primary cancers in the colon, stomach, pancreas, rectum, esophagus, breast, lung, or skin are the most likely to spread (metastasize) to the liver. It is not unusual for the metastatic cancer in the liver to be the first noticeable sign of a cancer that started in another organ. After cirrhosis, metastatic liver cancer is the most common cause of fatal liver disease.

Genetic profile

Hepatocellular carcinoma has occasionally been reported to occur in familial clusters. It appears that first-degree relatives (siblings, children, or parents) of people with primary liver cancer are 2.4 times more likely to develop liver cancer themselves. This finding indicates a small overall genetic component; however, specific disease genes that are directly causative of HCC had not been identified as of 2021.

Certain genetic diseases are, however, associated with a higher risk of liver cancers. These include hereditary hemochromatosis, an iron-storage disease most often caused by mutations in the *HFE* gene on the short arm of chromosome 6 at 6p22.2; alpha-1 antitrypsin deficiency, a disorder caused by mutations in the *SERPINA1* gene on the long arm of chromosome 14 at 14q32.13 that leads to deposits of an abnormal protein in liver cells as well as emphysema and other respiratory symptoms; glycogen storage diseases, classified into 11 different genetic types as of 2015; tyrosinemia, a group of three genetic disorders characterized by the body's inability to metabolize the amino acid tyrosine; Fanconi anemia, a clinically heterogeneous disorder associated with mutations in the *FANCA* gene on the long arm of chromosome 16 at 16q24.3; and Wilson disease, a disorder in which copper accumulates in body tissues. Wilson disease is caused by mutations in the *ATP7B* gene on the long arm of chromosome 13 at 13q14.3.

A 2021 study sought to determine the role of microRNA-145-5p and AFR6 on how HCC cancer cells



Light micrograph of a metastatic carcinoma in the human liver. Normal liver cells (above center) are seen in contrast with malignant tumor cells (purple). (John Burbidge/Science Source)

migrate, invade, and metastasize. Low expression levels of miR-14505p were found to be linked with poor prognosis in patients with HCC and with some features of metastatic tumors. Further study could provide an opportunity for better understanding of HCC metastasis and lead to new therapy options.

Although much work needs to be done before research will lead to more effective therapies for HCC, molecular profiling of liver tumors is being done in order to develop targeted therapies for the disease. As of spring 2021, genomic sequencing has found that some gene mutations perform as drivers of HCC, although further study was needed. Among these are *TP53*, a tumor suppressor gene, along with *TERT*, *CTNNB1*, *ARID1A*, and *ARID2*.

Demographics

Hepatocellular carcinoma is the sixth most common cancer of men and the eleventh most common cancer of women worldwide, affecting 250,000 to one million individuals annually. HCC is responsible for about 782,000 deaths each year worldwide. Although liver cancer is becoming more common in the United States, it is 10

times more common in Africa and Asia, where it is the most common type of cancer. In China, 90% of cases of HCC are caused by hepatitis B infection; in Japan, 90% of cases are associated with hepatitis C. Liver cancer affects men more often than women; men in the United States have a lifetime risk of one in 81 of developing primary liver cancer, while women have a lifetime risk of one in 196.

Like most cancers, liver cancer in the countries is more common in older individuals; the average age at diagnosis is 63. Only 2% of patients with HCC in North America are younger than 35. In Africa, however, the average age of patients with HCC is about 30, largely because of the continent's high rates of hepatitis infection.

Risk factors for primary liver cancer

The exact cause of primary liver cancer is still unknown. In adults, however, certain factors are known to place some individuals at higher risk of developing liver cancer, including:

- Exposure to hepatitis B (HBV) or hepatitis C (HCV) viruses. In Africa and most of Asia, exposure to hepatitis B is an important factor; in Japan and some Western countries, exposure to hepatitis C is connected with a higher risk of developing liver cancer. In the United States, nearly 25% of patients with liver cancer show evidence of HBV infection. Hepatitis is commonly found among intravenous drug abusers.
- Exposure to substances in the environment that are known to cause cancer (carcinogens). These include a substance produced by a mold that grows on rice and peanuts (aflatoxin); thorium dioxide, which was used at one time as a contrast dye for x-rays of the liver; and vinyl chloride, a now strictly regulated chemical used in manufacturing plastics.
- Cirrhosis. Hepatomas appear to be a frequent complication of cirrhosis of the liver. Between 30% and 70% of hepatoma patients also have cirrhosis. It is estimated that a patient with cirrhosis has 40 times the chance of developing HCC as a person with a healthy liver.
- Obesity and type 2 diabetes. Both conditions increase the risk of cirrhosis of the liver.
- History of smoking. People who have quit smoking are at lower risk of HCC than those who continue to smoke, but both groups are at higher risk of HCC than people who have never smoked.
- Use of anabolic steroids (male hormones) for medical reasons or strength enhancement. Cortisone-like steroids do not appear to increase risk for liver cancer.

- Hereditary hemochromatosis. Hemochromatosis is a disorder characterized by abnormally high levels of iron storage in the body. It often develops into cirrhosis.
- Geographic location. Liver cancer is ten times more common in Asia and Africa than in the United States.
- Ethnicity. In North America, HCC is most common in Asian Americans and Pacific Islanders, followed by Native Americans, Hispanics, African Americans, and Caucasians.
- Male sex. The male/female ratio for hepatoma is three to one as of 2015.

Signs and symptoms

The early symptoms of primary as well as metastatic liver cancer are often vague and not unique to liver disorders. The long lag time between the beginning of the tumor's growth and signs of illness is the major reason why the disease has such a high mortality rate. At the time of diagnosis, patients are often tired, complaining of fever, abdominal pain, unintended weight loss, and loss of appetite. They may look emaciated and generally ill.

As the tumor grows bigger, it stretches the membrane surrounding the liver (the capsule), causing pain in the upper abdomen on the right side. The pain may extend into the back and shoulder. Some patients develop a collection of fluid known as ascites in the abdominal cavity. Others may show signs of bleeding into the digestive tract, including blood in the stool. In addition, the tumor may block the ducts of the liver or the gall bladder, leading to jaundice. In patients with jaundice, the whites of the eyes and the skin may turn yellow, and the urine becomes dark-colored.

Diagnosis

Physical examination

If the doctor suspects a diagnosis of liver cancer, he or she will check the patient's history for risk factors and will pay close attention to the condition of the patient's abdomen during the physical examination. Masses or lumps in the liver and ascites can often be felt while the patient is lying flat on the examination table. The liver is usually swollen and hard in patients with liver cancer; it may be sore when the doctor presses on it. In some cases, the patient's spleen is also enlarged (splenomegaly). The doctor may be able to hear an abnormal sound (bruit) or rubbing noise (friction rub) if he or she uses a stethoscope to listen to the blood vessels that lie near the liver. The noises are caused by the pressure of the tumor on the blood vessels.

Laboratory tests

Blood tests may be used to test liver function or to evaluate risk factors in the patient's history. Between 50% and 75% of primary liver cancer patients have abnormally high blood serum levels of a particular protein (alpha-fetoprotein, or AFP). The AFP test alone cannot be used to confirm a diagnosis of liver cancer, because cirrhosis or chronic hepatitis can also produce high alpha-fetoprotein levels. Tests for alkaline phosphatase, bilirubin, lactic dehydrogenase, and other chemicals indicate that the liver is not functioning normally. About 75% of patients with liver cancer show evidence of hepatitis infection. Again, however, abnormal liver function test results are not specific for liver cancer.

Blood tests also might reveal an important biomarker for HCC in patients who have hepatitis B. Values of serum Integrin beta-like 1 (ITGBL1) can indicate an early diagnosis of HCC associated with hepatitis B. This early diagnosis is important to reducing mortality from the disease in at-risk populations.

Imaging studies

Imaging studies are useful in locating specific areas of abnormal tissue in the liver. Liver tumors as small as an inch across can now be detected by ultrasound or computed tomography (CT) scan. Imaging studies, however, cannot tell the difference between a hepatoma and other abnormal masses or lumps of tissue (nodules) in the liver. A sample of liver tissue for biopsy is needed to make the definitive diagnosis of a primary liver cancer. CT or ultrasound can be used to guide the doctor in selecting the best location for obtaining the biopsy sample. Chest x-rays may be used to see whether the liver tumor is primary or has metastasized from a primary tumor in the lungs.

Liver biopsy

Liver biopsy is considered to provide the definite diagnosis of liver cancer. In about 70% of cases, the biopsy is positive for cancer. In most cases, there is little risk to the patient from the biopsy procedure. In about 0.4% of cases, the patient develops a fatal hemorrhage from the biopsy because some tumors are supplied with a large number of blood vessels and bleed very easily.

Laparoscopy

The doctor may also perform a laparoscopy to help in the diagnosis of liver cancer. A laparoscope is a small, tube-shaped instrument with a light at one end. The doctor makes a small cut in the patient's abdomen and inserts the laparoscope. A small piece of liver tissue is removed and examined under a microscope for the presence of cancer cells.

KEY TERMS

Ablation—A general term for medical techniques for destroying a cancer (or other unwanted tissue) without removing it.

Aflatoxin—A mycotoxin, produced by several species of *Aspergillus* fungi, that is a known carcinogen.

Ascites—An abnormal collection of fluid in the abdominal cavity. It is most often caused by cirrhosis, metastatic liver cancer, or other severe liver disease.

Carcinogen—Any substance or radioactive material that is directly implicated in causing cancer.

Chemotherapy—Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of the cancerous cells or by killing them.

Cirrhosis—A condition of liver dysfunction resulting from long-term damage, most often caused by heavy alcohol consumption, hepatitis B or C infection, or non-alcoholic fatty liver disease.

Embolization—A technique for treating some types of bleeding disorders or cancer by blocking blood vessels.

Hemochromatosis—A condition in which iron accumulates in the body, as a result of either a

genetic mutation or frequent blood transfusions. It is also known as iron storage disease.

Hepatectomy—The medical term for surgical removal of the liver. A hepatectomy may be either partial or total.

Metastasis (plural: metastases)—The spreading of cancer from the original site to other locations in the body.

Primary tumor—The organ or tissue where a tumor began.

Protocol—A set of guidelines for medical tests or treatments.

Radiation therapy—Treatment using high-energy radiation from x-ray machines, cobalt, radium, or other sources.

Stage—The extent of a tumor's progress. Tests are done to determine whether a tumor is localized to an organ or whether it has spread to the lymph nodes and/or other organs. Treatment is determined by the stage of the cancer.

Tumor—An abnormal growth of cells. A tumor may be benign (noncancerous) or malignant (cancerous).

Treatment and management

Treatment of liver cancer is based on several factors, including the type of cancer (primary or metastatic); the stage (early or advanced); the location of other primary cancers or metastases in the patient's body; the patient's age; and other coexisting diseases, including cirrhosis. Treatment options include surgery, radiation, and chemotherapy. At times, two or all three of these may be used together. For many patients, treatment of liver cancer is primarily intended to relieve the pain caused by the cancer but cannot cure it.

Surgery

The goal of surgery is to remove the entire tumor, curing liver cancer. However, few liver cancers in adults can be cured by surgery, because they are usually too advanced by the time they are discovered. If the cancer is contained within one lobe of the liver, and if the patient does not have cirrhosis, jaundice, or ascites, surgery is the best treatment option. Patients who can have their entire tumor removed have the best chance of survival.

If the entire visible tumor can be removed, about 25% of patients will be cured. The operation that is

performed is called a partial hepatectomy, or partial removal of the liver. The surgeon will remove either an entire lobe of the liver (a lobectomy) or cut out the area around the tumor (a wedge resection).

Doctors may also offer tumor embolization or ablation. Embolization involves killing a tumor by blocking its blood supply. The newest form of embolization, called radioembolization, involves injecting small beads containing a radioactive isotope of yttrium into the hepatic artery. The beads both seal off the artery and release small amounts of radiation into the area of the tumor. Ablation is a method of destroying a tumor without removing it. One method of ablation, cryosurgery, involves freezing the tumor, thereby destroying it. In another method of ablation, ethanol ablation, doctors kill the tumor by injecting alcohol into it. A third method is called radiofrequency ablation, or RFA. In RFA, the tumor is destroyed by heat generated by high-frequency radio waves. Unlike some other therapies, RFA can be repeated several times if needed.

Chemotherapy

Chemotherapy involves using very strong drugs, taken by mouth or intravenously, to suppress or kill tumor

QUESTIONS TO ASK YOUR DOCTOR

- What type of liver cancer do I have—primary or metastatic?
- What stage is the cancer?
- Is my cancer related to a genetic disorder?
- What treatment(s) will you recommend?

cells. Chemotherapy also damages normal cells, leading to such side effects as hair loss, vomiting, mouth sores, loss of appetite, and fatigue.

Some patients with incurable metastatic cancer of the liver can have their lives prolonged for a few months by chemotherapy. If the tumor cannot be removed by surgery, a tube (catheter) can be placed in the main artery of the liver, and an implantable infusion pump can be installed (hepatic artery infusion, or HAI). The pump allows much higher concentrations of cancer drugs to be carried directly to the tumor.

Hepatocellular carcinoma is resistant to most drugs. Such drugs as capecitabine, gemcitabine, doxorubicin, and sorafenib are being used to treat this type of cancer. Systemic chemotherapy is used most often; however, in clinical trials as of 2015 it was not found effective in prolonging patients' lives.

Radiation therapy

Radiation therapy is the use of high-energy rays or x-rays to kill cancer cells or to shrink tumors. In liver cancer, radiation can give only brief relief from some of the symptoms, including pain. Liver cancers are not sensitive to levels of radiation considered safe for surrounding tissues. Radiation therapy has not been shown to prolong the life of a patient with liver cancer.

Liver transplantation

Removal of the entire liver (total hepatectomy) or liver transplantation is used only rarely in treating liver cancer, and then only for patients with early-stage HCC. On average, about 1,300 liver transplants are performed in the United States for people with liver cancer. Few patients are eligible for this procedure, however, either because the cancer has spread beyond the liver or because there are no suitable donors. Further research in the field of transplant immunology may make liver transplantation a possible treatment method for more patients in the future.

Targeted therapy

As researchers learn more about the genes associated with HCC, they can design targeted therapies. As of 2021, tyrosine kinase inhibitors were used to target some primary liver cancers. The inhibitors can get through a cancer cell membrane and block signals that make the cells grow and divide. Another targeted approach is tepotinib, a MET inhibitor for patients who have HCC and MET overexpression and have not responded to the drug Nexavar.

Prognosis

Liver cancer has a poor prognosis because it is often not diagnosed until it has metastasized. Another reason for the poor prognosis is that many patients with HCC also have cirrhosis or hepatitis, conditions that can be fatal in themselves. The overall five-year survival rate for patients with hepatomas was around 15% as of 2015. Many patients with primary liver cancer die within several months of diagnosis. Patients with liver cancers that metastasized from cancers in the colon live slightly longer than those whose cancers spread from cancers in the stomach or pancreas. There are no useful strategies at present for preventing metastatic cancers of the liver. Primary liver cancers, however, are 75% to 80% preventable. Current strategies focus on widespread vaccination for hepatitis B; early treatment of hereditary hemochromatosis; and screening of high-risk patients with AFP testing and ultrasound examinations.

Lifestyle factors that can be modified in order to prevent liver cancer include avoidance of exposure to toxic chemicals and foods harboring molds that produce aflatoxin. In the United States, laws protect workers from exposure to toxic chemicals. Changing grain-storage methods in other countries may reduce aflatoxin exposure. Avoidance of alcohol and drug abuse is also an important preventive measure. Alcohol abuse is responsible for 60% to 75% of cases of cirrhosis, which is a major risk factor for eventual development of primary liver cancer.

A vaccine for hepatitis B has been available since 1982. The National Cancer Institute (NCI) considers immunization with this vaccine to be one of the most important preventive measures a person can take to reduce the risk of HCC. Widespread immunization prevents infection, reducing a person's risk of liver cancer. Other protective measures against hepatitis include using protection during sex and not sharing needles. Scientists have found that interferon injections may lower the risk for someone with hepatitis C or cirrhosis to develop liver cancer.

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American Cancer Society, 250 Williams Street NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org>

American Liver Foundation, P.O. Box 299, West Orange, NJ 07052, (800) 465-4837, <http://www.liverfoundation.org>

National Cancer Institute, BG 9609 MSC 9760, 9609 Medical Center Drive, Bethesda, MD 20892-9760, (800) 422-6237, <http://www.cancer.gov>

Judy C. Hawkins, MS
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Revised by Teresa G. Odle, BA, ELS

Hepatorenal glycogenosis see **Fanconi-Bickel syndrome**

Herceptin

Definition

Herceptin is a medicine that is used to slow or stop the growth of a cancerous tumor associated with the human epidermal growth factor receptor 2.

Purpose

Herceptin is used to treat cancer that has spread to other parts of the body in patients whose tumor cells produce an overabundance of a protein known as the human epidermal growth factor receptor 2 (HER2). Types of cancer currently treated by Herceptin include breast cancer and gastric cancer.

Description

Also known by its generic name, trastuzumab, Herceptin is an antineoplastic drug manufactured by Genentech, Inc. A monoclonal antibody, Herceptin works differently than chemotherapy or hormonal anticancer drugs. It targets cancer cells that make too much of the HER2 protein, which is found on the surface of the cancer cells and is thought to fuel cancer growth. Used only to treat cancers that make an overabundance of HER2 protein, Herceptin works by binding to the protein's particles and blocking its effect, thereby slowing down or stopping the cancer cell growth. The HER2 proteins with Herceptin are removed from the surface of the cell. When this happens, they cannot tell the cell to grow and divide.

In addition, Genentech, Inc., explains that there may be two other factors that account for Herceptin's effectiveness: Herceptin signals the immune system and works with chemotherapy. After Herceptin binds to the HER2 protein, the natural killer cells of the immune system are attracted to Herceptin. Herceptin, in turn, binds to the natural killer cells and determines which ones are abnormal and helps to kill them. When this occurs, chemotherapy may be enhanced. Although Herceptin and chemotherapy work differently, Genentech points out that when used together, "the two drugs can be synergistic. Treatment with Herceptin prevents DNA repair following the impact of DNA-damaging chemotherapy that stops the tumor cells from growing."

According to the National Cancer Institute, approximately 25%–30% of breast cancers make too much HER2 protein. These kinds of tumors tend to grow faster and are more likely to recur. The amount of HER2 that is present in a tumor is determined by a lab test, and a score from 0 (which is a negative score) to 3+ (which is a highly positive score) is assigned. Only patients with high scores are expected to benefit from Herceptin treatment.

Clinical use

Two groundbreaking clinical trials were conducted to test the safety and efficacy of Herceptin. One of them, conducted by Dr. Dennis Slamon and colleagues, produced data that led to Herceptin's approval by the U.S. Food and Drug Administration (FDA) in 1998. In 2001, the *New England Journal of Medicine* published the study results by Slamon and colleagues, which involved 234 randomly assigned patients who received chemotherapy alone and 235 patients who received chemotherapy plus Herceptin. All the patients in the study were diagnosed with metastatic breast cancer that overproduced HER2. Ultimately, Slamon and colleagues concluded that the addition of Herceptin to chemotherapy was associated with "a longer time to disease progression, a higher rate of response [to the treatment], longer survival, and a 20% reduction in the risk of death," as compared to treatment with chemotherapy alone. Specifically, for example, Herceptin combined with paclitaxel proved to be especially valuable; the overall response rate rose from 15% in women treated with paclitaxel to 38% in women treated with Herceptin and paclitaxel. All factors considered, Herceptin seems to increase the clinical benefits of first-line chemotherapy.

In another clinical trial, as explained by the National Cancer Institute, "Women were given only Herceptin. In 14% of these women, the tumor got smaller or disappeared." Therefore, in September 1998 the FDA announced its approval of Herceptin for the treatment of metastatic breast cancer. Use of the medicine has since been successful. Herceptin was specifically approved in combination with paclitaxel as therapy for HER2 breast cancer. It is also used alone as a therapy after other therapies have failed. Used by itself or with chemotherapy, Herceptin is the first FDA-approved therapy that targets a particular genetic defect known to play a role in cancer development.

Herceptin has also been used in the treatment of gastric cancer. Although it has been successful in treating gastric cancer, Herceptin-resistant gastric cancer and Herceptin-resistant breast cancer has been noted.

Other possible uses for Herceptin

Herceptin is also being studied as an adjuvant therapy for the treatment of nonmetastatic breast cancer that has spread to the lymph nodes but not anywhere else.

Herceptin may also be useful in fighting cancers of the lung, colon, prostate, and bladder in patients whose tumors have an overabundance of HER2. Several studies are underway to test the effectiveness of Herceptin with and without other anticancer drugs.

Recommended dosage

Herceptin is administered intravenously on a weekly basis in a hospital or clinic setting. Based on the patient's body weight, the typical dosage is 0.9 to 3.6 mg per pound.

Precautions

It is important to have periodic blood tests while taking Herceptin because it can cause anemia and a low white blood cell count in many patients. Monitoring the cardiac health of patients taking Herceptin is imperative because using it can lead to congestive heart failure. Therefore, some patients may not be able to take Herceptin.

It is not known whether Herceptin is safe to take while a patient is pregnant. Nonetheless, patients should avoid becoming pregnant while they are taking Herceptin. Pregnant patients should talk with their physicians regarding any possible risks to the fetus. Mothers should not breastfeed their babies while they are being treated with Herceptin because it does pass to the breast milk. In fact, mothers should not breastfeed for at least six months after being treated with Herceptin.

Side effects

The two most serious side effects associated with the use of Herceptin are cardiac and lung related. Damage to the heart muscle (which can cause heart failure) and lung complications (which can cause serious breathing problems) can occur. In both cases, immediate medical attention is required. Whether during or after treatment, patients experiencing difficulty breathing or any of the signs associated with heart failure, such as shortness of breath, a fast heartbeat, or swelling in the feet or legs, should contact their physicians without delay. Cardiac side effects are more frequently experienced by elderly patients. In clinical trials, it was found that patients receiving Herceptin with anthracycline chemotherapy were more likely to experience cardiac dysfunction than those who did not receive anthracyclines. Patients treated with Herceptin must be monitored carefully and screened prior to their treatment for any lung or heart problems. It is sometimes necessary to discontinue treatment with Herceptin.

The National Cancer Institute cautions patients that Herceptin can cause severe allergic reactions, such as low blood pressure, shortness of breath, rashes, and wheezing. These reactions are usually more common in patients who already have lung disease.

Fever and chills are common during the first infusion and occur less frequently thereafter. Throughout Herceptin

treatment it is not uncommon for patients to experience nausea, vomiting, diarrhea, dizziness, sleeplessness, appetite loss, cough, abdominal and back pain, headache, and sore throat. Depression, tingling in the hands or feet, fluid retention, sinus irritation, and flu-like symptoms are less commonly reported. Uncommon side effects are acne, cold sores, and urinary infection, as well as pain in the joints, bones, or nerves. As reminded by the National Cancer Institute, it is important to note that patients being treated with Herceptin alone in comparison to patients being treated with Herceptin and chemotherapy may have different side effects. For example, when Herceptin is used in combination with chemotherapy, patients are more likely to experience anemia leukopenia, diarrhea, and infection. Therefore, blood tests may be required more frequently for patients being treated with both Herceptin and chemotherapy. Rare side effects can develop in any part of the body, regardless of whether a patient is being treated with Herceptin only or in combination with chemotherapy. Patients should inform their physicians when they experience any side effects, regardless of whether the side effects are mild or severe. Some side effects, such as pain, can be managed medically.

Whether in the early or advanced stages, cancer itself can cause pain. In fact, numerous studies have validated that patients with advanced cancer are likely to have a number of symptoms in addition to pain, such as insomnia, depression, and fatigue. Therefore, it is valuable, if possible, to determine whether the source of the pain is the drug therapy or the cancer itself. Once the source of the pain is determined, it is easier to decide what the next course of action should be. Patients should be their own healthcare advocates and work as closely as possible with their physicians regarding treatment strategies for adverse side effects and cancer-related pain. Patients should talk with their physicians about a variety of treatment modalities that range from conventional options to alternative therapies, such as acupuncture.

Pain intensity should also be considered when developing a treatment plan to cope with unpleasant side effects. Certain pain measurement tools, such as the Visual Analogue Pain Scale (VAPS) and the McGill Pain Questionnaire, are commonly used by physicians to assess pain intensity. Patients having difficulty coping with the pain associated with cancer and cancer drugs might find it helpful to be referred to a physician who specializes in pain management or a pain clinic. Physicians specializing in the treatment of pain come from a variety of medical backgrounds, such as anesthesiology, obstetrics and gynecology, neurology, and surgery. Because of the complicated nature of cancer and cancer-related pain, ideally a pain management team should be formed that works with the patient's primary care physician, oncologist, and radiologist to provide comprehensive care to the patient.

Advances in cancer treatment lengthen survival among cancer patients. It is important for cancer patients to understand that they are not alone. Support groups exist to help patients cope not only with the physical aspects of having cancer but also with the psychological ones. In addition, the positive support (both emotional and otherwise) provided by caregivers can help to improve a patient's quality of life.

Interactions

There are no known food interactions with Herceptin. However, as mentioned earlier, cardiac dysfunction is especially high in patients who received Herceptin in combination with anthracycline chemotherapy. Patients should discuss any medications (over-the-counter, herbal, and prescription) that they are taking with their physician so that an assessment can be made regarding the risk of interactions.

There are, in fact, a multitude of precautions and interactions related to chemotherapy treatment. The best thing for patients who are undergoing chemotherapy to do is to discuss all the precautions and interactions with their physicians. Usually a patient's doctor will provide patient education pamphlets regarding chemotherapy treatment. Pamphlets are also available from local cancer centers and the American Cancer Society.

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American Cancer Society, 250 Williams St. NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org>

National Cancer Institute, BG 9609 MSC 9760, 9609 Medical Center Dr., Bethesda, MD 20892-9760, (800) 422-6237, <http://www.cancer.gov>

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Hereditary angioneurotic edema

Definition

Hereditary angioneurotic edema (HANE) is a non-sex-linked (autosomal) dominant disease that results from mutations in a gene responsible for producing one of the proteins responsible for human immunity. This disease is also known as hereditary angioedema (HAE) or hereditary C1 inhibitor deficiency because it is a deficiency of the protein (C1-INH) that inhibits the action of the enzyme known as C1, which causes this disease.

Description

There are two recognized forms of HANE. Type I represents approximately 80%–85% of the cases of hereditary angioneurotic edema. In this type, the protein C1-INH is not produced in sufficient quantities. Type II HANE represents the remaining 15%–20% of cases. In this type, C1-INH concentrations are normal, but the C1-INH protein produced is defective.

Related to the two types of hereditary angioneurotic edema are acquired types of this disease (acquired angioneurotic edema [AANE] and acquired angioedema [AAE]) that are not based on a defective gene. Type I AAE is caused by a disorder that causes overgrowth (proliferation) of the lymph tissues and destroys C1-INH. Type II AAE is caused by the presence of autoantibodies (antibodies that attack the host organism that produced them) that destroy C1-INH. Both of these acquired forms of angioedema can generally be differentiated from the two types of HANE by the age of onset. Symptoms of the acquired diseases usually do not occur until the fourth decade of life, while those of the hereditary forms are generally present prior to puberty.

The human body has two distinct immune systems: the innate (nonspecific) immune system and the adaptive (specific) immune system. The complement system is a part of the innate immune system. The complement system uses at least 30 different proteins to “mark” any foreign cells in the body that do not have certain protective proteins on their cell membranes, which identify them as belonging in the body. These complement proteins are designated C1, C2, C3, etc. Once the foreign cells have been “marked,” a particular form of white blood cell, called a phagocyte, is dispatched to the area with the marked cells and destroys them.

Phagocytes will eventually destroy any cell that is marked by complement; therefore, it is important to make sure that the complement proteins are not marking non-foreign cells. When cells are improperly marked, these

cells will also be destroyed, causing what is called an autoimmune response. In effect, this autoimmune response means that the body is recognizing itself as foreign and attempting to destroy healthy cells. Inhibitors of the various complement proteins are necessary to prevent these proteins from marking the wrong cells or from continuing to mark cells after the foreign cells have been destroyed.

C1 inhibitor (C1-INH) is a chemical that is involved in the regulation of the complement system by inhibiting the action of the first complement protein (C1). C1-INH acts by binding free C1 molecules in the humor, preventing them from being able to function. It also limits the activation of other complement proteins.

Because C1-INH is diminished or defective in people affected with HANE, C1 is not inhibited and this inappropriately initiates the complement reaction that causes the swelling (acute inflammatory response) characteristic of HANE.

C1-INH also binds to the chemicals kallikrein and plasmin that are involved in blood clotting. Kallikrein is necessary for the activation of chemicals that cause dilation of blood vessels to allow increased blood flow to an area that requires more blood than normal. Plasmin is the chemical responsible for dissolving blood clots. A lack of binding of plasmin means that the formation of initial blood clots is difficult, a problem that is exacerbated by high levels of unbound kallikrein, which allows higher than normal blood flow.

With the absence or dysfunction of the C1-INH protein, the functions of blood flow, blood clotting, and immune response are impaired in individuals affected by hereditary angioneurotic edema, leading to swelling of the bodily tissues.

Genetic profile

The central Pyncheon family in Nathaniel Hawthorne's *The House of the Seven Gables* carries an ancestral curse of dying from choking on their own blood. Hawthorne describes members of the family who made odd sounds in the throat and chest when agitated and sometimes died from choking: “This mode of death has been an idiosyncrasy with his family, for generations past.... [The] prophecy was probably founded on a knowledge of this physical predisposition in the Pyncheon race.” It seems possible that Hawthorne was not only describing the symptoms of HANE but also acknowledging it to be an inherited genetic disorder.

All hereditary forms of HANE are caused by mutations in the gene responsible for the production of C1-INH. This gene is located on the long arm (q) of chromosome 11, at the specific location q11.2-q13. There are at

KEY TERMS

Acquired angioneurotic edema—Abbreviated AANE, or AAE, a nonhereditary form of angio edema that generally begins to show symptoms in, or after, the fourth decade of life.

Androgens—A group of steroid hormones that stimulate the development of male sex organs and male secondary sexual characteristics.

Angioneurotic edema—Recurrent episodes of swelling of the tissues of the body caused by an overactive immune system. This is also called angioedema.

C1 inhibitor—Abbreviated C1-INH, a protein that is responsible for preventing the action of the C1 complement molecules in the body. It is this protein that is either deficient or malformed in HANE.

Complement system—Class III MHC (major histocompatibility complex) proteins capable of destroying invading organisms directly via natural immunity, as well as indirectly through an interaction with other components of the immune system.

Hereditary angioneurotic edema—Abbreviated HANE, or HAE, an inherited kind of angioneurotic edema. Type I HANE is caused by a deficiency of C1-INH. Type II HANE is caused by a malformation of the C1-INH protein.

Kallikrein—A protein necessary for the activation of chemicals that cause dilation of blood vessels to allow increased blood flow to an area that requires more blood than normal. It is also capable of cleaving the complement, C5, into C5a, a much more robust and active form of this complement molecule.

Phagocyte—White blood cells capable of engulfing and destroying foreign antigen or organisms in the fluids of the body.

Plasmin—The blood protein that is responsible for dissolving blood clots.

Urticaria—Also known as hives. Usually associated with an allergic reaction.

least 13 different mutations of the *C1-INH* gene that cause the symptoms of HANE. Six of these are known to cause type I HANE, while another six are known to cause type II HANE. The final mutation has only been found in one individual. In this case, an acquired form of angioedema was determined to be caused by a mutation in a different region of the C1-INH gene than those mutations causing type I or type II cases of HANE.

Demographics

HANE affects approximately 50,000 people in the United States and Europe. It is estimated to occur in approximately 1 in every 50,000 to 150,000 live births. HANE appears to affect males and females equally and does not have a racial preference.

As an autosomal dominant trait, only one copy of an abnormal gene needs to be inherited for an individual to be affected. Therefore, if one child is affected with HANE, the likelihood that a second child will be affected with HANE is 50%. In cases of parents related by blood (consanguineous parents) the likelihood of HANE is increased.

Signs and symptoms

Individuals affected with either form of HANE have episodes of swelling of the hands, feet, trunk, face, digestive tract, and airways (angioneurotic edema or angioedema). These attacks of angioedema are often accompanied by attacks of nausea, vomiting, and abdominal pain. The frequency and severity of these attacks is not predictable and varies from individual to individual. These attacks may occur without cause, or they may be triggered by anxiety, stress, or minor traumas, such as dental procedures. If these symptoms are accompanied by hives (urticaria) a diagnosis other than HANE is indicated.

Symptoms of HANE generally first occur prior to puberty and episodes generally increase in severity after puberty.

Diagnosis

A diagnosis of HANE is suspected in individuals who have recurrent attacks of swollen tissues (angioedema). Diagnosis of type I HANE is confirmed by blood tests showing abnormally low levels of C1-INH, C2, and C4. Diagnosis of type II HANE is confirmed by blood tests showing normal levels of C1-INH and C2 but abnormally low levels of C4. Abnormally low levels of C1-INH and C4 without the presence of autoantibodies suggest a diagnosis of type I acquired angioedema, while abnormally low levels of C1-INH and C4 and the presence of autoantibodies suggest a diagnosis of type II acquired angioedema.

Hives (urticaria) are not generally associated with HANE. If hives are present with tissue swelling, this may suggest an allergic reaction, not a case of HANE. Occasionally, individuals affected with HANE also develop hives, but they are usually secondary to the angioedema. In a severe allergic reaction, hives are generally prominent as the major symptom.

Treatment and management

The treatment of both hereditary forms of angioedema is the same. Androgens (male sex hormones) such as winstrol, danazol, and oxandrolone have been shown to be effective in preventing chronic recurrences of swelling. These drugs are seldom used to treat acute attacks. In instances of abdominal attacks, fluid replacement therapy via intravenous injection may be required. Demerol and Compazine suppositories are often prescribed to relieve abdominal pain and vomiting.

Edema (swelling) of the airways is the most life-threatening feature of HANE. Without prompt medical attention, individuals affected with HANE can die from an obstruction of the airway caused by this swelling. Unfortunately, if the attending physician does not recognize HANE, attempts at tracheal intubation (formation of an airway directly in the neck) may aggravate the swelling rather than produce a functioning airway.

Treatment with vapor-heated C1-INH concentrate has proven to be an effective treatment both as a prophylactic (preventive) and a treatment for acute attacks of angioedema in all individuals affected with HANE. The C1-INH concentrate is derived from human blood plasma; therefore, it may possibly be contaminated. It is vapor-heated to inactivate possible hepatitis and HIV. However, because HANE is a disease of the immune system, many doctors are reluctant to use C1-INH from other people, and many patients are unwilling to accept such a treatment. The use of human recombinant C1-INH should alleviate any concerns arising from possible contamination of the blood supply.

Androgens are still the preventive treatment of choice because they are more cost-effective than treatments with C1-INH. However, androgens should not be given to women who are pregnant or who might become pregnant. In these cases, C1-INH treatment is required.

In 1999, the U.S. Food and Drug Administration (FDA) granted Orphan Drug Designations to human recombinant C1-INH for both preventive and acute treatment of HANE. On March 21, 2000, Baxter Healthcare's Hyland Immuno division and Europe's Pharming Group announced an agreement to jointly develop recombinant human C1-INH. Because of the Orphan Drug Designations from the FDA, this treatment for HANE was automatically fast-tracked and approved for human use in 2007.

Prognosis

The key to successful management of HANE is a proper medical diagnosis. With proper medical treatment, HANE is completely controllable, and individuals

affected with HANE have no diminishment in quality of life.

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- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>
- U.S. Hereditary Angioedema Association, Seven Waterfront Plaza, 500 Ala Moana Blvd., Suite 400, Honolulu, HI 96813, (866) 798-5598, <http://www.hereditaryangioedema.com>

Paul A. Johnson

Hereditary arthro-ophthalmopathy see **Stickler syndrome**

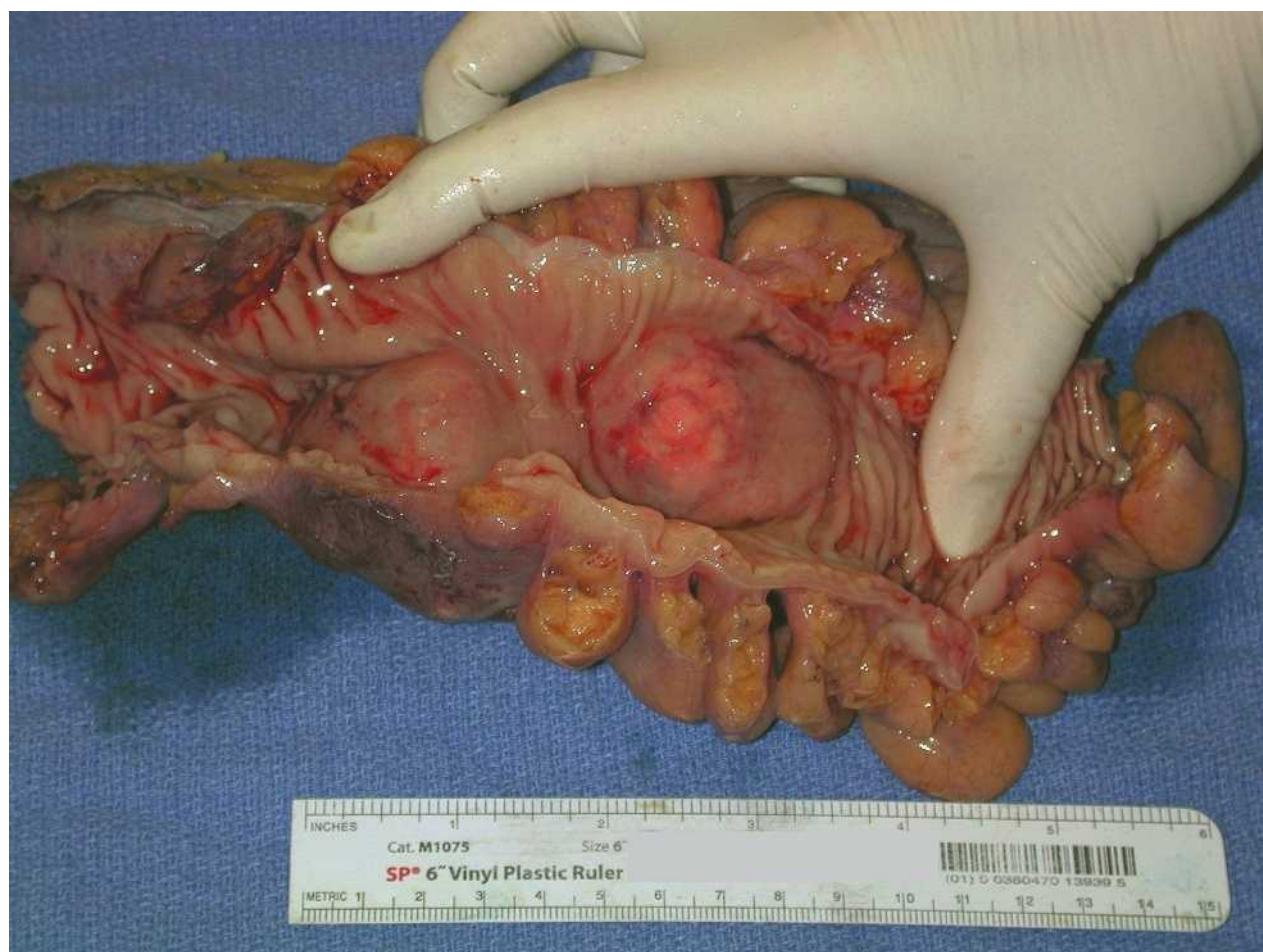
Hereditary colorectal cancer

Definition

Hereditary colorectal cancer (CRC) is cancer of the colon or rectum that develops chiefly as a result of inherited gene variants.

Description

The colon, or the large intestine, is a long, muscular tube that absorbs water from stool and advances the stool toward the rectum. The rectum works in conjunction with the anus to coordinate the process of defecation. The colon and rectum are jointly referred to as the colorectum.



A colectomy specimen displaying poorly differentiated metastatic endometrial malignant adenocarcinoma. (*Boilershot Photo/ Science Source*)

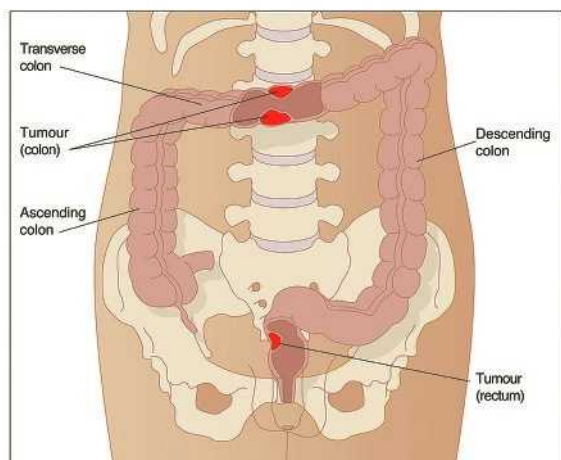
Colorectal cancer is a relatively common cancer. It results from tumors that start on the inner wall of the colorectum (mucosa) and first grow inwardly. Eventually, the tumor spreads outwardly until it reaches lymph nodes or other organs in the abdomen. Ultimately, cancer cells may detach from the original tumor and spread to distant parts of the body, such as the liver, lungs, bone, and brain. This is called metastasis.

Colorectal cancer arises from polyps on the colon. A polyp is a growth made up of tissue from the inner lining of the colon (mucosa). An adenomatous polyp (adenoma) is derived from the glandular elements of the mucosa. This type of polyp is the most common type associated with colorectal cancer. The more adenomas someone has, the more likely that one of them will transform into cancer. The larger the size of an adenoma, the more likely it will become cancerous. Early detection and removal of non-cancerous polyps is important since it decreases the risk of colorectal cancer.

In order for the adenoma to transform into a cancer cell, genes in a cell in the adenoma need to change (mutate). Usually cancer occurs from multiple mutations over time. That is why cancer happens more frequently in people who are older. Genes contain the instructions for the production of proteins. Proteins control the functioning of the cells of the body. A mutated gene will produce an abnormal protein that can cause the cells to multiply uncontrollably and become cancerous. In most cases, the mutation is caused by environmental factors like smoking, UV radiation, or age.

Some people can inherit a mutation (pathogenic variant) in a gene that makes them more likely to get colorectal cancer, because the pathogenic variant is in every cell of their body. These variants may also increase the risk for other cancers. Not all people with one of these variants will get colorectal cancer, since they have another backup copy of the gene without the variant. These variants can be passed down in the family. The two most

COLON/RECTAL CANCER



Cancers of the colon and rectum are among the commonest cancers in developed countries.

Illustration showing malignant tumors (red) in a patient's colon (large intestine) and rectum. Symptoms of colon cancer include rectal bleeding and abdominal pain. Treatment is with surgery to remove the affected area. (Peter Gardiner/Science Source)

common categories of inherited colorectal cancer syndromes caused by a pathogenic variant are 1) polyposis syndromes, which include familial adenomatous polyposis and MUTYH-associated polyposis, and 2) Lynch syndrome.

Familial adenomatous polyposis (FAP)

People with familial adenomatous polyposis (FAP) develop adenomas in the colon and rectum at an average age of 15. Eventually, they will have hundreds to thousands of adenomas. The presence of such a large number of adenomas ensures that at least one of these adenomas will develop into cancer if the colon is not surgically removed. In people with FAP, the average age of occurrence of colorectal cancer is 39. Some patients will develop cancer in their teens, and almost every patient will have cancer by age 45.

Other types of polyps are also common in patients with FAP. Polyps may develop in the stomach or duodenum. Those in the stomach are benign, while those in the duodenum may become cancerous (malignant). The cancer risk in these other polyps is much less than the risk associated with colorectal polyps. FAP is caused by pathogenic variants in the *APC* gene

Three variants of FAP have been identified:

- Gardner syndrome is a rare variant of FAP characterized by colorectal polyps and a marked prominence of

growths that occur outside the intestine. Examples of these growths include non-cancerous bone tumors, harmless bumps under the skin, and non-cancerous connective tissue (desmoid) tumors. Although these growths usually present only cosmetic problems, desmoid tumors can occasionally compress nearby tissue in a harmful way. People with Gardner syndrome can also have extra teeth and a pigmented spot in the eye.

- Turcot syndrome is another rare type of FAP. Patients with this syndrome have the typical colorectal polyps as well as malignant tumors of the central nervous system, such as medulloblastoma, astrocytoma, ependymoma, and glioblastoma multiforme.
- Attenuated adenomatous polyposis is a milder form of FAP. Patients with this type have many colonic polyps but not the hundreds or thousands seen in typical FAP. The chance of developing colorectal cancer approaches but does not reach 100%, and colorectal cancer usually appears later than in patients with typical FAP.

MUTHYH-associated polyposis

MUTHYH-associated polyposis (MAP) is associated with mutations of the *MUTHY* gene. Much like FAP, MAP is characterized by the formation of many polyps in the colon. People with MAP tend to have fewer than 100 polyps, far fewer than what is seen in FAP. Individuals with MAP are at a greater risk of developing tumors in the upper gastrointestinal tract. Polyps and tumors develop, on average, by age 50.

Hereditary nonpolyposis colorectal cancer

Hereditary nonpolyposis colorectal cancer (HNPCC) is also known as Lynch syndrome. People with Lynch syndrome have more polyps than average, but not the hundreds or thousands of polyps associated with FAP. Frequently, a patient with Lynch syndrome will have multiple cancers at the same time (synchronous) or may develop cancers at different time periods (metachronous). The age of onset of colorectal cancer likely varies by type of pathogenic variant. Some research suggests that the average age of onset is in the 40s, while other studies have found that men have a median age of onset of 54 years, while women have a median age of onset of 70 years. Men with Lynch syndrome have about a 22% to 75% risk, while women have a 20% to 52% risk of colorectal cancer. The risk that someone with Lynch syndrome will get colorectal cancer also depends on which gene variant they have.

People with Lynch syndrome are at increased risk for other cancers. Women with Lynch syndrome have a 12% to 46% chance of getting cancer of the lining of the uterus (endometrial cancer). They also have a 3% to 17% chance

of ovarian cancer. Men and women with Lynch syndrome also have an increased risk for stomach, kidney, bladder, brain, and possibly breast cancer. Muir-Torre syndrome is a rare form of Lynch syndrome. In addition to polyps and cancer of the colon and rectum, patients exhibit various types of skin cancer. Lynch syndrome is caused by pathogenic variants in a group of genes that help repair DNA called the mismatch repair genes (MMR).

Genetic profile

Colorectal cancer is caused by a combination of genetic and environmental factors. We all inherit variants (mutations) in our genes that may have influence on our risk of getting cancer. Some of these variants might increase our risk, while others might decrease it. Some people inherit a major pathogenic gene variant that can significantly increase their risk for getting colorectal and possibly other cancers. Individuals with this pathogenic gene variant have what is called a colon cancer syndrome. This does not necessarily mean that they will get cancer, as their risk will be affected by environmental factors and other genes.

One study found that about one in six (16%) people with colorectal cancer have a pathogenic variant in a gene that predisposed them to colorectal cancer. If someone has relatives (especially young relatives) with colorectal cancer, that increases the chances that there is a major pathogenic variant in the family. However, someone can have inherited a pathogenic variant that increases their risk of colorectal cancer and not have a significant family history. One study found that 60% of people with a pathogenic colorectal cancer variant did not have a significant family history of cancer, because not all people who inherit the pathogenic variant will get cancer, or it might happen later in life. Pathogenic variants associated with colorectal cancer often increase the risk for other cancers as well.

Colorectal cancer is linked to pathogenic variants in proto-oncogenes, tumor suppressor genes, DNA mismatch repair genes, and modifier genes. These variants can be inherited and/or occur spontaneously. Proto-oncogenes help regulate cell growth. A pathogenic variant in a proto-oncogenes turns it into an oncogene, which is less effective at regulating the cell. This can make a cell more likely to become cancerous. Examples of proto-oncogenes are K-ras, src, and c-myc. Tumor suppressor genes normally help prevent cancer from developing in a cell. variants in tumor suppressor genes make the cell more likely to become cancerous. Examples of tumor suppressor genes are the *APC*, *TP53* (p53), *STK11* (*LKB1*), *PTEN*, *BMP1A*, and *SMAD4* (*MADH/DPC4*) genes. The mismatch repair genes are *MLH1*, *MSH2*,

MSH6, *PMS2*, *EPCAM* (*TACSTD1*, *MYH*(*MUTYH*), *POLD1*, and *POLE*. Modifier genes affect other genes. Pathogenic variants in modifier genes can affect the functioning of other genes, which in turn can result in an increased risk of cancer. Examples of modifier genes are the *COX2* gene, the *CD44v* gene, and the *phospholipase A2* gene.

FAP genetics

FAP results from pathogenic variants in the *APC* gene. The *APC* gene is a tumor suppressor gene. It is an autosomal dominant condition, which means that an individual with FAP has inherited a pathogenic variant in one copy of their *APC* gene. This pathogenic variant is in all cells of their body. If the other copy of the *APC* gene spontaneously gets a pathogenic variant in one of their cells, that cell will be more likely to become cancerous. Individuals with a pathogenic variant in the *APC* gene have a 50% chance of passing it on to their offspring.

MUTHYH-associated genetics (MAP)

MAP is caused by pathogenic variants in the *MUTHY* gene. It is inherited in an autosomal recessive pattern. Individuals with MAP have inherited a pathogenic variation in both copies of their *MUTHY* gene. They have inherited a pathogenic variant from each of their parents. Their parents are carriers, which means that they have a 25% chance of having a child with MAP, a 50% chance of having a child who is a carrier, and a 25% chance of having a child without a pathogenic variant in their *MUTHY* gene. All children of individuals with MAP will be at least carriers. Carriers have a slightly increased risk of colorectal cancer.

Lynch Syndrome genetics

Lynch Syndrome is most commonly caused by pathogenic variants in mismatch repair genes *MLH1*, *MSH2*, *MSH6*, or *PMS2* or a piece missing of the *EPCAM* gene. The *EPCAM* gene is not a mismatch repair gene, but pieces missing in this gene can inactivate the *MSH2* mismatch repair gene. Not all gene variants associated with this syndrome are known. Lynch syndrome is autosomal dominant, which means that individuals how have it have a pathogenic variant in one copy of their gene, while the other copy is normal. They have a 50% chance of passing on Lynch syndrome to their children.

Genetic Testing

It is recommended that everyone with colorectal cancer have their tumor tested to see whether there is instability in the tumor, (MSI) which is a sign of Lynch

KEY TERMS

Adenomatous polyps (adenomas)—A growth in the colon that may become cancerous if not removed.

Desmoid tumors—Abnormal growths found in the connective tissue of the body.

Duodenum—The first segment of the small intestine.

Epidermoid cysts—Harmless cysts that occur on the skin.

Extra-intestinal—Outside of the intestine.

Neoplasm—An abnormal growth in tissues of the body, caused by rapidly multiplying cells.

Osteoma—A bony tissue tumor, either benign or malignant.

syndrome. If this instability is found, then genetic testing for Lynch syndrome would be recommended. MMRpro, MMRpredict, and PREMM5 (PREdiction Model are three validated computer models that estimate risk for Lynch Syndrome. Genetic testing is recommended for individuals with a risk of 2.5% or greater on PREMM5 or 5% or greater on MMRpro and MMRpredict.

Genetic testing can also be done on a family member with colorectal cancer to see whether they have a pathogenic variant in any of the genes associated with colorectal cancer. At-risk family members can then be tested to see whether they have inherited this same variant. Genetic testing can detect a pathogenic variants in approximately 60% to 80% of FAP families and about 50% of Lynch syndrome families. If no family member with cancer is available for testing, then someone without cancer can be tested. If no variant is detected in this person, then it is still possible that others in the family have a variant. Although genetic testing can provide useful information, it may be associated with psychosocial risks. Genetic counseling is therefore recommended.

Extrachromosomal Drivers of Cancer

Some tumors seem to have bits of DNA that are found outside of the chromosome, called extrachromosomal DNA (ecDNA). The ecDNA is separate from the DNA found in the 46 chromosomes that contain the genes inherited from our parents. The ecDNA often includes multiple cancer-triggering genes, called oncogenes, and genes that are involved in tumor formation and progression. The ecDNA can make the cancer more aggressive and more resistant to treatment. Cancer patients with ecDNA appear to have a significantly shorter survival

time. EcDNA appears to be unique to cancer and found in at least 14% of human tumors.

Demographics

Colorectal cancer is relatively common, with approximately 160,000 new cases diagnosed each year. One study found that about one in six (about 16%) of people with colorectal cancer have a syndrome that results from a pathogenic variant. The incidence of all colorectal cancer increases with age.

Signs and symptoms

The clinical manifestations of colorectal cancer depend largely on location and tumor size. Tumors in the proximal colon can grow large before detection. They may cause weight loss, abdominal pain, or bleeding. The bleeding may be readily noticed by the patient as frank blood in the toilet or smears of blood in the stool. Less-extensive bleeding may be detected by the fecal occult blood test, in which a sample of stool obtained during a rectal exam is tested for microscopic amounts of blood. Anemia, or low red blood cell count, detected by a laboratory test may prompt further examination of the colon to determine whether a tumor is the source of bleeding. In the smaller, distal colon, tumors are more likely to cause obstruction, which in turn may cause gas pains and decrease in the caliber of the stool. Additionally, these cancers may cause bleeding or a change in bowel habits. In FAP, the first symptom is usually diarrhea.

Diagnosis

The presence of symptoms such as abdominal pain, weight loss, change in bowel habits, or decrease in stool caliber may point to a diagnosis of colorectal cancer. Of course, these symptoms must be interpreted within the context of the patient's age, previous medical history, and family history of colorectal cancer.

Ideally, the diagnosis of colorectal cancer should be made before symptoms develop. A number of screening tests are useful for detecting colorectal cancer. The fecal occult blood test is a simple test performed in the doctor's office. The normal result is the absence of blood in the stool. If blood is found in the stool, the suspicion for colorectal cancer becomes higher.

Standard screening also includes an endoscopic exam—either sigmoidoscopy or colonoscopy. In these exams, a thin, specially lighted tube is inserted directly into the anus and advanced into the colon. The physician can view the inside of the colon and check for polyps or tumors. Sigmoidoscopy allows examination of the lower part of the colon, while colonoscopy allows a more extensive view. Sometimes a barium enema is added to the

QUESTIONS TO ASK YOUR DOCTOR

- I have a family member with colorectal cancer; do I need to get a screening test?
- If I have colorectal cancer, what are my treatment options?
- Should I get a second opinion? How do I do that?
- What risks and side effects should I expect from testing or treatment?
- If I need treatment, what should I do to get ready?

screening procedure. In that test, a dye is injected into the anus and up into the colon. The dye coats the inside of the colon so that tumors can be detected by plain x-ray.

New screening tests are currently under investigation. In wireless endoscopy, a pill-sized camera is swallowed. As it traverses the gastrointestinal tract, it transmits video footage that can be examined for suspicious abnormalities. Eventually, the camera is passed out of the anus with the stool. Virtual colonoscopy generates a three-dimensional image of the colon by applying advanced computer graphics technology to images obtained by computed tomography (CT) scanning. These processes can spare the patient the usual discomfort of traditional endoscopy. However, they are not yet fully developed nor approved for colorectal cancer screening.

If any of the screening tests identifies an abnormality that appears to be a tumor, the diagnosis must be confirmed by biopsy, which is performed during colonoscopy. A small piece of tissue is removed and examined in the laboratory for cancerous cells.

Most medical organizations recommend that screening begin in the general population at age 40 to 50. The fecal occult blood test is performed annually, and sigmoidoscopy every three to five years. If a first-degree relative has colorectal cancer, then screening should begin at age 35 to 40. Alternatively, screening can begin five years earlier than the age of a young relative who has had colorectal cancer.

Individuals in families affected by hereditary colorectal cancer syndromes are at increased risk for developing cancer early in life. Therefore, screening is initiated at a young age. It can be reserved for those family members who have been proven by genetic testing to carry the abnormal gene, or it can be applied to all family members if the specific mutation cannot be identified. Some experts propose that in families with a history of FAP, screening should begin at age 10 to 12 and be repeated

every one to two years. In families with Lynch syndrome, colorectal screening should begin at age 20 to 30 and be repeated every one to two years.

Since FAP and Lynch syndrome are associated with other cancers, affected patients should undergo appropriate screening for those malignancies as well. Those with FAP require regular upper endoscopy to detect tumors of the stomach and duodenum. Women with Lynch syndrome should undergo screening for uterine cancer by way of random biopsies of the inner lining of the uterus.

Factors that make it more likely that someone has inherited a pathogenic variant that predisposes them to colorectal cancer are:

- many people in the family with colorectal cancer or polyps
- more than one cancer in a patient with colorectal cancer
- other cancers associated with colorectal cancer syndromes, such as endometrial cancer; and
- early onset of colorectal cancer

Treatment and management

The treatment of sporadic colorectal cancer requires surgical removal of the tumor and surrounding tissue. Chemotherapy or radiation therapy may also be necessary. Treatment of colorectal cancer in the hereditary syndromes is more aggressive. In these cases, the entire colon must be removed, since cancer will almost certainly develop in any remaining colon. Sometimes the rectum is also removed; alternatively, the patient may undergo frequent examination of the rectum for polyps or cancers. Experts strongly recommend that individuals with known FAP consider surgical removal of the colon and/or rectum early in life as a prophylactic measure, before cancer is diagnosed. Although the role of prophylactic surgery in patients with Lynch syndrome is less well defined, many experts favor it. The patient faces a choice between prophylactic surgery and frequent, lifelong screening.

Some studies have shown that the drug sulindac may reduce the number of adenomatous polyps that develop in FAP and its variants. In addition, certain nonsteroidal anti-inflammatory drugs such as aspirin may reduce the incidence of colorectal cancer in general.

Prognosis

Patients with a hereditary colorectal cancer syndrome such as FAP, Lynch syndrome, or its variants have a much higher likelihood of developing colorectal cancer than the general population. Individuals with FAP or MAP syndrome have close to a 100% chance of getting colorectal cancer if untreated. If colorectal cancer does develop, survival depends on the extent to which the

cancer has spread. Cancer that is isolated to the colon is associated with much better chances survival than cancer that has spread to distant organs such as the liver or lungs.

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- Hereditary Colorectal Cancer Foundation, P.O. Box 2005, Park City, UT 84060, info@HCCtakesGuts.org, <http://www.hcctakesguts.org>
- National Cancer Institute, BG 9609 MSC 9760, 9609 Medical Center Dr., Bethesda, MD 20892-9760, (800) 422-6237, <http://www.cancer.gov>

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Hereditary coproporphyrria

Definition

Hereditary coproporphyrria is a genetic disorder that may cause abdominal pain, sometimes accompanied by extreme sensitivity to sunlight and skin problems associated with photosensitivity. Up to half of the individuals who have this disorder experience very mild or no symptoms.

Description

Hereditary coproporphyrria (HCP) is one of a group of at least eight disorders collectively known as porphyria. Although the eight disorders have many differences, they do share an underlying characteristic: In all of them, chemicals known as porphyrins or porphyrin precursors (substances that will become porphyrins) build up to abnormally high levels in the body. The disorders differ from one another in the specific porphyrin or porphyrin precursor that accumulates.

In hereditary coproporphyrria, the accumulating chemical is coproporphyrin (especially coproporphyrin type III). It results because of a mutation in the gene that carries the instructions for making a certain enzyme, known as coproporphyrinogen oxidase. Normally, coproporphyrinogen oxidase participates in one of the steps of heme production. Heme is a compound that is an essential component of hemoglobin and other iron-containing proteins in the body. Hemoglobin delivers oxygen through the blood and to the body's cells. Coproporphyrinogen oxidase is necessary for the step in the pathway that speeds the conversion of coproporphyrin to another compound (protoporphyrinogen), which then continues through other steps to eventually yield heme. In most

KEY TERMS

Coproporphyrin—Excrement in the urine or feces indicative of unused porphyrin in the body due to overaccumulation of porphyrin.

Heme—The deep red iron-containing prosthetic group $C_{34}H_{32}N_4O_4Fe$ of hemoglobin and myoglobin that is a ferrous derivative of protoporphyrin and readily oxidizes to hematin or hemin.

Photosensitivity—Sensitivity to light.

Porphyrin—Chemicals involved in the production of heme.

cases, coproporphyrinogen oxidase enzyme activity is reduced by 50%.

When a person has a mutation in this gene, too little coproporphyrinogen oxidase is produced, and the heme-production pathway does not work as it should. Since the enzyme is specifically connected to the step that converts coproporphyrin type III, this chemical does not go through its conversion quickly enough and can build up to unhealthy levels. Such an accumulation can lead to various symptoms, including abdominal pain and nausea, a fast pulse, dark-colored urine, and skin sensitivity. Not all persons who have the mutated gene have these, or indeed any symptoms, so some people with this disorder experience few, if any, problems.

Porphyrins, including coproporphyrin, are chemicals that are involved in the chemical process by which the body produces heme. In hereditary coproporphyria, a genetic mutation hinders one of the chemical-conversion steps in the heme-production pathway: the step that would otherwise convert coproporphyrin. When this happens the pathway makes coproporphyrin as it should, but the coproporphyrin does not then convert quickly enough into the chemical that is needed for the next step along the way. As a result, coproporphyrin accumulates, and associated symptoms may develop. Besides coproporphyrin, two other precursors of coproporphyrin also accumulate: porphobilinogen and amino-levulinic acid.

Hereditary coproporphyria is a rare autosomal dominant disorder, which means that individuals can inherit it if just one of their parents has the mutated gene.

An even rarer form of this disease is known as harderopporphyria. Individuals with this disorder are homozygous for the mutated gene. In other words, they have inherited a mutated gene from each of their parents. Individuals with this condition have neonatal hemolytic

anemia, a condition in which too few red blood cells are present in the blood.

Genetic profile

HCP is an autosomal dominant genetic mutation. A mutation in the *CPOX* gene causes coproporphyria. Located on the long arm of chromosome 3, the *CPOX* gene carries the blueprint for making the enzyme coproporphyrinogen oxidase that plays an important role in the production of heme, which is a vital protein. Mutations in this gene produce coproporphyrinogen oxidase that does not work as well as it should and, consequently, the heme-production pathway suffers.

Scientists have identified at least 45 mutations of the *CPOX* gene that cause hereditary coproporphyria. In some cases, the mutations involve the switch of a single amino acid (amino acids are the building blocks of proteins).

Because hereditary coproporphyria is an autosomal dominant disorder, adults with the mutated gene have a 50% chance of passing it to each child they may have. If both parents have the disorder, their child has a 25% chance of inheriting two copies of the mutated gene, which results in the very rare homozygous form of the disease called harderopporphyria.

Demographics

Hereditary coproporphyria is a very rare genetic disorder. It is not associated with a higher incidence in any geographic location, any ethnic group, or either gender. Harderopporphyria is an even rarer form of this hereditary coproporphyria. As of 2013, the incidence of HCP had been documented as .3 per 100,000 in Europe.

Signs and symptoms

Many individuals with hereditary coproporphyria—up to half—have no noticeable symptoms. The typical symptoms, when they do occur, vary from one individual to the next, and may include the following: Photosensitivity (sensitivity to sunlight, sometimes even sunlight through a window) that can lead to burning, blistering, and scarring of the exposed skin; dark-colored urine, or urine that darkens when it is left standing; increased pulse/heart rate; pain, especially in the abdomen and back; and nausea, vomiting, and constipation. Neurological symptoms may also be present including motor dysfunction and/or central nervous system dysfunction.

There are additional symptoms, although extremely rare (especially when the patient receives proper treatment and takes precautionary measures): muscle

QUESTIONS TO ASK YOUR DOCTOR

- How will I know when an attack is coming on?
- Are there support groups for me and my family?
- What treatment options are right for me?

weakness; paralysis of respiratory muscles, sometimes resulting in death; dizziness; and hallucinations.

Also, patients with harderoporphyrria may experience neonatal hemolytic anemia.

Diagnosis

Diagnosis can be difficult, because a patient's symptoms can often be attributable to a variety of disorders and are not specific to hereditary coproporphyrria. The diagnosis of HCP can be determined via physical examination, laboratory testing, and genetic confirmation of a *CPOX* gene mutation.

Examination

The suite of symptoms in a particular patient may lead a doctor to suspect a range of disorders, possibly including hereditary coproporphyrria. A family history will aid in the preliminary diagnosis.

Tests

The doctor may order various laboratory tests to check for the presence of high levels of coproporphyrin, porphobilinogen, and/or amino-levulinic acid in the blood, urine, or stool. These tests are often given during an acute attack of HCP. The test for fecal coproporphyrin is especially diagnostic.

Treatment and management

There is no cure for HCP. Treatment and management of the clinical manifestations of HCP are available, however. Doctors recommend various precautionary measures to reduce acute attacks. These measures may include the avoidance of sunlight, fasting, and certain drugs or alcohol, as well as the use of effective sunscreens. Doctors may recommend increased water intake or other measures to counter some of the effects of vomiting. Particularly acute abdominal pain may result in a hospital stay, although this is rare for hereditary coproporphyrria. In addition, a doctor may prescribe medications to help treat abdominal pain. Individuals may

receive hemin therapy by way of intravenous injection. Hemin therapy is a negative feedback therapy on the heme pathway and is widely administered in the early stages of an attack and also as a weekly infusion to help with hemoglobin production and function.

Before taking drugs for other maladies, patients should consult their doctor to ensure that the drugs will not promote an attack.

Due to a link between acute attacks and the menstrual cycle, attacks can be prevented in women by suppressing menses with pharmaceuticals and refraining from oral contraception use.

Adults who have the disease may wish to undergo genetic counseling before deciding to have children so that they understand the risks.

Prognosis

Up to one-half of the individuals with hereditary coproporphyrria experience no noticeable symptoms and live otherwise healthy lives. Of the remaining patients, symptoms range from mild to more severe. With proper precautions and medical intervention, when necessary, most individuals with this disorder do well.

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American Porphyria Foundation, 4900 Woodway, Suite 780, Houston, TX 77056-1837, (866) 273-3635, <http://www.porphyrifoundation.com>

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Hereditary desmoid disease

Definition

Hereditary desmoid disease (HDD) is a condition that causes people to develop a benign (noncancerous) growth known as a desmoid tumor. Desmoid tumors may also be called aggressive fibromatosis. Other names for HDD include familial infiltrative fibromatosis (FIF) and desmoid-type fibromatosis.

Description

In HDD, multiple family members from several generations develop desmoid tumors. These tumors are very rare, accounting for less than 0.1% of all tumors diagnosed. The term “desmoid” comes from the Greek word for “band” or “tendon.” That describes these tumors well, as they have a tendon- or ligament-like appearance. Desmoid tumors arise from myofibroblasts, which are cells that form connective tissue but also have some of the characteristics of smooth muscle cells. Desmoid tumors usually occur in the abdomen, but they may also develop in the neck, chest, arms, and legs. In women, they may occur in the breasts.

Most desmoid tumors—more than 97%—are *not* hereditary. These tumors occur sporadically, meaning that they occur in random individuals and are not caused by germ-line genetic mutations. Germ-line genetic mutations are those that occur in the germ cells that give rise to sperm and ova and are thus passed on to offspring. Most nonhereditary desmoid tumors are caused by what are known as somatic mutations. Somatic mutations are acquired during the person’s lifetime; they occur in any body cell other than sperm or ova. They can cause disorders or diseases but are not passed on to the next generation. In 1999, a patient was identified with a somatic mutation in the *CTNNT1* gene on the short arm of chromosome 3 at 3p21. The gene codes for a protein called beta-catenin. About 85% of sporadic desmoid tumors are now known to be caused by mutations in the *CTNNT1* gene. Health problems associated with the *APC* gene mutation are not present in people who develop sporadic desmoid tumors. These people do not have a family history of desmoid tumors.

Hereditary desmoid tumors may appear due to mutations (changes) in a gene called adenomatous polyposis coli (*APC*), located on the long arm of chromosome 5 at 5q21-q22. Mutations in the *APC* gene usually result in a disorder called familial adenomatous polyposis (FAP). This condition causes hundreds to thousands of polyps (tiny growths arising from mucous membranes) to develop in the tissues lining the colon. FAP is associated with a high risk of developing colon cancer. People

diagnosed with FAP must have their health monitored on a regular basis. Colon cancer can be prevented by careful medical screening and removal of the colon.

Some families with FAP develop extra-colonic symptoms (involving organs other than the colon), including desmoid tumors. The combination of colon polyposis and desmoid tumor is sometimes called Gardner syndrome, but it is now known that the two conditions are the same. Other extra-colonic features seen in families with FAP are cysts in the jawbone, skin cysts (epidermal cysts), bony bumps on the skull, a specific kind of spot on the retina of the eye, and thyroid cancer. About 13% of people with FAP will develop desmoid tumors. However, the precise risk differs from family to family.

In HDD, multiple family members over two or more generations develop desmoid tumors but not colon polyposis. Family members in subsequent generations have an increased risk of developing desmoid tumors.

Genetic profile

HDD is inherited in an autosomal dominant pattern, which means that every person diagnosed with HDD has a 50% chance of passing on the condition to each of his or her children. The chances that a child who has the gene mutation associated with HDD will develop a desmoid tumor are thought to be very high, maybe even 100%. It is possible that there may be other genes involved in HDD, but no gene other than *APC* had been identified as of 2015. The location of the mutation within the *APC* gene may predict the symptoms and health problems that a person will experience, but this association is far from clear.

Demographics

Hereditary desmoid disease is a rare condition. As of 2015, only five families had been reported in the medical literature. It is likely, however, that not all families with HDD have been described in the literature. Males and females are equally affected. Sporadic desmoid tumors are diagnosed in about 900 people each year in the United States.

Signs and symptoms

Desmoid tumors may cause a noticeable lump in the affected part of the body and/or pain resulting from the compression of nerves, muscles, or such organs as the kidneys or lungs. The overlying skin, however, is not usually affected. Other symptoms of desmoid tumors may include fever, obstruction of the digestive tract, or difficulties in using the hands, legs, feet, or other affected part of the body. Patients with desmoid tumors in the legs or feet may walk with a limp.

KEY TERMS

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

De novo—Latin term for “new.”

Familial adenomatous polyposis (FAP)—An inherited syndrome causing large numbers of polyps and increased risk of colon cancer and other cancers.

Fibromatosis—The medical term for a group of conditions marked by benign soft-tissue tumors that are aggressive, infiltrate other tissues, and frequently recur even though they are not cancerous. HDD is sometimes categorized as a type of fibromatosis.

Gardner syndrome—A term that is sometimes used for patients with familial adenomatous polyposis (FAP) who have desmoid tumors in the tissues covering the colon in addition to polyps inside the colon.

Germ-line mutation—A heritable change in the DNA of a germ cell (a cell destined to become an egg or in the sperm). When passed from one generation to the next, a germ-line mutation is incorporated in every cell of the body.

Myofibroblast—A fibroblast (cell that forms connective tissue) that has some of the characteristics of a smooth muscle cell.

Polyp—A mass of tissue bulging out from the normal surface of a mucous membrane.

Somatic mutations—De novo mutations that are acquired throughout life and affect only some cells in the body.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

Diagnosis

HDD is usually diagnosed solely upon family history. Evaluation for HDD requires filling out a detailed, three-generation family tree. Medical records and/or death certificates should be examined to confirm or clarify possible diagnoses of desmoid tumors. Medical records for family members developing colon polyps and/or undergoing colon surgery are requested in order to evaluate for FAP.

Genetic (or diagnostic) testing for *APC* gene mutations (changes) is another way of making a diagnosis. It may be offered to someone who has developed a desmoid

tumor and has a family history of such tumors. If a mutation is identified, the positive test result confirms the diagnosis. If no mutation is identified, this negative test result does not necessarily exclude the diagnosis of HDD.

Diagnostic testing for HDD may be offered to an individual who has no personal history of a desmoid tumor but whose family history is strongly suggestive of HDD. Prenatal diagnosis of HDD is available only if an *APC* genetic alteration has already been identified in the family. Such predictive genetic testing is best done with a geneticist (a doctor specializing in genetics) and/or a genetic counselor.

Genetic testing for mutations in the *CTNNB1* gene is also available for patients with the nonhereditary form of desmoid tumor.

Treatment and management

There is neither a cure for HDD nor a method for preventing it. Treatment depends upon the location of the tumor and may include one or more of the following: surgery, chemotherapy, hormonal therapy, and/or radiation. Surgical treatment is often challenging because desmoid tumors are composed of dense tissue resembling scar tissue. They cling very tightly to the underlying organ and are difficult to remove completely. The rate of recurrence is about 50%; therefore, more than one operation is usually required to remove the tumor permanently.

Everyone diagnosed with a desmoid tumor should be evaluated for FAP. This evaluation includes a detailed family history as well as colon screening through sigmoidoscopy or colonoscopy.

Treatment is not required until a tumor develops. Someone who has symptoms, however, must have regular medical check-ups.

There are no proven methods of screening for or preventing desmoid tumors, but it is suggested that people with or at risk for HDD have physical examinations every year. It is very important that an individual's physician be aware of the family history and the risk of developing a tumor.

Prognosis

An individual who has a genetic mutation for HDD has a high chance of developing a desmoid tumor. However, the tumor itself is treatable. Prognosis may be affected by a person's overall condition, so being healthy and engaging in healthy behaviors increase the chances of a good outcome. Some researchers think that HDD may increase a person's risk of other types of cancer, but this association was not known for certain as of 2015. It is also not known whether HDD affects a person's life expectancy.

QUESTIONS TO ASK YOUR DOCTOR

- Have you ever seen or treated a patient with either HDD or a sporadic desmoid tumor?
- What treatments would you recommend for a patient diagnosed with HDD?
- Are there any investigative treatments available for HDD?
- Would you recommend genetic testing for either HDD or a sporadic desmoid tumor?

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Desmoid Tumor Research Foundation (DTRF), PO Box 273, Suffern, NY 10901, marlene@dtfrf.org, <http://www.dtfrf.org>
National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06813, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Hereditary hearing loss and deafness

Definition

Hereditary hearing loss and deafness are caused by inherited genetic factors. It is estimated that 50% of congenital (present at birth) and severe early-onset deafness have genetic causes. More than 400 inherited genetic

syndromes are involved in hearing loss and deafness (syndromic). Hearing loss and deafness can also be inherited without an underlying genetic syndrome (nonsyndromic).

Description

In normal hearing, sound vibrations enter the large fleshy external part of the ear (the pinna) and travel down the auditory canal striking the eardrum (tympanic membrane), which begins to vibrate. As this membrane vibrates, it touches the first of a series of three small bones (the malleus, the incus, and the stapes) that mechanically transfer the vibrations to the cochlea. The cochlea is a fluid-filled tube that bends back on itself such that the two open ends lie on top of each other. One end is covered by a membrane called the oval window, and the other end is covered by a membrane called the round window. The oval window is struck by the stapes. Since the cochlea is filled with fluid, the oval window cannot vibrate without the assistance of the round window: as the oval window is pushed in by the stapes, the round window bulges out; as the oval window oscillates out, the round window bulges inward.

The vibrations imparted to the oval window and the round window are picked up by the organ of Corti within the cochlea. The organ of Corti consists of hair cells embedded in a gelatinous membrane (the tectorial membrane) that rests on the basilar membrane. Sensory neurons terminate at the hair cells of the organ of Corti. Vibration of the fluid in the cochlea causes the basilar membrane to move, which causes the hairs to bend, creating an electrical signal. This is picked up by the sensory neurons and transferred to the auditory (or cochlear) nerve, which sends the signal to the brain.

The ear is also involved in maintaining balance, and people with hearing loss may have balance problems. Body position, body movement, and balance are, in part, dependent on the vestibular apparatus of the inner ear, which consists of three functional parts. Two of these, the saccule and the utricle, signal the body position relative to gravity. The third structure consists of the three semicircular canals. These canals contain structures (ampullae) that detect movement of the internal fluid of the canals as the head moves. In most hearing-impaired people with balance problems, the semicircular canals do not function properly. Since the function of these canals is partially duplicated by the saccule and the utricle, most people can "learn" to use these other systems to compensate for dysfunction in the semicircular canals. Therefore, balance problems associated with hearing loss usually diminish over time.



A young boy signing the phrase "I love you" in American Sign Language to his baby brother. (Huntstock/Disability Images)

Syndromic hereditary hearing loss or deafness is associated with malformations of the external ear or other organs or with other genetic disorders affecting various organ systems. Nonsyndromic hereditary hearing loss or deafness is not associated with visible malformations of the external ear or other genetic disorders but can be associated with abnormalities of the middle or inner ear. Hereditary hearing loss and deafness are further classified as:

- prelingual (beginning before speech develops) or postlingual (beginning after speech develops)
- progressive (increasing over time) or nonprogressive (stable over time)
- bilateral (affecting both ears) or unilateral (affecting only one ear)
- symmetric (affecting both ears equally) or asymmetric (affecting each ear differently)
- conductive (resulting from abnormalities of the external ear or the ossicles of the middle ear with a normal auditory nerve), sensorineural (dysfunction of the inner ear or auditory nerve), a combination of the two types (mixed hearing loss), or central auditory dysfunction in the auditory brainstem or auditory regions of the brain
- severity from mild to profound as measured in decibels (dB)

Syndromic hearing loss

Syndromic hearing loss accounts for approximately 30% of hereditary hearing loss and deafness. Some of the more common genetic disorders associated with hearing loss include Waardenburg syndrome, Usher syndrome, Jervell and Lange-Nielsen syndrome, and Alport syndrome. In Waardenburg syndrome, hearing loss occurs in conjunction with pigmentation abnormalities of the skin,

eyes, and hair. In Usher syndrome, hearing loss is associated with eye abnormalities that progress to blindness. In Jervell and Lange-Nielsen syndrome, hearing loss is associated with heart abnormalities. In Alport syndrome, hearing loss is associated with kidney abnormalities.

Nonsyndromic hearing loss

Nonsyndromic hearing loss accounts for approximately 70% of hereditary hearing loss and deafness. Nonsyndromic prelingual hearing loss is most frequently sensorineural and inherited in an autosomal recessive pattern.

Otosclerosis is the most common form of nonsyndromic progressive conductive hearing loss in adults. It is caused by the growth of spongy bone tissue in the middle ear that prevents the ossicles (malleus, incus, stapes) from moving freely. In advanced cases of otosclerosis, there may also be damage to the auditory nerve (sensorineural hearing loss). Otosclerosis can occur in teenagers, but it is generally first observed in people between the ages of 20 and 50. It is very rare past the age of 50.

Dominant progressive hearing loss (DPHL) and presbycusis (hearing loss related to aging) are the most common forms of nonsyndromic progressive sensorineural hearing loss. Presbycusis is not believed to have a genetic basis. DPHL tends to have an earlier age of onset than presbycusis, but this varies greatly among affected families. Within families, the age of DPHL onset is generally fairly constant, most often beginning in early childhood, although in some families symptoms do not occur until early or middle adulthood. Some individuals with DPHL also have problems with balance because of an alteration of the semicircular canal structures within their inner ears. Balance problems are not observed in all cases of DPHL, suggesting that DPHL may be caused by more than one gene mutation.

Genetic profile

More than 100 different genes have been associated with hereditary hearing loss and deafness, and it is expected that more associated genes will be identified in the future. Furthermore, different changes (mutations) in the same genes can cause either syndromic or nonsyndromic hearing loss. Hearing loss and deafness can be inherited in different patterns: autosomal dominant inheritance, autosomal recessive inheritance, X-linked inheritance, and mitochondrial inheritance.

Individuals with an autosomal dominant form of hereditary hearing loss have a 50% chance of passing on the gene for hearing loss in each pregnancy, regardless of the gender of the parent or child. Most people with this

type of hereditary hearing loss have an affected parent; however, autosomal dominant hearing loss can occur as a new sporadic mutation in an individual with no family history. If the new mutation affects the person's germline (egg or sperm cells), there is a 50% chance of passing on the hearing loss to each child.

Individuals with an autosomal recessive form of hereditary hearing loss have inherited mutated genes from both their mother and their father. Most people with autosomal recessive hereditary hearing loss do not have affected parents; in most cases, the parents carry silent genes for hearing loss that never caused problems.

Individuals with X-linked hearing loss have inherited a gene for hearing loss located on the X chromosome. Females have two X chromosomes, whereas males have one X and one Y chromosome. Therefore, the vast majority of people affected by X-linked recessive hereditary hearing loss are male. Females may be carriers, but they are rarely affected. However, in the case of an X-linked dominant hearing loss gene, all of the daughters of an affected father will have hearing loss, because they have all inherited their father's X chromosome.

While most genetic information is carried on the chromosomes in the nucleus of the cell, there is also a small amount of DNA in the mitochondria of cells. Mitochondria are inherited from the mother. The percentage of hereditary hearing loss due to abnormalities in mitochondrial DNA is estimated to be about 1%. Hearing loss due to mitochondrial inheritance shows highly variable penetrance (the degree to which the hearing loss gene is expressed).

Syndromic hearing loss and deafness

AUTOSOMAL DOMINANT. Waardenburg syndrome is the most common autosomal dominant form of syndromic hereditary hearing loss. Even within a single family, however, symptoms vary. Affected family members may have white patches of skin or hair, differently colored and widely spaced eyes, and/or varying degrees of sensorineural hearing loss. Waardenburg syndrome types I and III are caused by mutations in the *PAX3* gene. Some cases of Waardenburg syndrome type II are associated with mutations in the *MITF* gene. Waardenburg syndrome type IV has been associated with mutations in three genes: *EDNRB*, *EDN3*, and *SOX10*.

The second most common autosomal dominant form of syndromic hereditary hearing loss is branchiootorenal (BOR) syndrome. Symptoms vary even within families. Affected people may have sensorineural, conductive, or mixed-type hearing loss, along with abnormalities of the external ear, cysts on the neck, and/or kidney problems. Mutations in the *EYA1* gene located on chromosome 8

have been found in about 40% of families with BOR syndrome. Still other families with BOR syndrome show mutations in the *SIX1* gene on chromosome 14. Other genes responsible for BOR syndrome have not yet been identified.

Stickler syndrome includes progressive sensorineural hearing loss. Mutations in the *COL2A1* and *COL11A1* genes cause severe nearsightedness as well as hearing loss. Mutations in *COL11A2* cause hearing loss without vision problems.

Neurofibromatosis 2, caused by mutations in the *NF2* gene that results in nerve cell tumors, is associated with a rare but potentially treatable form of deafness that begins in the third decade of life.

AUTOSOMAL RECESSIVE. The most common type of autosomal recessive syndromic hearing loss is Usher syndrome. Infants with Usher syndrome are born with severe sensorineural hearing loss. They later develop retinitis pigmentosa—degeneration of the retina, the light sensitive layer of tissue at the back of the inner eye. This leads to visual problems and sometimes total blindness. Usher syndrome is the cause of more than 50% of combined deafness and blindness in the United States and is estimated to account for 3%–6% of all congenital deafness. Usher syndrome has been divided into three types based on the severity of symptoms. The more severe type I is characterized by congenital severe-to-profound hearing loss, vestibular dysfunction, and retinal degeneration beginning in childhood. Usher syndrome type I can be caused by mutations in the *USH1B*, *USH1C*, *USH1D*, *USH1F*, or *USH1G* genes. The moderate Usher syndrome type II is characterized by congenital mild-to-severe hearing loss, normal vestibular function, and later onset of retinitis pigmentosa. Usher syndrome type II has been localized to three different chromosomal regions, and mutations in the *USH2A* gene have been associated with type II. The milder Usher syndrome type III is characterized by progressive hearing loss. Usher syndrome type III has been localized to the long arm of chromosome 3.

Pendred syndrome is the second most common type of autosomal recessive syndromic hearing loss. It is characterized by severe-to-profound congenital sensorineural hearing loss due to an abnormality in the bony labyrinth of the ear. Goiter, an enlarged thyroid gland, develops in puberty or adulthood. About half of Pendred syndrome-affected families carry pathogenic variants in the *SLC26A4* gene. Mutations in *SLC26A4* can also cause nonsyndromic hearing loss (DFNB4).

Jervell and Lange-Nielsen syndrome is the third most common type of autosomal recessive syndromic hearing loss. It is characterized by congenital deafness and a heart

abnormality called long QT syndrome. Pathogenic variants in two different genes have been associated with this syndrome.

X-LINKED. Alport syndrome is an example of X-linked syndromic hearing loss. Males with Alport syndrome have progressive kidney problems that lead to kidney failure and early death. Many males with X-linked Alport syndrome develop progressive sensorineural hearing loss beginning after age 10. They may also have an abnormality in the shape of the lens called anterior lenticonus. Females with X-linked Alport syndrome may have kidney problems and deafness but usually with a later onset and less rapid progression. Alport syndrome may be autosomal dominant or autosomal recessive as well as X-linked, but about 85% of cases show X-linked inheritance. About 15% are autosomal recessive. Autosomal dominant inheritance appears to be very rare.

MITOCHONDRIAL. Syndromic mitochondrial hearing loss is more common than nonsyndromic mitochondrial hearing loss due to the functioning of the mitochondria. Because mitochondria are responsible for energy production, faulty mitochondria result in decreased energy production. This lower level of energy production greatly affects the parts of the body that use the most energy, including the brain, heart, and muscles. Therefore, people with mitochondrial disorders generally have a spectrum of physical symptoms, including nervous system problems, visual problems, hearing loss, and muscle weakness. MELAS, MERRF, and Kearns-Sayre syndromes are mitochondrial syndromes that include hearing loss. More than half of people with diabetes mellitus and a specific mutation in the mitochondrial *MTTL1* gene in Japan have been found to have sensorineural hearing loss that develops after the onset of diabetes. This mutation is also associated with MELAS.

NONSYNDROMIC HEARING LOSS AND DEAFNESS. Most cases of hereditary hearing loss are nonsyndromic and autosomal recessive. Most autosomal recessive hearing loss is prelingual and severe-to-profound. Most autosomal dominant hearing loss is postlingual. Approximately 75%–80% of nonsyndromic prelingual hereditary hearing losses are due to autosomal recessive mutations, and about 20% are due to autosomal dominant mutations. The rare remaining cases of nonsyndromic hereditary hearing loss are attributed to X-linked and mitochondrial disorders (about 1% each). The gene loci associated with nonsyndromic deafness are designated DFN for “DeaF-Ness.”

- DFNA are autosomal dominant.
- DFNB are autosomal recessive.
- DFNX are X-linked.

Mutations in the *GJB2* gene that encodes the protein connexin 26 or the *GJB6* gene that encodes connexin 30 cause DFNB1 and account for 50% of all autosomal recessive nonsyndromic hearing loss, including 30% of hearing losses with no family history. It is estimated that at least 3% of people with normal hearing carry a silent mutation in one of their *GJB2* genes. If a mother and father each are unaffected carriers of a mutation in *GJB2*, each of their offspring has a 25% risk of inheriting hearing loss.

No single gene has been identified as responsible for most autosomal dominant nonsyndromic cases of hearing loss. However, many genes have been associated with nonsyndromic hearing loss and deafness, and different mutations in the same gene can cause different types of hearing loss.

- Different mutations in the *TECTA* gene that encodes the alpha-tectorin protein can cause either DFNA8/12 or DFNB21, depending on the location of the mutation in the gene.
- Mutations in the *GJB2* and *GJB6* gene can cause DFNA3 or DFNB1.
- Mutations in *MYO7A* can cause DFNA11 or DFNB2 as well as Usher syndrome type 1B.
- Mutations in *USH1C* can cause DFNB18 as well as Usher syndrome 1C.
- Mutations in *CDH23* can cause DFNB12 or Usher syndrome 1D.
- Mutations in *SLC26A4* can cause DFNB4 or Pendred syndrome.
- Mutations in *WFS1* can cause DFNA6/14/38 or Wolfram syndrome.

Otosclerosis is inherited in an autosomal dominant pattern but has reduced penetrance. A dominant condition with complete (100%) penetrance affects all individuals with the single gene mutation. However, many individuals with a genetic mutation known to cause otosclerosis do not have any symptoms of hearing loss. Furthermore, because otosclerosis can have a late onset, family members die before showing signs of hearing loss.

Several chromosomal locations are associated with nonsyndromic X-linked deafness (DFNX). DFNX3 is caused by mutations in the *POU3F4* gene located on the long arm of the X chromosome. People with mutations in this gene have mixed-type hearing loss. The conductive portion of their hearing loss is caused by abnormal attachment of the stapes.

Nonsyndromic mitochondrial hearing loss is associated with mutations in either the mitochondrial *MTRNR1* gene or the mitochondrial *MTTS1* gene. Nonsyndromic

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance in which only one abnormal gene is needed to express the trait or disease.

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are needed to express the trait or disease.

Branchiootorenal (BOR) syndrome—The second most common autosomal dominant form of syndromic hereditary hearing loss.

Cochlea—The spiral-shaped, fluid-filled hearing apparatus of the inner ear.

Conductive hearing loss—A blockage of sound vibrations from the eardrum to the inner ear due to a problem in the outer or middle ear.

Decibel (dB)—A logarithmic unit for expressing loudness or intensity; normal speech is typically in the range of 20–50 dB.

Dominant progressive hearing loss (DPHL)—The most common type of hereditary nonsyndromic progressive sensorineural hearing loss.

Hearing level (HL)—Hearing threshold; the sound level that can just barely be heard.

Mitochondrial inheritance—Genes located within the mitochondria of cells that are inherited from the mother.

Nonsyndromic hearing loss—Hereditary hearing loss that is not part of another underlying genetic disorder.

Ossicles—The three tiny bones in the middle ear

Otosclerosis—Growth of spongy bone in the inner ear that causes progressive hearing loss and deafness.

Pathogenic variant—A mutation or variation in a gene that causes a genetic disorder.

Sensorineural hearing loss—Hearing loss caused by an abnormality in or permanent damage to the inner ear, the auditory nerve, or the auditory center of the brain.

Syndromic hearing loss—Hearing loss that occurs as part of an underlying genetic syndrome.

Usher syndrome—The most common type of autosomal recessive syndromic hearing loss.

Waardenburg syndrome—The most common autosomal dominant form of syndromic hearing loss.

X-linked—A gene located on the X sex chromosome.

mitochondrial hearing loss varies from moderate to profound. One specific mutation in *MTRNR1* has been reported both in families with nonsyndromic hearing loss and in families with hearing loss induced by exposure to aminoglycoside antibiotics. People with this mutation develop hearing loss within a few days to weeks of taking the medication; without exposure to the antibiotic, hearing loss develops at a median age of 20 years. Hearing loss caused by *MTTS1* mutations often develops in childhood.

Demographics

It is estimated that approximately 10% of the population of the United States has hearing loss or deafness. This number is higher worldwide because many nongenetic causes of hearing loss are more prevalent outside of the United States. Congenital hearing loss is estimated to affect 2 to 3 out of every 1,000 babies born in the United States. It is estimated that approximately 50% of childhood hearing impairment in the United States is genetically based. Another 20%–25% of cases are attributed to environmental factors. The remaining 25%–30% of cases are of unknown cause. The incidence of hearing loss increases with age. Approximately 17 out of 1,000 children under age 18—but 40%–50% of people over 75

—have hearing loss. This age-related increase reflects the interaction of genetic susceptibility and environmental triggers.

Approximately 85%–90% of deaf individuals intermarry, but 90% of deaf couples have children with normal hearing, and 90%–95% of deaf children have parents with normal hearing. In general, if a hearing couple has a child with profound deafness of unknown cause, their risk of having another child with hearing loss is one in six for each future pregnancy.

Otosclerosis is estimated to affect between 10% and 18% of all white and Hispanic women and between 7% and 9% of all white and Hispanic men. People of Asian descent are affected with otosclerosis at about half the rate of whites and Hispanics, with the same observed sex differences. Only about 1% of African Americans are affected by otosclerosis, with minimal differences between males and females. Otosclerosis is exceedingly rare in people of Native American descent.

Signs and symptoms

Syndromic types of hearing loss generally have signs and symptoms associated with the particular syndrome.

QUESTIONS TO ASK YOUR DOCTOR

- Is my hearing loss inherited?
- Is my hearing loss conductive or sensorineural?
- Is my hearing loss part of a genetic syndrome?
- Is genetic testing available for my type of hearing loss?
- Is my hearing loss progressive?

Otosclerosis is characterized by an initial loss of hearing in the low frequencies, followed by a loss of the high frequencies, then a loss of the middle frequencies. It may rapidly advance through these stages or stabilize for a period of years before progressively worsening. Many affected individuals have symptoms only in one ear at first, but otosclerosis almost inevitably eventually affects both ears. The maximum hearing loss due to otosclerosis without involvement of the auditory nerve is in the moderate range. As an affected person ages and the auditory nerve becomes involved, hearing loss may progress to severe or even profound.

There are four main categories of DPHL: early-onset, high-frequency, mid-frequency, and low-frequency. Early-onset types of DPHL tend to occur in early childhood and progress at varying rates to deafness. The other three types are categorized by the frequency range in which hearing loss first occurs.

Hearing loss is categorized by the hearing threshold. Hearing threshold is the level of sound that can just barely be heard. The hearing threshold of an individual is the hearing level (HL) of that person. It is measured in decibels (dB). Normal hearing is up to a 25-dB HL. Mild hearing loss is defined as an HL in the 26- to 45-dB range. Moderate hearing loss is defined as an HL in the 46- to 65-dB range. Severe hearing loss is defined as an HL in the 66- to 85-dB range. Profound hearing loss is defined as an HL greater than 85 dB. The average person speaking English in a conversational tone tends to speak in the 30- to 60-dB range, depending on the particular sounds. People with mild hearing loss are generally able to hear and understand one-on-one conversations if they are close to the speaker, but they may have difficulty hearing a speaker who is far away, has a soft voice, or is surrounded by background noise. People with moderate hearing loss may have problems hearing conversational speech, even at relatively close range and in the absence of background noise. People with severe hearing loss have difficulty hearing in most situations, unless the

speaker is talking loudly and is at relatively close range. People with profound hearing loss may not hear loud speech or environmental sounds. These people are unlikely to use hearing and speech as primary means of communication.

Hearing loss is also measured in terms of the frequency (hertz) of the sounds that can be heard. The normal hearing range for humans is approximately 100–8,000 hertz (Hz). The normal frequency of sounds in the English language falls between approximately 240 Hz and 7,500 Hz. In individuals with progressive conductive hearing loss, it is generally the highest frequency range or the lowest frequency range that is lost first; the middle-frequency range is generally lost last. In individuals affected with progressive sensorineural hearing loss, any of the three frequency ranges may be lost first. Hearing loss is generally plotted on a graph called an audiogram. This is a graph of frequency (in Hz) versus HL (in dB).

Diagnosis

Genetic forms of hearing loss are diagnosed by an ear (otologic) exam, hearing tests (audiometry), a physical exam, family history, imaging studies such as computed tomography (CT) of the temporal bone, and molecular genetic testing. Genetic testing is available for many types of syndromic and nonsyndromic hearing loss and deafness. Prenatal testing may also be available.

Syndromic hereditary hearing loss is usually diagnosed by other signs of the particular syndrome. Types of nonsyndromic hereditary hearing loss may be diagnosed by the age of onset, degree of progressiveness, degree of symmetry between the two ears, and the type of hearing loss—conductive, sensorineural, or mixed.

Hearing is generally tested using earphones. Sounds are sent into the earphones at various decibel and frequency levels to determine the amount of hearing loss in dB and the range of hearing loss in Hz. Since hearing loss is not necessarily the same in both ears, each ear is tested independently. Another test is performed to determine whether hearing loss is conductive or sensorineural. A device called a bone vibrator is used in place of the earphones. The bone vibrator sends auditory signals through the bones of the ear, bypassing the ear canal and the ossicles of the middle ear. In the case of conductive hearing loss, the affected individual will be able to hear sounds at a lower decibel level using the bone vibrator than using the earphones. In the case of sensorineural hearing loss, the affected individual will generally hear sounds through the bone vibrator at the same decibel level as with the earphones.

Other diagnostic tests include:

- auditory brainstem response testing to evoke responses in the auditory nerve and brainstem
- auditory steady-state testing
- evoked otoacoustic emissions to determine the activity of the outer hair cells of the cochlea
- acoustic immittance testing to assess the peripheral auditory system, including middle-ear pressure
- various specialized types of audiometry

Newborn screening for congenital hearing loss is required in many states and offered to all in most other states.

Treatment and management

Certain types of conductive hearing loss can be treated by surgery to correct the dysfunctional portion of the ear. Sensorineural hearing loss is generally not surgically repairable. Children over 12 months with severe-to-profound hearing loss may be candidates for cochlear implants.

Most people with partial hearing loss can benefit from the use of hearing aids and/or sign language. Sign language and writing are often the primary forms of communication used by people who have severe or profound hearing loss or total deafness.

Prognosis

The prognosis for individuals affected with hereditary hearing loss is largely dependent on the type of hearing loss and the presence of additional symptoms in syndromic types. Hearing aids and/or sign language can greatly improve the quality of life for people affected by hereditary hearing loss and deafness.

Resources

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ORGANIZATIONS

Alexander Graham Bell Association for the Deaf and Hard of Hearing, 3417 Volta Pl. NW, Washington, DC 20007, (202) 337-5220, (202) 337-8314, info@agbell.org, <http://www.listeningandspokenlanguage.org>

American Society for Deaf Children, 800 Florida Ave. NE, No. 2047, Washington, DC 20002-3695, (800) 942-2732 (ASDC), (410) 795-0965, <http://www.deafchildren.org>

National Association of the Deaf, 8630 Fentor St., Suite 820, Silver Spring, MD 20910, (301) 328-1443, (301) 587-1791, <http://nad.org>

National Institute on Deafness and Other Communication Disorders, NIDCD Office of Health, 31 Center Dr., MSC 2320, Bethesda, MD 20892-2320, (301) 496-7243, (800)-241-1044, (301) 402-0018, <http://www.nidcd.nih.gov>

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Hereditary hemorrhagic telangiectasia

Definition

Hereditary hemorrhagic telangiectasia (HHT) is a disorder of the blood vessels, typically involving recurrent nosebleeds (epistaxis) and telangiectases (small malformations that result in small red spots on the skin) of the lips, mouth, fingers, and nose. Arteriovenous malformations (AVMs) are abnormal direct connections between the arteries and veins (blood vessels), causing abnormalities in blood flow. AVMs are often present in HHT and may occur in the lungs, stomach, liver, or brain. HHT was formerly known as Osler-Weber-Rendu (OWR) syndrome and is still called by that name by some physicians.

Description

HHT was first described in the late nineteenth and early twentieth centuries by several physicians, most notably the Canadian, Sir William Osler, who showed that HHT runs in families; the Englishman, F. Parkes Weber, who published a notable case series; and the Frenchman, Henri Jules Louis Marie Rendu, who distinguished HHT from hemophilia. The present preferred name, hereditary hemorrhagic telangiectasia, was introduced by an American physician, Frederick R. Haines, in 1909.



Close-up of the face of a patient affected by hereditary hemorrhagic telangiectasia. In this condition, telangiectases (collections of distended blood capillaries) develop on the skin and mucous surfaces. (P. Marazziti Science Source)

HHT is caused by genetic defects that affect angiogenesis, the process in which new blood vessels are formed out of preexisting ones. Because of these defects, abnormalities in the structure of the blood vessels lead to small vascular malformations known as telangiectases and larger ones known as arteriovenous malformations (AVMs) in various parts of the body. Telangiectases are most commonly found near the surface of the skin of the lips, nose, fingers, and face; in the mucous membranes lining the nasal passages; and in the tissues lining the digestive tract. Telangiectases are prone to recurrent bleeding, which explains why one of the most common symptoms of HHT is epistaxis, or nosebleeds.

The larger AVMs are usually found in the lungs, liver, or brain, with a very few occurring in the spinal cord, and may lead to more serious loss of blood and other health problems. AVMs in the brain itself may cause headaches. AVMs in the lungs may bypass the capillaries that normally filter out blood clots; the blood clots may then migrate to the brain and cause stroke.

It is very rare for an individual to have all the symptoms associated with HHT or to have them with equal severity. In addition, the time of symptom onset varies from patient to patient. Some patients develop symptoms in infancy, others in early childhood. However, puberty is the most common time for the onset of nosebleeds. Bleeding in the digestive tract is most likely to appear in adults in their 30s or 40s. The differences in symptom location, severity, and time of onset are related to the different genetic mutations linked to HHT.

People with HHT do not have any mental limitations and therefore have the same academic potential as anyone else. Children with HHT may develop anemia, however,

and may find it difficult to keep up the same level of activity as their peers.

Genetic profile

HHT is known to be characterized by genetic heterogeneity. Mutations in at least five different genes (two as yet unidentified) are known to cause HHT; it is highly likely that more genes linked to the condition will be discovered in the future. HHT is presently divided into five subtypes according to the genetic mutations that cause them:

- **Type 1:** HHT type 1 is caused by mutations in the *ENG* gene on the long arm of chromosome 9 at 9q34.1. Patients with type 1 HHT typically develop symptoms earlier than those with type 2 and are more likely to develop AVMs in the lungs and brain.
- **Type 2:** Type 2 HHT is caused by mutations in the *ACVRL1* gene on the long arm of chromosome 12 at 12q11-q14. Patients with type 2 HHT are usually older when their symptoms first develop and are more likely to develop AVMs in the liver. Types 1 and 2 taken together account for about 80% of cases of HHT.
- **Type 3:** Type 3 is caused by mutations in an unknown gene mapped to the long arm of chromosome 5 at 5q31.3-q32. Patients with type 3 HHT are also more likely to develop AVMs in the liver.
- **Type 4:** Type 4 HHT is caused by mutations in an unknown gene mapped to the short arm of chromosome 7 at 7p14. Types 3 and 4 are relatively rare.
- **Type 5:** Type 5 HHT is caused by mutations in the *MADH4* gene (also called the *SMAD4* gene) on the long arm of chromosome 18 at 18q21.2. Type 5 HHT is also known as juvenile polyposis hereditary hemorrhagic telangiectasia syndrome, or JPHT, because patients develop multiple polyps in the lining of the digestive tract at an early age, which increases their risk of cancer in addition to the other symptoms of HHT. This type accounts for only 2% of cases of HHT.

All five types of HHT are inherited in an autosomal dominant pattern, which means that only one copy of the defective gene is needed for the disorder to appear in an individual. The role that these specific genes play in the pathogenesis of HHT, however, is not fully understood. All the genes presently linked to HHT code for a family of signaling proteins known as TGF-beta/BMP, which affect such functions as cell survival, reproduction, and specialization (differentiation). It is thought that mutations in these genes interfere with cell signaling during the process of angiogenesis, leading to malformed blood vessels that are fragile and easily broken (friable). Over 600 different mutations in the HHT-associated genes had been identified as of 2015.

Demographics

HHT is believed to affect about 1 in every 5,000 people in most parts of Europe and Japan; it is less common in the United States, with one or two cases reported each year per 100,000 people—which likely reflects underdiagnosis. The exception for the United States is Vermont, with a reported incidence of 1 case per 16,500 residents.

HHT is found worldwide, but a higher prevalence exists in the Danish island of Funen (1 case per 3,500 people), the Dutch Antilles, and parts of France (1 case per 8,345 people). All types of HHT affect both males and females.

Signs and symptoms

The symptoms of HHT result from several AVMs, which may occur in differing severity and areas of the body. Ultimately, AVMs may lead to mild or severe bleeding in affected areas. About 90% of people with HHT experience frequent nosebleeds. These occur because the layers of mucous membranes in the nose are very sensitive and fragile, and telangiectases in this area can easily bleed spontaneously. Recurrent nosebleeds may begin by about 12 years of age and are not always severe enough to result in medical treatment or consultation. Occasionally, severe nosebleeds can cause mild to severe anemia, sometimes requiring a blood transfusion or iron replacement therapy.

Telangiectases commonly occur on the nose, lips, tongue, mouth, and fingers. They may vary in size from a pinpoint to the size of a small pea. Because telangiectases are fragile, sudden bleeding may occur from only a slight trauma, and bleeding may not stop by itself. Thirty percent of people with HHT report telangiectases first appearing before age 20, and 67% before age 40. Telangiectases and larger AVMs can be found anywhere in the gastrointestinal system, and if large enough they may cause a significant amount of internal bleeding. This bleeding may become more severe with age but usually does not appear until age 40.

Pulmonary AVMs (AVMs in the lung) may cause bleeding within the lungs. These are problematic because the abnormal connections between arteries and veins bypass the natural filtering system within the lung, allowing bacteria to enter the system. Low levels of oxygen and infection may result, causing migraine-like headaches. An individual with a pulmonary AVM may experience intolerance to exercise or may have areas of his or her skin turn blue (cyanosis, due to low oxygen levels). Complications in the brain may also result, sometimes causing stroke. Occasionally, AVMs may occur in the spine, liver, and brain. An AVM in the liver can cause blood to be drawn away from the normal circulation, increasing the

risk of heart failure because the heart must work harder to compensate for the large amounts of blood withdrawn from the rest of the body by the AVM in the liver.

Diagnosis

As of 2015, the clinical diagnosis of HHT was based on four criteria established by the scientific advisory board of the HHT Foundation International in 1999. The so-called Curaçao criteria are as follows:

- presence of epistaxis
- presence of telangiectases
- AVMs in the internal organs
- a first-degree relative (parent, child, or sibling) with HHT

A diagnosis of HHT is considered definite if the patient meets three or all four of the four criteria; possible or suspected if two are met; and unlikely if fewer than two are met.

In spite of the widespread use of the Curaçao criteria, HHT is difficult to diagnose (and is often underdiagnosed) because bleeding and venous malformations may occur in otherwise healthy individuals. For example, isolated nosebleeds are very common in the general population and may occur for a variety of reasons. Because nosebleeds are often the first sign in HHT, they may initially be ignored until they become so frequent that they are brought to medical attention. Isolated internal bleeding is quite common in the brain and GI tract. However, not all brain aneurysms are caused by AVMs, and their cause must be determined, as AVMs are more specific to HHT. Most individuals with a pulmonary AVM actually have HHT.

Telangiectases may sometimes be a sign of such other bleeding disorders as von Willebrand disease, which is a disorder of blood coagulation (clotting). Telangiectases may also naturally occur in pregnancy or chronic liver disease. Ataxia telangiectasia, another genetic condition involving telangiectases, should be considered if individuals have ataxia (problems with muscle coordination); movement and walking disorders are also often observed in patients with this condition.

Genetic testing is used to confirm a diagnosis of HHT. Tests are available for mutations in all of the known genes linked to HHT and will identify mutations in about 90% of patients who meet the Curaçao criteria for the disorder.

Treatment and management

Treatment for HHT is based on the specific symptoms an individual experiences. To assess the need for

KEY TERMS

Aneurysm—A localized blood-filled bulge or weak area in the wall of a blood vessel. The larger an aneurysm grows, the greater the risk of rupture. Aneurysms in the blood vessels of the brain are particularly dangerous.

Angiogenesis—The medical term for the formation of new blood vessels out of preexisting blood vessels.

Arteriovenous malformation (AVM)—Abnormal direct connection between the arteries and veins (blood vessels) that may range in size from very small to large. AVMs may lead to bleeding or aneurysm formation.

Cauterization—Process of burning tissue either with a laser or electric needle to stop bleeding or destroy damaged tissue.

Echocardiogram—A noninvasive technique that uses ultrasonic waves to examine the various structures and function of the heart.

Embolization therapy—Introduction of a coil or various substances into blood vessels in order to plug them and stop excessive bleeding.

Endoscope—A slender, tubular optical instrument used as a viewing system for examining an inner part of the body. With an attached instrument, the endoscope can be used for biopsy or surgery.

Epistaxis—The medical term for nosebleed.

Magnetic resonance imaging (MRI)—A diagnostic procedure that uses a combination of high-powered magnets, radio frequencies, and computers to generate detailed images of structures within the body.

Polyp—A mass of tissue bulging out from the normal surface of a mucous membrane.

Polyposis—The formation of numerous polyps in a body structure, most often the digestive tract or the nasal passages.

Stroke—A sudden neurological condition related to a block of blood flow in part of the brain, which can lead to a variety of problems, including paralysis, difficulty speaking, difficulty understanding others, or problems with balance.

Telangiectasis—Very small arteriovenous malformations that result in small red spots on the skin called “spider veins.”

treatment, a review of the patient’s medical history regarding nosebleeds and other bleeding episodes should be performed. About 35% of patients diagnosed with HHT have only mild symptoms and require no treatment.

There should be careful inspection of any telangiectases. Stool samples may be analyzed to determine whether there is any occult blood (blood that is not obvious to the naked eye); occult blood in the stool may indicate anemia. A complete blood count (CBC) can also determine whether anemia is a factor in the patient’s symptoms. Pulse oximetry involves studying a blood sample and determining whether the amount of oxygen absorption by red blood cells is normal. It can help to determine whether the lungs and heart are functioning properly, because their roles are to help oxygenate blood. Careful imaging of the heart by echocardiogram or chest x-rays can assess whether the heart structures are normal. Chest x-rays may identify pulmonary AVMs. Magnetic resonance imaging (MRI) of the head can visualize the brain to rule out any bleeding. Ultrasound of the liver and abdomen can help to rule out any AVMs in this area.

There are several options for those who experience chronic nosebleeds. Generally, sterile sponges and sprays may help absorb free-flowing blood. Another option is

laser therapy, used for individuals who have mild to moderate nosebleeds. A small laser beam is directed around each telangiectasis, causing clotting to occur and sealing the blood vessels. It is usually done under local anesthesia, and few complications exist. Nearly everyone sees improvements for several months, and the procedure may be repeated as needed. For more severe cases (sometimes requiring transfusions) there is septal dermoplasty, first pioneered in the 1960s. This procedure replaces the normally fragile lining of the nose with a tougher lining, using a skin graft from the thigh area. The procedure can be done with local or general anesthetic and has minimal complications. Some individuals never have nosebleeds again after the operation, but most of them experience a significant lessening of symptoms. Estrogen and aminocaproic acid (an amino acid) therapies have also been found to help with clotting in the nose. Estrogen improves the smoothness of layers of skin on the telangiectases, making them less fragile. Aminocaproic acid (Amicar) improves the clotting process by magnifying the protein responsible for clotting.

Gastrointestinal bleeding is one of the most difficult symptoms of HHT to treat. Endoscopy can help to identify the location of the AVM. Using an endoscopic probe, treatment can be attempted by laser or through

QUESTIONS TO ASK YOUR DOCTOR

- How do the various types of HHT differ from one another?
- How is HHT diagnosed?
- Would you recommend genetic testing for HHT?
- Please explain what telangiectasia is and how it affects my child's health.
- What is the prognosis for a child diagnosed with HHT, and on what factors is this prognosis based?

cauterization—sealing the injury with heat. These help to seal the telangiectasis or AVM. If bleeding is severe, iron therapy is often needed to help build more red blood cells and alleviate anemia. Hormone therapy (with estrogen and progesterone) has been helpful in many patients with chronic GI bleeding. No completely satisfactory treatment for liver AVMs has been established, but embolization therapy has been used. For more severe cases (usually in older individuals) liver transplantation may be considered.

Pulmonary AVMs are often treated with a procedure known as balloon embolization. A small tube is inserted into a large vein in the groin. It is passed through the blood vessels to the pulmonary AVM. A balloon or coil is placed into the artery leading into the AVM, blocking it completely, which stops the bleeding. The procedure usually takes one to two hours, with minimal recuperation time. Pulmonary AVMs can almost always be treated very well with this method. Women with HHT who become pregnant and have untreated pulmonary AVMs are at high risk of an internal lung bleed. They should be followed carefully throughout pregnancy and be treated during their second trimester to avoid this complication. Pregnant women with treated pulmonary AVMs appear to be at no higher risk for bleeding than pregnant women without pulmonary AVMs.

For generalized anemia, iron replacement and red blood cell transfusions may become necessary. People with HHT may develop medical problems unrelated to the condition, such as ulcers or colon cancer, which may cause additional GI blood loss.

Because telangiectases can occur in the mouth, dental work may be a particular problem for those with HHT. Bleeding in the mouth makes the area susceptible to oral bacteria, such as those on the gums. Bacteria can enter the bloodstream through the blood vessels in the

mouth and cause infections in other areas of the body. The best preventive measure is to take antibiotics before any dental work in order to prevent infection. Additionally, such medications as aspirin and NSAIDs (nonsteroidal anti-inflammatory drugs; examples include naproxen, ibuprofen, and ketoprofen) should be avoided because they can increase the risk of bleeding.

Experimental treatments for HHT include two anti-angiogenesis drugs: bevacizumab (Avastin), used to treat metastatic cancers, and thalidomide (Thalomid), used to treat multiple myeloma. As of 2015, neither drug had been approved by the Food and Drug Administration (FDA) specifically for the treatment of HHT.

Because effective treatment measures are available, unaffected at-risk individuals in a family should be screened for symptoms of HHT, especially for AVMs in the brain, lungs, and digestive tract.

Prognosis

Prognosis for individuals with HHT is good, assuming those with moderate or severe symptoms receive appropriate and timely treatments. Because many treatments are effective, proper screening is crucial to a good prognosis. Most patients will have a normal life expectancy.

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ORGANIZATIONS

American Academy of Otolaryngology—Head and Neck Surgery, 1650 Diagonal Rd., Alexandria, VA 22314, (703) 836-4444, <http://www.entnet.org>

HHT Foundation International, PO Box 329, Monkton, MD 21111, (410) 357-9932, (410) 357-0655, hhtinfo@curehht.org, <http://curehht.org>

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Hereditary hypertrophic cardiomyopathy

Definition

Hereditary hypertrophic cardiomyopathy (HCM) is a genetic disorder characterized by abnormal thickening (hypertrophy) of the heart muscle (myocardium) in the absence of any other disease capable of causing such thickening. In HCM, the cardiomyocytes (the cells that make up the heart muscle) increase in size, resulting in the thickening of the muscle tissue. In addition, the cardiomyocytes are no longer in proper alignment, a condition known as myocardial disarray. Instead of being lined up in parallel rows, the cells form circular or disorganized patterns around small areas of connective tissue. Lastly, HCM disrupts the electrical functions of the heart.

HCM has been given many alternate names since the 1970s—by one account, as many as 75 different names. Some of the more common names that are still used include familial hypertrophic cardiomyopathy, asymmetric septal hypertrophy, hereditary ventricular hypertrophy, and rare familial disorder with hypertrophic cardiomyopathy. Increasingly, however, physicians are using the simple term “hypertrophic cardiomyopathy,” abbreviated HCM, because it is universally recognized that genetic mutations are the single most common cause of HCM. These mutations account for 50%–60% of diagnosed cases of HCM.

Description

HCM is characterized by functional impairment of the myocardium as a result of the thickening of the heart muscle. The most common location of this thickening is the intraventricular septum, which is the wall of tissue that divides the two lower chambers (ventricles) of the heart. However, any portion of the left ventricle may be affected. This condition is known as left ventricular hypertrophy, or LVH. As a result of the thickening of the muscle tissue, the left ventricle has less room to receive oxygenated blood, and the outflow of blood from the left ventricle through the aorta to the rest of the body is reduced.

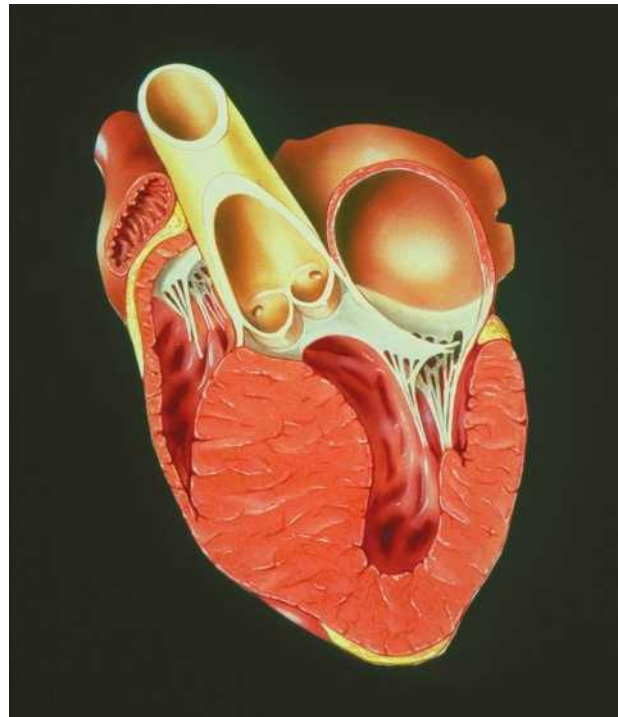


Illustration of hypertrophic cardiomyopathy, showing enlargement of the muscular septum separating the left and right ventricles. (David Gifford/Science Source)

HCM can be divided into two types, obstructive and nonobstructive, depending on whether the outflow of blood through the aorta is obstructed by the movement of the mitral valve in the heart toward the intraventricular septum during the phase of the cardiac cycle known as systole (obstructive HCM), or whether the outflow of blood is simply less efficient (nonobstructive HCM). Obstructive HCM usually causes a heart murmur that a doctor can hear through a stethoscope during an office examination. The symptoms of both types of HCM are, however, similar, and both types are equally serious conditions.

Although most people with hereditary hypertrophic cardiomyopathy have no symptoms or report only mild occasional chest pains or shortness of breath, the condition can have major consequences. HCM can lead to life-threatening cardiac arrhythmias (abnormal heart rhythms). It is also the single most common cause of sudden cardiac death (SCD, which is unexpected death due to heart-related causes within an hour of symptom onset) among young athletes and a common cause of SCD in all age groups. In many people with HCM, sudden cardiac death is the first symptom of the disorder. Children as well as adolescents and adults with HCM can experience SCD, especially during exertion. It is most common, however, for the left ventricular hypertrophy associated

with HCM to become apparent in the patient's late teens or early twenties.

Genetic profile

HCM is inherited in an autosomal dominant pattern and is caused by mutations in any one of a number of genes that code for the proteins found in sarcomeres, which are the basic structures found in muscle cells. Sarcomeres are composed of alternating thick and thin protein filaments that alternately attach to and release from each other. This movement of the protein filaments relative to each other coordinates the contraction and relaxation of the heart muscle. Mutations in any of at least 22 different genes that code for various components of the sarcomere can lead to HCM, and over 1,500 mutations of these genes had been identified as of 2015. About 50%–60% of patients with clinical symptoms indicating HCM will have a mutation in at least one of nine sarcomere genes. The most common genes with mutations affecting the sarcomeres in cardiac muscle are as follows:

- **MYH7.** About 40% of mutations associated with HCM involve this gene, which codes for myosin, the major protein constituting the thick filament in cardiac sarcomeres. It is not clear, however, how mutations in the *MYH7* gene lead to the symptoms of HCM. The gene is located on the long arm of chromosome 14 at 14q12.
- **MYBPC3.** Another 40% of mutations found in patients with HCM involve this gene, located on the short arm of chromosome 11 at 11p11.2. It codes for a protein that provides structural support for the thick filaments in sarcomeres.
- **TNNT2.** About 5% of HCM mutations are associated with this gene, which codes for troponin, a protein found on the thin filaments in sarcomeres. This gene is located on the long arm of chromosome 1 at 1q32.
- **TPM1.** About 2% of cases of HCM are associated with mutations in this gene. It is located on the long arm of chromosome 15 at 15q22.1.
- **PRKAG2.** This gene codes for an enzyme that monitors the energy levels in cells. It is located on the long arm of chromosome 7 at 7q36.
- **TNNI3.** This gene codes for a protein found only in heart muscle that coordinates the contraction of the heart. It is located on the long arm of chromosome 19 at 19q13.4. Mutations in this gene account for about 57% of cases of HCM.
- **MYL3.** Mutations in this gene account for about 1% of known cases of HCM. It is located on the short arm of chromosome 3 at 3p21.31.
- **TTN.** This gene codes for a muscle protein known as titin or connectin. It is located on the long arm of chromosome 2 at 2q24.3.

- **MYL2.** The *MYL2* gene codes for a type of myosin that is found in the ventricular muscle of the heart. It is located on the long arm of chromosome 12 at 12q23-q24.
- **ACTC1.** This gene codes for a form of actin (the protein found in the thin filament of sarcomeres) that is found only in cardiac muscle. The gene is located on the long arm of chromosome 15 at 15q14.
- **CSRP3.** This gene codes for a protein that plays an important role in the production and differentiation of muscle cells. It is located on the short arm of chromosome 11 at 11p15.1.

Other genes with mutations that have been linked to HCM include the *MYH6* gene on chromosome 14 at 14q12, the *VCL* gene on chromosome 10 at 10q22, the *MYOZ2* gene on chromosome 4 at 4q26, the *JPH2* gene on chromosome 20 at 20q12, the *PLN* gene on chromosome 6 at 6q22.1, the *CALR3* gene on chromosome 19 at 19p13, the *NEXN* gene on chromosome 1 at 1p31.1, the *MYPN* gene on chromosome 10 at 10q21, the *ACTN2* gene on chromosome 1 at 1q43, the *LDB3* gene on chromosome 10 at 10q23, and the *TCAP* gene on chromosome 17 at 17q12. Given the high number of genes already known to be associated with HCM, it is highly likely that additional genes linked to the condition will be identified in the future.

Not all cases of HCM result from genetic mutations. Other causes include disorders that increase pressure within the heart, such as untreated hypertension or aortic stenosis (narrowing of the aorta). Other systemic diseases that may cause HCM include amyloidosis (accumulation of abnormally folded proteins called amyloids in the heart) and Fabry disease (a disorder in which fatty substances called glycolipids build up in the blood vessels and tissues of the heart).

Demographics

HCM is the single most common genetic disease of the heart in the United States, affecting about 1 in every 500 people or between 0.05% and 0.2% of the population. There were about 600,000 people in the United States with HCM as of 2015. Most cardiologists believe that the rate is similar worldwide. HCM is found in all races and ethnic groups and affects males and females equally.

Among athletes with HCM, African American athletes appear to be at greater risk of SCD than Caucasian or Asian athletes, but the reason for this difference is unclear.

Signs and symptoms

It is possible for a person with HCM to have no symptoms at all or to have sudden cardiac death as the

initial symptom. In families with a history of HCM, different members may vary considerably in the severity of the symptoms they report. Patients who do have symptoms usually report one or more of the following. It should be noted, however, that none of these is unique to HCM.

- **Dyspnea** (feeling short of breath or having difficulty breathing): This is the single most common symptom of HCM.
- **Syncope and presyncope**: Syncope refers to fainting and loss of muscle strength due to a decrease of blood flow to the brain, usually as a result of low blood pressure. Presyncope is a milder form of the condition in which the person does not completely lose consciousness or muscle strength but feels lightheaded and weak.
- **Angina**: Angina is a sensation of pain, squeezing, or pressure in the chest caused by a restriction in the blood supply to the cardiac muscle. Angina associated with HCM is typically increased by exertion.
- **Dizziness**.
- **Palpitations**: Palpitations are feelings or sensations that the heart is racing, beating irregularly, or pounding. They may be felt in the neck or throat as well as the chest.
- **Congestive heart failure (CHF)**: This condition is uncommon in HCM but is sometimes seen when the patient's left ventricle becomes stiff as well as abnormally thick. Stiffening of the ventricle lowers its ability to fill with enough blood to meet the body's needs, as well as reduces its ability to pump effectively.
- **Orthopnea**: Orthopnea refers to shortness of breath that occurs when a person is lying flat; for example, in bed trying to fall asleep.

The following factors increase a patient's risk of SCD: family history of SCD, recurrent episodes of syncope, prior history of cardiac arrest or ventricular fibrillation, thickness of the left ventricle equal to or greater than 30 mm (about 1.18 in.), and abnormal blood pressure readings during exercise.

Diagnosis

Clinical diagnosis

The diagnosis of HCM is based on a combination of a detailed family history as well as a history of the patient's symptoms, followed by an office examination and more detailed tests of heart function. When the doctor listens to the patient's heart through a stethoscope, he or she may hear various abnormal heart sounds, including a heart murmur, a double apical impulse, a split-second heart sound, and a so-called fourth heart sound.

No specific blood or urine tests are used to diagnose HCM. The diagnostic tests used most often are electrocardiography; echocardiography, in which two- or three-dimensional or Doppler ultrasound is used to create images of the heart; cardiac catheterization, in which a catheter is inserted into the left ventricle to determine the degree of outflow obstruction; and cardiac MRI, which is particularly useful when echocardiography does not give clear results. Cardiac MRI can also be used to evaluate the effectiveness of surgical treatments for HCM.

Genetic testing

Genetic testing for HCM is a complex process because of the sheer number of genes known to be associated with HCM. It is not ordinarily used simply to confirm a clinical diagnosis of HCM. It is also not used to screen large populations, such as student or professional athletes, because its use as a screening tool is not cost-effective.

In families with a history of SCD and other heart disorders that suggest HCM, genetic testing is considered a test of the family as a whole rather than of a specific individual. Such testing begins with the family member who best meets the diagnostic criteria for HCM. That person is then tested using a multigene panel. If a disease-causing mutation is identified, the next step is to test at-risk family members (usually first-degree relatives) for the family-specific mutation. Those who do not have the mutation do not need routine cardiac evaluation. Those who do have the mutation are asked to have cardiac evaluations at regular intervals. Family members are also usually asked to meet with the cardiologist and a genetics counselor to discuss the findings of the test and treatment recommendations.

Genetic testing for HCM also has limitations. About 30% of mutations causing HCM are *de novo*, which means that the mutation will not appear in other family members. In addition, not all persons diagnosed with HCM will have a mutation that can be identified with current testing strategies. Lastly, the identification of a disease-causing mutation cannot be used by itself to predict the age of onset of symptoms in a given individual or the outcome of treatment.

Treatment and management

There is no cure for HCM. Treatment and management of the disease is based on a combination of lifestyle modification, medications, and surgical interventions. The basic goals of treatment are to increase the volume of the left ventricle, increase the compliance (flexibility) of the ventricle, and increase the dimensions of the ventricle's

KEY TERMS

Actin—A protein that interacts with myosin during the process of muscle contraction.

Angina—A sensation of chest pain, squeezing, or pressure, usually arising from reduced blood supply to the heart muscle due to obstruction or spasm of the coronary arteries.

Atria (singular, atrium)—The two upper chambers of the heart.

Cardiac arrest—A sudden stop in the circulation of the blood due to the failure of the heart to contract effectively or at all. It is potentially reversible but if untreated can lead to sudden cardiac death.

Cardiomyocytes—The muscle cells that make up heart muscle tissue.

Cardiomyopathy—A thickening of the heart muscle.

De novo mutation—A genetic mutation that is seen for the first time in the affected person, not inherited from the parents.

Dyspnea—Shortness of breath or difficulty in breathing.

Hypertrophy—Increase in the size of a tissue or organ brought on by the enlargement of its cells rather than cell multiplication.

Mitral valve—The heart valve that lies between the left ventricle of the heart and the left atrium. It is also called the bicuspid valve because it has two leaves or flaps.

Myocardial disarray—A condition in which the cells in the heart muscle are aligned in a disorderly fashion rather than in parallel lines.

Myocardium—The medical term for the muscle of the heart.

Myosin—The most common protein in muscle cells, which interacts with actin during muscle contraction to form actomyosin.

Palpitations—Perceived rapid or abnormal heartbeats associated with awareness of the heart's contractions in the chest. Palpitations may be caused by anxiety, caffeine, some drugs of abuse, or certain prescription medications, as well as by structural abnormalities of the heart.

Sarcomeres—The basic functional units of striated muscle tissue. Sarcomeres consist of fibrous proteins that slide past each other as the muscle contracts and relaxes.

Septum—In anatomy, a wall of tissue that divides a body cavity or structure into smaller sections. The intraventricular septum is the tissue that divides the two lower chambers of the heart.

Sudden cardiac death (SCD)—A term used to describe an unexpected death due to cardiac causes that occurs within an hour of symptom onset in a person with known or unknown heart disease.

Syncope—A brief loss of consciousness caused by insufficient blood flow to the brain.

Systole—The rhythmic contraction of the heart, particularly of the ventricles, in which blood is pumped through the aorta and the pulmonary artery.

Ventricles—The two lower chambers of the heart. The right ventricle pumps blood to the lungs, and the left ventricle pumps oxygenated blood through the aorta into the general circulation.

outflow tract. The medications and surgical interventions used to treat adults are also used in children with HCM.

Lifestyle modification

Adults diagnosed with HCM must abstain completely from high-energy competitive athletic activity and such highly strenuous activities as shoveling snow or lifting very heavy objects. These precautions are necessary to lower the risk of sudden cardiac death. Other lifestyle modifications include maintaining a healthy weight and using alcohol only in moderation, as heavy drinking can trigger heart arrhythmias.

Children diagnosed with HCM require careful monitoring of their activities, particularly as they approach puberty. They should be given an annual echocardiogram

as they progress through puberty. They should also be advised to avoid competitive sports and strenuous activity.

Medications

The types of medications most often prescribed for patients with HCM are beta blockers, calcium channel blockers, and antiarrhythmic agents. Beta blockers, which include such drugs as propranolol, nadolol, sotalol, atenolol, and metoprolol, are given to slow the heart rate and reduce the heart's force of contraction. These drugs relieve palpitations, chest pain, and dyspnea.

Calcium channel blockers, which are also called calcium antagonists, improve the filling of the heart, lower blood pressure, and slow the heart rate. Verapamil is the drug in this class most often used to treat HCM.

QUESTIONS TO ASK YOUR DOCTOR

- How can you tell the difference between hereditary hypertrophic cardiomyopathy and other heart disorders that produce the same symptoms?
- Which diagnostic tests will you order to determine whether I have HCM or some other heart disorder?
- If I do have HCM, will you recommend genetic testing for me or for another family member?
- Do you think my HCM can be managed with medications, or will I need to have surgery?
- Will I have a normal life expectancy?

Antiarrhythmic drugs given to treat HCM include amiodarone, which is a very powerful medication with potentially severe side effects. It requires strict monitoring by the patient's physician. The other drug in this group is disopyramide, which can be used to help relieve obstruction in the obstructive form of HCM.

Some patients with HCM benefit from the use of diuretics to reduce fluid overload, although diuretics must be used with caution in patients with obstructive HCM. Some patients with a risk of blood clots in the atria (the upper chambers of the heart) are prescribed anticoagulants (blood thinners). Warfarin is the anticoagulant most often given to patients with HCM.

Surgery

Surgical interventions in the management of HCM are usually done when the patient's symptoms cannot be controlled by medications alone. Surgical treatment may include the following:

- **Septal myectomy.** This procedure involves open heart surgery to remove a portion of the intraventricular septum in order to decrease obstruction of the ventricle's outflow tract. It has been performed since the 1990s and has an 85% success rate. The risks of septal myectomy include bleeding, infection, perforation of the septum, stroke, and possible death.
- **Alcohol septal ablation** (also called catheter septal ablation). This is a technique invented by German surgeon Ulrich Sigwart in 1994. It involves the injection of 96% alcohol through a catheter into one or more branches of the left anterior descending artery. The alcohol causes infarction (tissue death) of some of the tissue in the intraventricular septum, thus reducing the

abnormal thickness of the septum. Alcohol septal ablation is in effect a controlled heart attack. It produces results similar to a septal myectomy but is less invasive because it does not involve opening the chest wall. It appears to be beneficial in older patients for whom a septal myectomy would be relatively risky. It is the procedure of choice for HCM in a growing number of medical centers.

- **Implantation of an ICD.** An implantable cardioverter defibrillator, or ICD, is a device that can be implanted in the patient's chest to lower the risk of sudden cardiac death. The device automatically recognizes and treats arrhythmias. It appears to be most useful in patients at high risk of SCD.
- **Heart transplantation.** Heart transplantation is the treatment of last resort for patients with HCM who do not benefit from medications or other surgical interventions. It is also the only option for patients in end-stage heart failure. The procedure has a high rate of success, with 94% of patients still alive seven years after transplantation.

Prognosis

The mortality rate for adults diagnosed with HCM has been variously reported as low as 1% per year to a higher rate of 3%–6% per year. In general, mortality rates in adults with HCM have improved since the 1970s, partly as a result of better diagnostic techniques and a higher index of suspicion, and partly as a result of more effective treatments. Most adults with HCM, particularly those with milder symptoms, will have a normal life expectancy with appropriate treatment and monitoring.

The prognosis for children diagnosed with HCM is better than was previously thought, largely as a result of improved recognition of the condition in its earliest stages. The mortality rate among children with HCM is about 1% per year, although a small subset has been reported as having a mortality rate of 4%–5% per year. Among adolescent athletes who die of SCD, the median age is 17 years, with basketball and football being the most common sports associated with SCD. Children who are not in this high-risk subgroup may have a normal life expectancy.

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ORGANIZATIONS

American College of Cardiology (ACC), Heart House, 2400 N St. NW, Washington, DC 20037, (202) 375-6000 or (800) 253-4636, (202) 375-7000, resource@acc.org, <http://www.acc.org>
 American Heart Association (AHA), 7272 Greenville Ave., Dallas, TX 75231, (800) 242-8721, <http://www.heart.org>
 Children's Cardiomyopathy Foundation (CCF), PO Box 547, Tenafly, NJ 07670, (866) 808-2873, (201) 227-7016, info@childrenscardiomyopathy.org, <http://www.childrenscardiomyopathy.org>
 Hypertrophic Cardiomyopathy Association (HCMA), 1450 Western Ave., Suite 101, Albany, NY 12203, (973) 983-7429, (973) 983-7870, support@4hcm.org, <https://www.4hcm.org>

Rebecca J. Frey, PhD

Hereditary iron-loading anemia see **X-linked sideroblastic anemia**

Hereditary multiple osteochondromas

Definition

Hereditary multiple osteochondromas (HMO), previously known as hereditary multiple exostosis (HME), refers to a group of disorders characterized by abnormal bone growth. The major symptom is the development of osteochondromas. Osteochondromas are classified as benign growths of bone tumors covered with cartilage that begin in the metaphysis of long bones and grow outward into the surrounding tissue. Osteochondromas typically produce pain and other complications by pressing on nearby tissue, they may limit movement of joints, and in some cases they must be surgically removed.

Description

An osteochondroma is a benign (noncancerous) bony growth. This does not refer to a normally shaped bone that has simply grown larger than normal. Rather, an osteochondroma is a bump, or nodule, of excess bone on a long bone, usually with overlying cartilage. That is why HMO is sometimes referred to as the "bumpy bones" disease. Other names for the disorder include multiple hereditary exostosis (MHE), multiple cartilaginous exostosis, osteochondromatosis, and diaphyseal aclasis.

People with HMO typically develop anywhere from several to many osteochondromas during their life, mostly during childhood and adolescence due to the growth of bone that occurs at this stage of life. Osteochondromas vary in size and can develop on most long bones in the body. An osteochondroma may present no signs or symptoms, or it may cause pain and other complications by pressing on nearby soft tissue (nerves, blood vessels, tendons, internal organs) or on another bone at a joint. Osteochondromas that do cause problems are often surgically removed. HMO can cause differences in the shape of bones or reduce their growth rate. Thus, people with HMO tend to be somewhat shorter than average and may have limited movement in certain joints. People with HMO are not at risk for tumor development in other tissues.

HMO is an autosomal dominant condition, and most people with the disorder have family members who are affected. A small percentage of people who carry an *HMO* gene do not develop any recognizable osteochondromas. The vast majority of osteochondromas are benign growths, but a small percentage can become malignant (cancerous chondrosarcoma).

Genetic profile

Three different types of HMO are known to exist: HMO type I, HMO type II, and HMO type III. There appear to be no obvious differences in the presentation and course of the disorder among the three types. Instead, the designations correspond to the three genes—*EXT1*, *EXT2*, and *EXT3*, respectively—that have been linked to HMO. The protein produced by the *EXT1* gene on chromosome number 8 is called exostosin-1, and the *EXT2* gene on chromosome number 11 produces exostosin-2. The *EXT3* gene is located on chromosome number 19.

HMO is an autosomal dominant condition, which means that any person who carries an *HMO* gene has a 50% chance of passing it on each time he or she has a child. Ninety percent of people with HMO have a positive family history. In the other 10% of cases, HMO occurred in that person for the first time as the result of a new mutation in one of the *EXT* genes. Regardless of whether someone inherits HMO from a parent or it occurs

KEY TERMS

Chondrosarcoma—A malignant tumor derived from cartilage cells.

Diaphysis—The middle portion, or shaft, of a long bone.

Epiphysis—The end of long bones, usually terminating in a joint.

Exostosis—An abnormal growth (benign tumor) on a bone.

Metaphysis—An area of softer bone and cartilage in long bones between the diaphysis (shaft) and epiphysis (end).

Osteochondromatosis—Another name for hereditary multiple exostoses, meaning a growth of bone and cartilage.

in him or her for the first time, each of that person's children is still at a 50% risk.

A tumor is the result of cells that undergo uncontrolled replication/division. People often equate the word “tumor” with cancer. However, a tumor is simply a growth, and it may be malignant (cancerous) or benign (noncancerous). Technically, osteochondromas are tumors, but they are nearly always benign.

EXT1 and *EXT2* belong to a class of genes known as *tumor suppressors*. In normal circumstances, tumor suppressor genes prevent cells from either replicating at all or replicating too quickly. If both copies of a tumor suppressor gene are mutated (inactivated), control of cell replication/division is lost. A person who inherits HMO type I or HMO type II already has one *EXT1* or *EXT2* gene inactivated from the moment he or she is conceived. However, abnormal bone growth does not occur unless the other gene of the pair also becomes inactivated. This second gene mutation, called loss of heterozygosity (LOH), appears to be an unlikely, random event, which explains why there is not abnormal growth throughout all of the bones. Only the occasional bone cell that undergoes LOH has a chance of becoming an osteochondroma. Any person without HMO can develop a single osteochondroma, and 2% of all people do. However, osteochondroma development is much less likely when two random mutations of an *EXT* gene in a bone cell must occur, rather than just one.

Demographics

The prevalence of HMO is estimated at about one in 75,000. There does not appear to be any significant

difference in prevalence between the major ethnic groups. Most studies have found that males with an *HMO* gene tend to have more obvious and severe symptoms than females. The reason for this is unknown. This makes it appear as though males are more likely to inherit HMO, when in fact they are just more likely to be diagnosed.

Most people with HMO have either HMO type I or HMO type II. Only a small percentage of HMO cases are linked to the *EXT3* gene. Further study of the *HMO* genes should establish an accurate prevalence for each type.

Signs and symptoms

About half of all people with HMO are diagnosed by the time they are three years old. Only 5% of newborns that carry an *HMO* gene show some signs at birth, but 95% of all people with the condition show noticeable signs by the time they are 12 years of age.

Osteochondromas primarily develop during the period of rapid bone growth from infancy through late adolescence. A small percentage of newborns already have noticeable osteochondromas at birth, and rare individuals with HMO may develop osteochondromas as adults. The number of osteochondromas varies from person to person, even within families. The average affected person develops six osteochondromas during his or her life.

Both the locations and sizes of osteochondromas vary. The most commonly affected bones are those of the arms (humerus, radius, and ulna), legs (femur, tibia, and fibula), hands (carpals and metacarpals), and feet (tarsals and metatarsals). Osteochondromas on the arm or leg nearly always develop near the joints (elbow, wrist, knee, or ankle) due to the fact that osteochondromas develop from the metaphysis, rather than in the middle of the long bones. About 70% of people with HMO have an osteochondroma or bone deformity around the knee. Flat bones, such as the scapula (shoulder blade) and pelvis, may be affected. The ribs and bones of the shoulder girdle occasionally develop growths, but osteochondromas are hardly ever seen on the spine or bones of the skull. Some osteochondromas under the skin may be barely noticeable to the touch (less than 1 cm in height), while others produce a noticeable bump (1–2 cm in height). Growths on the flat bones may be somewhat larger.

The most common problem in HMO is osteochondromas that cause compression and irritation of adjacent soft tissue, such as skin, nerves, and blood vessels. These types of growths can cause chronic pain until they are removed, and accidentally hitting them against something solid can be especially painful. Osteochondromas that

QUESTIONS TO ASK YOUR DOCTOR

- Am I/is my child a surgical candidate?
- How can I/my child prevent the osteochondroma from turning into a chondrosarcoma or worse?
- How often should I/my child be monitored for new growths?
- Will I/my child be able to play sports?

grow near the ends of long bones may interfere with normal movement of a joint. Many children with HMO have difficulties with their knees, both in range-of-motion and with angular deformities (“knock-kneed”). An uncommon, but more complicated problem is a large osteochondroma on the inside of the pelvis that results in compression of the intestine or urinary tract.

HMO affects the growth centers of bones (metaphyses and epiphyses), which can result in abnormal modeling (structure) of the affected bones. Reduction in size and bowing of bones are the most frequent structural anomalies seen. Consequently, people with HMO tend to be somewhat shorter than average—final height in men averages 170 cm (66 in.), while the average height in women is 160 cm (62 in.). Differential rates of growth between a child’s legs or arms can result in leg- or arm-length discrepancy, sometimes reaching 2 cm (1 in.) or more. Leg-length discrepancy can result in hip pain and problems with walking caused by tilting of the pelvis.

The most serious complication in HMO is the progression of a benign osteochondroma to a malignant (cancerous) state, known as a chondrosarcoma. This happens in slightly less than 1% of all people with the condition. Chondrosarcomas can develop in children, but those few cases that do occur are usually in adults. An undetected bone malignancy always presents a risk for metastasis—the spreading of cancerous cells elsewhere in the body—which is one of the most dangerous complications of any cancer. Most chondrosarcomas should be detected and treated early because they are usually associated with rapid growth of an osteochondroma accompanied by pain.

Diagnosis

The diagnosis of HMO is usually made when noticeable osteochondromas first appear. Any person who is at risk for the condition because of a family history is more likely to be accurately diagnosed at a younger age. The occurrence of a single osteochondroma in an otherwise

healthy person is not rare. Therefore, two or more osteochondromas must be present in order to make the diagnosis of HMO (although a single osteochondroma detected in someone who is known to be at 50% risk for HMO is highly suggestive of the diagnosis).

Osteochondromas are not always detectable by physical examination. Consequently, an x-ray study of the commonly affected bones (skeletal survey) in questionable cases is the best method of confirming or excluding the diagnosis. This is especially true in cases in which a child is known to be at risk for HMO (positive family history).

Unlike some genetic disorders with which many people with the condition have the same gene mutation, most individuals/families with HMO tested so far have had different mutations in either *EXT1* or *EXT2*. Therefore, while predictive or confirmatory genetic testing might be possible within a family (assuming the gene mutation is detectable), direct testing of *EXT1/EXT2* in a person with a negative or uncertain family history is not yet reliable enough to use as a diagnostic tool.

Treatment and management

The only treatment for osteochondromas that present problems is to remove them surgically. In those instances in which the osteochondroma is easily accessible, surgical removal is straightforward and carries very little risk. On the other hand, an osteochondroma that involves one of the joints or is less accessible—somewhere on the inner surface of the pelvis, for instance—may require involved surgery. A few people with HMO will never require surgical intervention, but most have at least one surgery, and some will have many. A child who is noted to have uneven or accelerated growth of a long bone in the arm or leg may be offered a procedure to straighten the bone or reduce its growth rate.

No external factors are known to cause or prevent the growth of osteochondromas. Those persons diagnosed with HMO, as well as children at risk, must be taught to monitor themselves for unusual changes in bone growth.

Anyone with HMO should have lifelong, periodic examinations by an orthopedic surgeon to look for and address any problematic osteochondromas and to screen for chondrosarcoma. Since osteochondromas and other bone-growth problems occur primarily in childhood, special attention, care, and education about their disorder is often needed for children with HMO.

Prognosis

The majority of people with HMO lead active lives, and their lifespan is not reduced. Surgery to remove

problematic osteochondromas will likely remain the primary method of treatment for some time. The hope is that further analysis of the *EXT* genes and their protein products will lead at some point to a more targeted approach to reducing or eliminating abnormal bone growths altogether.

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ORGANIZATIONS

MHE Coalition, 6783 York Rd. #104, Parma Heights, OH 44130, (845) 258-6058, <http://www.mhecoalition.org>

MHE Research Foundation, 8019 Harbor View Terrace, Brooklyn, NY 11209, (917) 848-7774, <http://www.mheresearchfoundation.org>

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Hereditary neuropathy with liability to pressure palsies

Definition

Hereditary neuropathy with liability to pressure palsies (HNPP) is a rare disease that can range in severity from benign to serious. It is characterized by swelling of the myelin sheath that leads to irritation of the nerves, particularly in the arms and legs. Many people who have the condition are unaware that they have it. For a small percentage of affected people, HNPP may be painful and debilitating.

Other names for HNPP include:

- tomaculous neuropathy
- compression neuropathy
- entrapment neuropathy
- familial pressure-sensitive neuropathy
- hereditary motor and sensory neuropathy
- inherited tendency to pressure palsies

Description

HNPP is characterized by episodes of numbness, tingling, and weakness in extremities. The physical sensations may be accompanied by physiologic symptoms such as foot drop, difficulty walking, and difficulty with fine motor skills such as writing. These episodes may vary in length and duration, occurring rarely or regularly and lasting anywhere from a few minutes to several weeks or months.

These episodes are called "pressure palsy" and are caused by nerve injury from routine activities, stretching, or repetitive motions. In individuals with HNPP, activities that would not injure others cause nerves to demyelinate, or to lose the protective covering. When this occurs, it leaves the nerves exposed and leads to the symptoms of HNPP. Eventually, the nerves may heal or remyelinate as the covering grows back, and the symptoms may subside.

In most individuals with HNPP, symptoms usually begin after adolescence. Episodes generally occur for a short period of time. Some people with HNPP have no symptoms, leading researchers to suspect that the condition may be more common than previously thought. Others may have an extreme form in which episodes are near continuous. In this event, the condition may become a permanent disability.

Genetic profile

HNPP is caused by mutations in the *PMP22* gene. Researchers are not certain of the exact function of this gene, but they suspect the *PMP22* gene is involved in production of myelin, the substance that provides a protective covering for nerves. It is likely that mutations in the *PMP22* gene affect myelin production, causing it to become unstable and leading to the symptoms of HNPP.

HNPP is inherited in an autosomal dominant pattern, which means an individual only needs to have one mutated copy of the gene for the condition to develop.

Demographics

HNPP is an extremely rare condition, affecting between 2 and 5 per 100,000 individuals. The estimated age range for observed symptoms is from 8 to 72 years.

KEY TERMS

Myelination—Production and maintenance of the myelin sheath.

Neuropathy—A general term for disorders of the nerves of the peripheral nervous system.

Neurotransmitters—Chemicals that relay signals between a neuron and another cell.

Paralysis—Complete loss of muscle function for one or more muscle groups, often with loss of feeling and mobility in the affected area.

Most occurrences of observed symptoms take place during the affected person's 20s and 30s.

Signs and symptoms

HNPP is characterized by numbness, tingling, and weakness of the extremities. The numbness may vary, occurring as a mild discomfort to some, while others experience significant numbness even describing it feeling as if “an arm has been deadened with Novocain.” Similarly, muscle weakness may be a mild irritant or a debilitating condition, varying from hand weakness to the inability to hold a pen and write, walk, or use the arm or leg.

The duration of symptoms may be highly variable as well. Some individuals experience only momentary discomfort, other have symptoms for periods of hours or days, and others still may have almost continuous symptoms that are so limiting the condition becomes a disability.

The cause of HNPP is a mutation that eliminates an important protein on gene *PMP22* on chromosome 17. The effect of this mutation is the swelling of the myelin sheath of the nerve cells in the peripheral nervous system. The myelin sheath serves as insulation for the axon, which is the cable of the nerve cell through which neurotransmitters run with messages from the brain to the muscular-skeletal system and from the muscular-skeletal system to the brain. Without the tight insulation of the myelin sheath, the neurotransmitters running through the axon are not contained, which interferes with effective neural communication.

How this neurological problem is manifested depends on the metabolism of the person affected and the severity of the event generating the emergence. When the symptoms are recurrent, they are not usually manifested in the same nerves as in previous episodes. The usual symptoms are numbness, pain, weakness, or paralysis. Some of those affected experience carpal tunnel

syndrome. Genetic researchers are particularly interested in HNPP because of its relationship with another, more common disorder. Charcot-Marie-Tooth disease (CMT) is caused by a duplication of the *PMP22* gene, whereas HNPP is caused by a deletion or mutation of that gene. The two disorders sometimes share symptoms and are often mistaken for each other.

Diagnosis

The diagnosis of HNPP begins with observing a patient who has recurring episodes characterized by numbness, pain, weakness, paralysis, or a combination of these. The diagnosis would also be dependent on a search of the family history for evidence that the condition may have been inherited.

The only sure diagnosis is a genetic screening that detects mutations in the *PMP22* gene.

Treatment and management

The main goal of treatment is to relieve the irritation of the nerve damage. Adaptive equipment such as wrist splints, protective pads for elbows and knees, and ankle-foot orthoses (braces) can relieve episodes. Prevention of the nerve pressure is the best treatment for those who have been diagnosed. Pacing is an important habit to develop, as it relieves pressure. Avoiding repetitive movements as well as staying in one position for any prolonged period is recommended.

Under extreme conditions, surgery to remove the compression on the nerve may be recommended. Many individuals with HNPP experience spontaneous remission, and their condition wanes without treatment. In such cases, surgery is unnecessary. Furthermore, surgery does not always bring results, and when it does, the results do not always last.

Many people with HNPP avoid any episode by maintaining good physical fitness. Once diagnosed, individuals with HNPP must avoid activities and conditions that could put undue pressure on the nerves. Activities that could become repetitive can be interchanged with other activities to reduce repetitive motion. People can avoid remaining in one position too long by getting up, stretching, or pacing.

Prognosis

There is no cure for HNPP. However, with conscientious maintenance, most affected people do not have any prolonged periods of troublesome episodes. Nerves destroyed in an episode eventually repair themselves. However, with increased episodes, the nerves take longer to repair.

QUESTIONS TO ASK YOUR DOCTOR

- What are the chances that I will have continuous episodes of HNPP?
- What adaptive equipment is best for me?
- How often do people with my condition become disabled?
- Would surgery help my condition?
- How do other people with my level of HNPP adapt their lifestyles?
- Should my relatives have testing for HNPP?

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ORGANIZATIONS

Foundation for Peripheral Neuropathy, 485 Half Day Rd., Suite 350, Buffalo Grove, IL 60089, (877) 883-9942, (847) 883-9960, <https://www.foundationforpn.org>

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Hereditary pancreatitis

Definition

Hereditary pancreatitis is a rare genetic condition beginning in childhood that is characterized by recurrent episodes of inflammation of the pancreas, causing intense abdominal pain, nausea, and vomiting. Most episodes

resolve on their own, but serious complications can arise, ranging from diabetes and poor digestion to bleeding, infection, pancreatic cancer, and death. Medical treatment can help alleviate some of the symptoms, and occasionally surgery may be needed to treat some of the complications.

Description

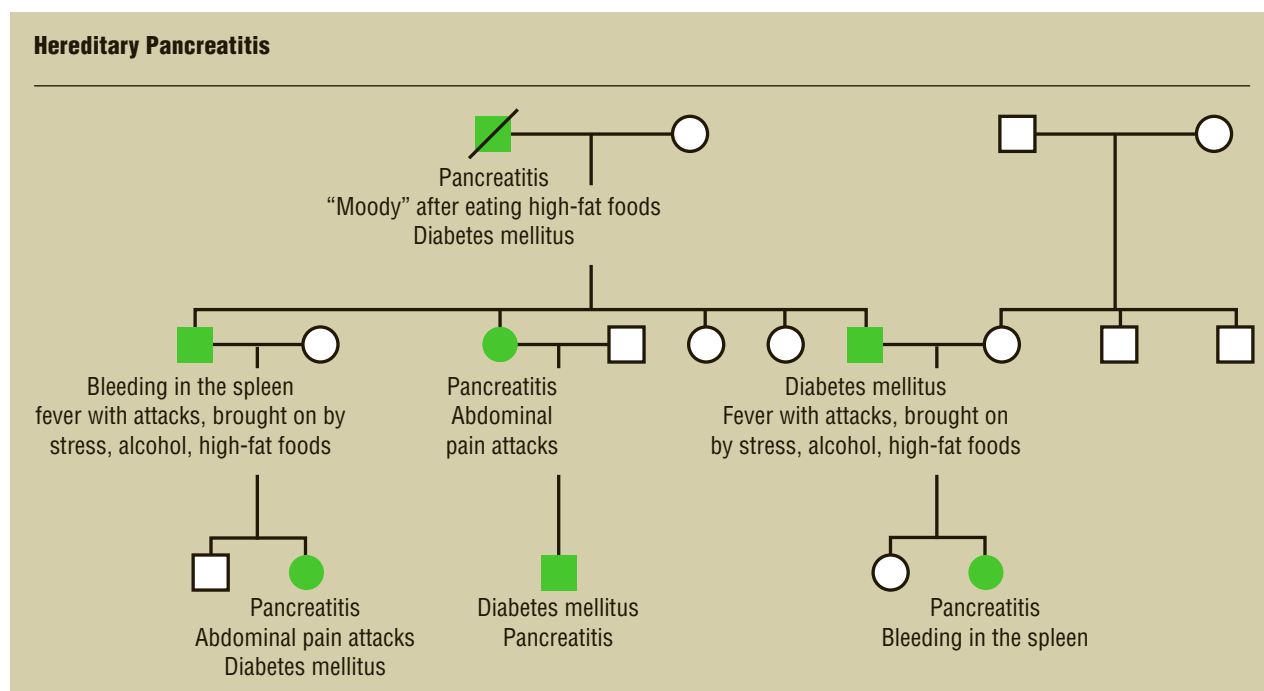
The pancreas is an organ located in the abdomen that has several functions. First, the pancreas aids in the digestion of food through the production of digestive enzymes. Digestive enzymes are proteins that break down food components, including sugars, fats, and other proteins, so that they can be absorbed and used by the body. Normally, the digestive enzymes are stored within the pancreas in an inactive form. In response to food intake, the enzymes are released from the pancreas and travel through the pancreatic duct into the small intestine, where they become activated and begin to digest food.

The second function of the pancreas is to maintain proper sugar balance in the blood. The pancreas produces several hormones, including insulin and glucagon, that are secreted into the bloodstream and act to increase or decrease sugar levels within the blood.

Pancreatitis is a condition in which the pancreas becomes irritated and inflamed. In most cases, the condition is caused by excessive alcohol use or by the presence of gallstones, but it can also be caused by medications, viral infections, injury to the abdomen, abnormal structures of the pancreas, and several metabolic disorders. In some rare instances, pancreatitis is caused by a genetic abnormality that is passed down from parent to child and is called hereditary pancreatitis.

In hereditary pancreatitis, an individual inherits a genetic abnormality in one of the digestive enzymes produced by the pancreas, called trypsin. Normally, trypsin is stored within the pancreas in an inactive state and only becomes activated when it travels to the small intestine and encounters food to digest. However, in individuals with hereditary pancreatitis, the trypsin becomes activated while still in the pancreas and begins to digest the pancreas itself, causing irritation and inflammation. Damage to the blood vessels in the pancreas can result in bleeding or fluid leaks from the blood vessel into the abdominal cavity. The digestive enzymes also gain access to the bloodstream through the damaged blood vessels and begin circulating throughout the body, causing further damage.

It is unclear what causes the abnormal trypsin enzyme to become activated and begin digesting the pancreas, but some studies have shown that emotional stress, alcohol, or fatty foods may trigger the process. After



Hereditary Pancreatitis: pedigree analysis chart. (Gale)

time, recurrent episodes of pancreatitis may leave the pancreas permanently irritated and damaged, a condition called chronic pancreatitis.

Genetic profile

Hereditary pancreatitis is a genetic disease and can be inherited or passed on in a family. The genetic abnormality for the disorder is inherited as an autosomal dominant trait, meaning that only one abnormal gene is needed to inherit the disease and that a parent with the disease has a 50% chance of transmitting the abnormal gene and disease to a child.

Changes in the gene for the digestive enzyme trypsin (located on human chromosome 7, at 7q35) are responsible for the disease, and more than five different genetic changes in the trypsin gene have been identified. Changes in other genes may also cause hereditary pancreatitis, as recent studies have discovered families with this condition with mutations in other genes, possibly on chromosome 12.

Demographics

The annual incidence of all forms of pancreatitis is about 1 per 10,000 people. However, hereditary pancreatitis is a rare cause of all pancreatitis and makes up only about 2% of the total cases. While the true prevalence of the condition is difficult to measure, it is estimated that

at least 1,000 individuals in the United States are affected by hereditary pancreatitis.

Approximately 100 different families with hereditary pancreatitis have been identified since the condition was first recognized in 1952. The largest concentration of hereditary pancreatitis in the United States is in the central Appalachian region, which extends from southern Ohio to eastern Kentucky and Tennessee, western Virginia and North Carolina, and northern Georgia.

Signs and symptoms

Hereditary pancreatitis begins with recurrent episodes of pancreatitis during childhood. The age of the first episode of pancreatitis may range from infancy to over 30 years old, but 80% of patients will show the first episode of pancreatitis before 20 years old, and the average individual shows a first episode at approximately 10 to 12 years old.

People who are experiencing an episode of pancreatitis have severe abdominal pain, nausea, and vomiting that is greatly worsened by eating. The pain is often described as steady and dull pain that is centered on the navel and may extend to the back. As a result of fluids that leak from the pancreas and surrounding vessels into the abdomen, the abdomen may swell.

The severity and duration of each episode may range from only occasional abdominal discomfort to prolonged,

KEY TERMS

Abscess—A localized collection of pus or infection that is walled off from the rest of the body.

Amylase—A digestive enzyme found in saliva or pancreatic fluid that breaks down starch and sugars.

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a non-sex chromosome is required for a disease or inherited trait to develop in an individual.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Diabetes—An inability to control the levels of sugar in the blood due to an abnormality in the production of, or response to, the hormone insulin.

Digestive enzyme—Proteins secreted by the pancreas that enter the small intestine and break down food so it can be absorbed by the body.

Gastroenterologist—A physician who specializes in disorders of the digestive system.

Hormone—A chemical messenger produced by the body that regulates specific bodily functions such as growth, development, and reproduction.

Insulin—A hormone produced by the pancreas that is secreted into the bloodstream and regulates blood sugar levels.

Intravenous—A route for administration of fluids, nutrients, blood products, or medications. A small flexible plastic tube is inserted into a vein by way of a needle to establish this route.

Lipase—A digestive enzyme found in pancreatic fluid that breaks down fats.

Nasogastric tube—A long flexible tube inserted through the nasal passageways, down the throat, and into the stomach. Used to drain the contents of the stomach.

Pancreas—An organ located in the abdomen that secretes pancreatic juices for digestion and hormones for maintaining blood sugar levels.

Pseudocyst—A fluid-filled space that may arise in the setting of pancreatitis.

Ranson criteria—A system of measurements, including age and blood testing, that can be used to predict the outcome of a person who has been hospitalized for an episode of pancreatitis.

Shock—An inability to provide the body with the oxygen it requires, sometimes due to large amounts of bleeding or fluid loss.

Trypsin—A digestive enzyme found in pancreatic fluid that breaks down proteins. This enzyme is abnormal in hereditary pancreatitis.

life-threatening attacks that appear to last for weeks. The number of attacks is also quite variable. For example, severe attacks may occur three or four times in a year followed by a year without attacks.

Most episodes of pancreatitis resolve without problems. However, certain complications can arise that may worsen the condition and threaten the life of the patient. Because of the loss of large amounts of fluid into the abdomen, circulatory shock may occur. Shock occurs when fluid leaks from blood vessels, leaving an insufficient amount of blood volume to provide the body with the oxygen that it needs. Prolonged lack of appropriate levels of oxygen causes damage to many different organs of the body. If not immediately treated, shock can lead to death.

Another complication of pancreatitis is the development of a fluid collection that contains decaying products of an inflamed pancreas and other substances. This fluid collection is called a pseudocyst. A pseudocyst can become life threatening if it becomes infected (abscess) or if the fluid collection ruptures into the abdomen.

Other dangerous and life-threatening complications of pancreatitis include severe bleeding from the pancreas (hemorrhagic pancreatitis), higher risk for the formation of blood clots, and a higher risk of serious infections in the abdomen or damaged pancreas. In addition, people with hereditary pancreatitis have a much higher risk of developing pancreatic cancer for reasons that are not clear. Studies indicate that people with hereditary pancreatitis are at least 53 times more likely to develop pancreatic cancer than the general population and that 40%–75% of people with hereditary pancreatitis will develop pancreatic cancer by the age of 70. Pancreatic cancer is very difficult to treat and is nearly always fatal.

Over time, recurrent episodes of pancreatitis may leave the pancreas permanently damaged and unable to carry out its routine functions. The absence of digestive enzymes normally secreted by the pancreas results in poor digestion, chronic diarrhea, weight loss, and malnutrition (5%–45% of people), leaving a person generally weakened. The pancreas may also become unable to

QUESTIONS TO ASK YOUR DOCTOR

- How is pancreatitis inherited?
- What are the treatments for hereditary pancreatitis?
- What is my risk of developing pancreatic cancer?

secrete insulin in the bloodstream normally, creating imbalances in blood sugar and causing diabetes in 10%–25% of people with hereditary pancreatitis.

Diagnosis

Hereditary pancreatitis is diagnosed through a combination of medical history, physical examination, and laboratory testing. The onset of abdominal pain consistent with pancreatitis before the age of 20 in multiple family members without any other risk factor for pancreatitis (drinking large amounts of alcoholic beverages, gallstones) suggests a diagnosis of hereditary pancreatitis. The medical history and physical examination of these individuals during an episode of pancreatitis will show abdominal pain, nausea, vomiting, and abdominal swelling.

Diagnosis of pancreatitis can be made by noting high levels of pancreatic enzymes (amylase and lipase) circulating in the blood. Further abnormalities in the blood that suggest pancreatitis include increased white blood cells, changes in the blood substances that occur with dehydration and fluid loss, and decreases in calcium levels.

Other diagnostic methods can be used to track the progress of the disease and monitor for any complications. X-rays of the abdomen may show deposits of calcium that occur in 50% of cases of hereditary pancreatitis. Also, the intestines may show signs of inactivity because of the nearby inflammation. Computed tomography (CT) scans of the abdomen may reveal the inflammation of the pancreatitis and are very useful in monitoring for complications such as pseudocyst, infections, and bleeding.

Genetic testing allows for the definitive diagnosis of hereditary pancreatitis by identifying abnormalities in the trypsin gene. However, these tests are currently used only for research purposes and are not generally available.

Treatment and management

There is no cure for hereditary pancreatitis. The goals for treatment consist of pain control, establishing

alternate routes of feeding and fluid administration, and prevention or control of complications.

A person experiencing an episode of pancreatitis is nearly always admitted to the hospital for treatment. Since drinking or eating by mouth often worsens the patient's condition, alternative routes are needed. Large amounts of fluid are given by a small tube placed in a vein (intravenous or IV fluids) to replace the fluid that has leaked into the abdomen. This IV route can also be used to administer nutritional products and medications to relieve pain.

Fluids and acid that are produced by the stomach can worsen a patient's condition and increase pain. In order to drain these fluids, a small, flexible tube is inserted through the nose, down the throat, and into the stomach (nasogastric tube). The tube is then connected to a weak vacuum to remove the contents of the stomach. Complications may arise in the setting of pancreatitis. Bleeding may require administration of donor blood products by vein, while infections are treated using antibiotics also given by vein. Abscesses, large pseudocysts, or decaying portions of the pancreas may require drainage with a needle or may need to be removed surgically. People with a permanently damaged pancreas may require digestive enzyme supplements by mouth to assist with digestion and insulin injections to control diabetes.

People diagnosed with hereditary pancreatitis should be seen regularly by a team of healthcare professionals, including a primary-care physician, gastroenterologist, and medical geneticist. Individuals with this condition should refrain from drinking alcohol and avoid fatty foods. They may benefit from consultation with a licensed nutritionist.

Prognosis

Several systems have been developed to predict the outcome for people who are experiencing an episode of pancreatitis. The most widely used system utilized by health professionals is called "Ranson criteria," which utilizes a list of measurements that are determined during the first two days of the hospital stay.

In general, children who experience an episode of pancreatitis do well and are released from the hospital in three to five days. However, the development of any of the complications of pancreatitis worsens the prognosis and will likely result in a longer hospital stay. In the extreme, severe complications of pancreatitis can even lead to death.

Most people with hereditary pancreatitis will develop permanent damage to the pancreas as they grow older. Half of people will require surgery, and up to one-fourth will develop diabetes by the age of 70. Of even greater

concern, a significant percentage will develop pancreatic cancer, a diagnosis that is nearly always fatal within several years.

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National Pancreas Foundation, 3 Bethesda Metro Center, Suite 700, Bethesda, MD 20814, (301) 961-1508 or (866) 726-2737, (301) 657-9776, info@pancreasfoundation.org, <http://pancreasfoundation.org>

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Hereditary spastic paraplegia

Definition

Hereditary spastic paraplegia (HSP) is not a single entity, but a group of clinically and genetically diverse hereditary degenerative disorders that have in common degeneration of the corticospinal tracts and posterior column tracts in the spinal cord. Patients with HSP consequently suffer from severe and progressive weakness and spasticity in the legs and feet. The corticospinal tracts are made of nerve fibers that convey motor information from the brain to the limbs. The posterior column carries sensory information regarding position sense from the arms and legs to the brain. The fibers that carry motor information to the legs are more often affected than those of the arms, resulting in progressive stiffness and

weakness of leg, thigh, calf, and lumbar spinal muscles. The age of onset, extent of degeneration, and severity of symptoms vary among affected people, even those in the same family. Some families show a pattern of disease called anticipation, with symptoms developing earlier in each new generation. In most individuals, however, the disease onset occurs between the second and the fourth decades of life.

Description

Dr. Adolf von Strümpell, a German neurologist, first described this disease in 1883. He was followed by Maurice Lorrain, a French physician, which explains why another name for HSP is Strümpell-Lorrain syndrome. Other names for this disorder are hereditary spastic paraparesis, Strümpell disease, familial spastic paraparesis, spastic spinal familial paralysis, hereditary Charcot disease, silver syndrome, French settlement disease, and Troyer syndrome. When the only manifested symptom is progressive spasticity, HSP is also known as pure hereditary spastic paraplegia.

People with early symptoms of HSP may notice only mild stiffness in the lower legs and some difficulties with their gait. As the disease progresses, they will require assistive devices like canes, walkers, or wheelchairs. They may also experience disturbances of urinary bladder function. Patients with complicated HSP develop such additional symptoms as cataracts and other visual disorders, epilepsy, deafness, ataxia, and dementia or other forms of cognitive impairment.

Genetic profile

There were over 76 genetic loci linked to different types of HSP as of 2015, and the mode of inheritance is known for 38: 18 types are inherited in an autosomal dominant pattern, 17 in an autosomal recessive pattern, and 3 in an X-linked pattern. The risk of an individual's inheriting an abnormal gene depends on the mode of transmission and whether the mutated gene is present on a sex chromosome or an autosome. Mutations in a number of different genes can result in a similar phenotype of HSP; this phenomenon is known as genetic heterogeneity. These genes are generically known as spastic paraplegia genes, or SPGs; 59 different SPGs had been identified as of 2015.

SPGs are thought to contain genetic information regarding proteins that help in microtubule formation and function. Some SPGs are known to code for such proteins as spastin and atlastin-1. Spastin helps to regulate the length of microtubules while atlastin-1 fuses microtubules together to form a network that makes up the endoplasmic reticulum of neurons (nerve cells). Microtubules combine

to form the protein framework of a nerve cell and their dysfunction leads to degeneration of the nerve cells. Other SPGs appear to be associated with mitochondrial dysfunction, leading to loss of protein quality.

HSP can be complicated when other neurological impairments are seen in addition to spasticity; or they may be uncomplicated. Uncomplicated or pure HSP is inherited as an autosomal dominant mutation in about 70% of cases, but the mutated gene varies from one family to another.

Autosomal dominant HSP

This is the most common form of HSP inheritance, with the mutated gene present on an autosome (non-sex chromosome). Only one copy of the abnormal gene is required to produce the disease. There is a 50% chance that an affected person will transmit the gene to an offspring. The disease can be present in both males and females; it can be transmitted from either the mother or the father to a son or a daughter, and there is usually an affected family member in each generation. Exceptions to the latter rule occur when the disease presented with very mild symptoms in earlier generations and was misdiagnosed as arthritis or walking difficulty due to old age. Also, the affected person might have died prior to manifesting full-blown symptoms. SPGs for autosomal dominant types of HSP have been identified on chromosomes 1p at 1p31.1 (gene presently unknown), 2p at 2p22.3 (the *SPAST* gene), 2p at 2p11.2 (the *REEP1* gene), 8q at 8q24.13 (the *KIAA0196* gene), 9q (gene presently unknown), 10q at 10q23.3 (gene presently unknown), 12q at 12q13.3 (the *KIF5A* gene), 14q at 14q22.1 (the *ATL1* gene), 15q at 15q11.2 (the *NIPA1* gene), 19q at 19q13.32 (the *RTN2* gene), and 20. In more than 50% of cases, the two most common gene mutations identified are on chromosome 2p and chromosome 14q, and are called the *spastin* and *atlastin-1* genes, or *SPAST* and *ATL1* genes. In complicated autosomal dominant HSP, one identified gene is on chromosome 10q. In a rarer form of infantile onset-ascending HSP, there is a deletion mutation in the *ALS2* gene at 2q33.1.

Autosomal recessive HSP

In autosomal recessive HSP, the mutant gene is present on an autosome. Two copies of the abnormal gene (one of maternal and one of paternal inheritance) are required for disease expression. Both males and females can express the disease and also transmit the abnormal gene. A mutant HSP gene that is recessive can be passed down silently for generations until someone finally inherits the recessive gene from both parents and develops the disorder. The parents of the affected person are called carriers, as they carry only one copy of the abnormal gene and do not express the disease. If a mother and father are

carriers for a recessive HSP gene mutation, each of their children has a 25% chance of developing HSP, a 50% chance of being a carrier, and a 25% chance of being normal. It is unlikely for individuals with autosomal recessive HSP to have children with the disorder, because their spouse would have to have the disorder or be a carrier. This possibility is more common in consanguineous marriages (i.e., marriage between cousins).

SPGs associated with this pattern of inheritance are located on chromosomes 2q at 2q37.3 (the *KIF1A* gene), 6q at 6q23 (gene currently unknown), 8p at 8p11.23 (the *ERLIN* gene), 8q at 8q12.3 (the *CYP7B1* gene), 10q at 10q22.1 (gene presently unknown), 13q at 13q14 (gene presently unknown), 13q at 13q13.3 (the *SPG20* gene), 14q at 14q22.1 (the *PAPLA1* gene), 15q at 15q21.1 (the *SPG11* gene), or the *SPG7* gene on 16q at 16q24.3. One form of autosomal recessive HSP, Troyer syndrome, is associated with the SPG on chromosome 13q.

X-linked HSP

X-linked HSP is a rare form in which the mutant genes are located on the X chromosome at Xq28, Xq11.2 (gene not currently known), Xq13.2 (the *SLC16A2* gene), or Xq22. Transmission is usually through the mother; the risk of inheriting this mutated gene and expressing the disease depends on the patient's gender. Women with an X-linked mutant HSP gene are generally not affected by the disorder; or if they are affected, they usually have less severe symptoms than males. Each son of a woman who is a carrier for X-linked HSP has a 50% chance of developing HSP. Each daughter of a woman who is a carrier for X-linked HSP has a 50% chance of being a carrier (female carriers of X-linked disorders often have no symptoms).

Sporadic HSP

In some instances, a definite mode of inheritance cannot be identified when there is no other affected family member. This difficulty can occur if the inheritance pattern has been autosomal recessive or X-linked, as it can skip generations, remain silent, and suddenly appear in the present generation. Also, the disease could have been milder (incomplete penetrance) and undiagnosed in prior generations; or the affected persons could have died prior to full symptom onset. Due to the phenomenon of anticipation, a child may exhibit symptoms even before the parent. Truly sporadic HSP is rare; it is caused by a new mutation occurring only in the affected individual.

Demographics

As usually happens with other rare neurological diseases, HSP symptoms may overlap or be mistaken for

KEY TERMS

Anticipation—A genetic phenomenon in which the symptoms of a disease appear at an earlier age in each successive generation.

Ataxia—Lack of coordination of voluntary muscle movements.

Atlastin-1—A protein encoded by the *ATL1* gene that is important in building and maintaining the structure of the endoplasmic reticulum in the nerve cells of the brain and spinal cord.

Autosome—Any chromosome that is not a sex chromosome.

Clonus—Involuntary rhythmic muscular contractions and relaxations.

Contracture—A tightening of muscles, usually near a joint, that prevents normal movement of the associated limb or other body part.

Endoplasmic reticulum—A network of flattened membranes and tubules within the cytoplasm of a cell that synthesizes and transports lipids (fats) and proteins.

Gait—A person's habitual pattern of walking, or the pattern of movement of his or her lower limbs.

Genetic heterogeneity—The production of apparently identical disorders by genes at different loci or by different genetic mechanisms.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Paraplegia—Impairment in the sensory or motor functions of the lower limbs.

Paresthesias—The medical term for prickling, burning, or “pins-and-needles” sensations.

Spasticity—Tightness, stiffness, increased muscle tone, or sustained involuntary contractions of the muscles.

Spastin—A protein encoded by the *SPAST* gene that regulates the length of microtubules and dissolves microtubule structures that are no longer needed.

Sporadic—Occurring randomly in the population with no known or apparent cause.

those of other neurodegenerative disorders. Consequently, HSP incidence is only estimated and is thought to be approximately 3 cases out of 100,000 individuals in the United States and Europe. Between 10,000 and

20,000 people in the United States are estimated to have this disease, of which about 10% have the complicated form of HSP. Ninety percent of HSP cases are uncomplicated and the patient's life expectancy is unaffected.

As far as is known, HSP occurs in all races and ethnic groups worldwide.

Signs and symptoms

Previously, HSP was classified into early-onset (type I) HSP and late-onset (type II) HSP. In type I, symptoms of spasticity occurred prior to age 35 but progressed slowly. In type II HSP, symptom onset occurred after age 35 with weakness, spasticity, mild sensory loss, and bladder problems, and the disease progressed faster. This classification is confusing as both early- and late-onset disease can occur in the same family due to the phenomenon of anticipation. Therefore, categorization into uncomplicated (pure) and complicated HSP is considered a more specific and useful distinction.

Uncomplicated HSP

Pure or uncomplicated HSP is usually inherited in an autosomal dominant pattern. It may start at any age, mostly in the second to fourth decades, but can also occur in infancy, early childhood, or old age. Mutations in the *ATL1* gene cause childhood-onset autosomal dominant HSP, also known as spastic paraplegia type 3A; and a defective *SPAST* gene causes the adult-onset form known as spastic paraplegia type 4. In children, the disease progresses until adolescence and then stabilizes, resulting in partial disability in walking. Complete paralysis of the legs is rare in uncomplicated HSP, regardless of age of onset.

Progressive difficulty walking is the main problem and occurs due to taut and weak muscles. This difficulty manifests initially as stumbling, stubbing the toe, catching the feet on uneven surfaces and sidewalks, clumsy gait, or difficulty with balance. The muscles that are most commonly affected include those on the inner side, front, and back of the thighs and calves, leading to difficulty with hip and ankle flexion. This distorted gait can lead to uncontrollable shaking (clonus) of the feet and scissoring of the legs while walking. Often the changes are so slowly progressive that patients do not notice subtle symptoms for several years. Arms are affected to a much lesser degree. Spasticity is worsened by cold, high humidity, emotional stress, and infections.

Other common symptoms include urinary urgency and frequency, hyperactive tendon reflexes, diminished vibration and position sense in the feet, leg paresthesias, muscle spasms, cramps, and pain. Muscles can atrophy at a late stage. High-arched feet (*pes cavus*) and bunions

QUESTIONS TO ASK YOUR DOCTOR

- How can you tell the difference between HSP and other conditions that resemble it?
- When should a person suspected of having HSP consider genetic testing?
- When should other family members be tested for HSP?
- Are there medications or treatments that will help to slow the progress of HSP?
- What resources are available for patients with HSP?

can occur due to imbalance in the strength and tone of muscles that maintain proper alignment of bones in the feet.

Complicated HSP

Complicated HSP is usually inherited in an autosomal recessive pattern with symptom onset between two and 16 years of age. Symptoms are progressive and may be associated with other neurological conditions, such as epilepsy, mental retardation, peripheral neuropathy, ocular degeneration such as retinopathy, and/or the destruction of the optic nerve. Other clinical complications are ataxia (loss of coordination), dysarthria (difficulty speaking), deafness, nystagmus (involuntary eye movements), decreased functioning of the adrenal glands, and ichthyosis (abnormal dryness, scaling, and thickening of the skin). However, these neurological symptoms may be caused by other disorders present at the same time. For instance, a person with uncomplicated HSP may have peripheral neuropathy due to diabetes.

Diagnosis

A detailed personal and family history along with physical and neurological examinations is the first tool in HSP diagnosis. The physician will conduct comparative examination of muscle tone and strength between arms and legs and look for signs of weakness in specific muscle groups of the thigh, presence of abnormal increase of deep tendon reflexes in the legs, loss of ankle flexibility, and decrease of sensation in the legs. A thorough clinical examination is vital to avoid misdiagnosing other conditions like vitamin B₁₂ deficiency, vitamin E deficiency, amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), and tropical spastic paraparesis, all of which mimic HSP.

Genetic screening for various SPGs is the definitive test to avoid misdiagnosis and is commercially available. The University of Michigan Neurogenetic Disorders Clinic is the largest clinical and research program for HSP in the United States, and one of the few that offers comprehensive evaluation, including genetic testing. As of 2015, there were several laboratories in the United States and Europe that offered molecular genetic testing for panels of genes associated with HSP; the number of genes tested in these panels ranged from 10 to 40 different genes. Other ancillary tests like nerve conduction studies, spinal tap, magnetic resonance imaging (MRI), and blood tests help to exclude some of the other mimickers of the disease.

Treatment and management

There was no curative or preventive treatment for HSP as of 2015. Symptomatic treatment for muscle spasm and spasticity includes oral medications like baclofen, tizanidine, and benzodiazepines like diazepam to relax muscles and decrease the intensity of spasms. Major side effects from these drugs include confusion, dry mouth, drowsiness, and sedation. Symptomatic treatment for painful neuropathy includes medications like gabapentin and the selective serotonin reuptake inhibitors (SSRIs) or the tricyclic antidepressants. Medications like oxybutynin can help in treating an overactive bladder. Baclofen can also be administered through a mechanical pump implanted in the space around the spinal cord to minimize systemic adverse effects.

Newer approaches involve the local injection of botulinum toxin (Botox) into the spastic muscles to reduce muscle hyperactivity; the effect tends to last three to six months after an injection. Surgery may be necessary to relieve tendon contractures and to lengthen spastic muscles. An electrical stimulator device implanted in the nerves near the tailbone can help in stimulating the bladder for complete urinary evacuation. A newer medication being tried for treatment of HSP is dalfampridine (Ampyra), a drug used in the United States since 2010 for the treatment of multiple sclerosis.

Supportive care includes physical therapy, which helps to improve muscle strength and range of motion, and prevent joint contractures and bedsores. Therapies may include stretching, strengthening and aerobic exercises, balance and coordination training, gait training (including a new approach that uses robots as gait trainers), and appropriate use of such assistive devices as canes, braces, and walkers. Treatments can also include such techniques as massage, ultrasound, electrical stimulation, or whirlpool treatments. Exercise also enhances the patient's sense of well-being and reduces stress and depression.

Prognosis

The prognosis of HSP varies widely, but most often it is compatible with a normal life expectancy. The rate of progression varies considerably and is influenced by the mode of inheritance. Some patients have serious disability not only from the spasticity but also from associated neurological problems. Others have very mild disability and can lead a very productive and almost normal life. Complications arising from falls and immobility, however, may inadvertently shorten a patient's life.

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National Institutes of Health/National Institute of Neurological Disorders and Stroke (NINDS), PO Box 5801, Bethesda, MD 20824, (301) 496-5751 or (800) 352-9424, <http://www.ninds.nih.gov>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Spastic Paraplegia Foundation, 1605 Goularte Place, Fremont, CA 94539, (877) 773-4483, <http://www.sp-foundation.org>

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Hereditary spherocytosis

Definition

Hereditary spherocytosis (HS) is a relatively common and highly variable inherited disorder of the red blood cells. In HS, red blood cells become sphere-shaped instead of the usual biconcave (hourglass) shape. The hourglass shape is vital for the blood cells to function—it offers increased surface area so that oxygen

and carbon dioxide can diffuse more easily through the cell's tissue, and the shape lets the cells circulate more easily in tight places, like small capillaries. These spherocytes are broken down more quickly than normal red blood cells, resulting in anemia and related complications.

Description

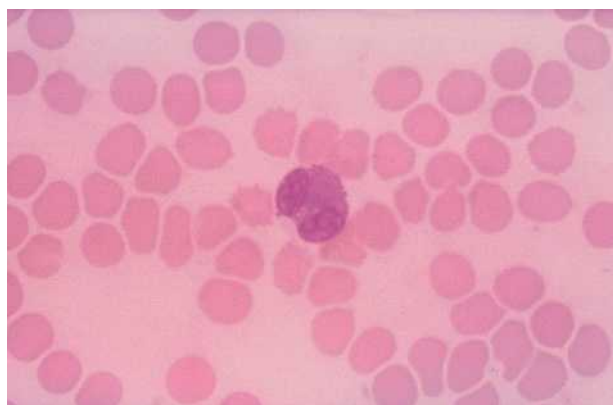
Hereditary spherocytosis results from a molecular change in one of the proteins making up the cytoskeleton of the red blood cell, which consists of the network of proteins that support and maintain the integrity of the red cell membrane. Genetic mutations in membrane proteins lead to loss of these and related membrane components. As the membrane becomes unstable, and the surface area of the membrane decreases, spherocytes form. The spleen provides an environment that encourages spherocyte breakdown. Due to their increased rigidity, spherocytes tend to become trapped in the spleen and then broken down by macrophages, which are specialized white blood cells. This hemolytic process most often leads to mild, chronic anemia. Depending in part on the particular genetic mutation underlying HS in a given individual, anemia can be severe and can require chronic blood transfusions. Additional complications related to anemia can arise.

Genetic profile

About 75% of all cases of HS are due to the presence of an autosomal dominant mutation, one in which the mutated gene is passed on from either parent. Most of these cases result from the inheritance of a mutation from one parent, but one in four of these cases is sporadic and due to a new mutation that has occurred in the affected individual. A minority of cases of HS are recessively inherited. HS-causing mutations have been described in four genes, each of which codes for a protein involved in maintaining stability of the red blood cell membrane. The cytoskeleton can be thought of as a "scaffolding" or "frame" that is attached to and maintains the "wall" that is the cell membrane. The red blood cell membrane is made up of lipids, which are fat and fat-like molecules, and proteins called integral membrane proteins. The cytoskeleton lies just below the cell membrane and is made up of additional proteins, including spectrin, ankyrin, protein 4.1, and others.

Ankyrin

The ankyrin gene is located on the short arm of chromosome 8 (8p11.2). A total of 34 mutations in the ankyrin gene have been associated with HS. These account for 35% to 65% of all HS cases, including both



Light micrograph showing the abnormal round convex blood cell of hereditary spherocytosis. (Biophoto Associates/Science Source)

dominant and recessive forms. Dominant-acting mutations tend to be those that result in a shortened ankyrin protein, including so-called frameshift and nonsense mutations. Recessive-acting mutations tend to be those that result in subtler changes to the protein. These include so-called missense mutations, which result in the substitution of a single amino acid—the building block of proteins—which can have an effect on protein function. Recessive mutations also include those in the area “upstream” from the gene, in the promoter region that helps to determine the quantity of protein made from the gene. Rarely, spherocytosis can be one symptom within a larger syndrome that is due to a deletion of a portion of chromosome 8. Such a microdeletion syndrome can affect several genes, including the ankyrin gene, and there can be a range of physical and mental effects.

Spectrin

Spectrin is a cytoskeleton protein made of two components: alpha spectrin and beta spectrin. Two recessive mutations have been identified in the alpha spectrin gene on chromosome 1. This recessive form of the disease tends to have relatively severe hemolytic anemia. Nineteen mutations have been described in the beta spectrin gene on chromosome 14. These result in dominantly inherited HS.

Band 3 and others

Mutations in the gene for band 3, an integral membrane protein, account for 15% to 25% of all cases of HS. Five dominant mutations have been described, most of which result in a shortened protein. Disease-causing mutations in other cytoskeleton or red cell membrane proteins are rare but have been described.

Modifying genetic factors

Disease severity is affected not only by the nature of the primary genetic mutation but also by other genetic variations. Individuals with HS who also have Gilbert syndrome have an increased risk of gallstones. Gilbert syndrome is caused by a change in the UGT 1A1 gene that results in increased levels of bilirubin. Researchers have also hypothesized that persons with other inherited or acquired forms of hemolytic anemia may also be at increased risk of gallstones if they have a disease-causing HS mutation. The presence of hereditary hemochromatosis in addition to HS increases the propensity toward iron overload. Hereditary hemochromatosis is a relatively common recessive condition that can lead to organ failure due to iron overload if untreated.

Demographics

HS has been seen in individuals of many ethnic backgrounds but is particularly common among people of northern European backgrounds, affecting about one in 2,000 of such individuals.

Signs and symptoms

Symptoms of HS can be extremely variable. Some individuals may experience onset as early as the neonatal period and require treatment. Others may have only mild anemia that does not require treatment and does not become evident until later in life. Some individuals with few and subtle signs may even go undiagnosed. Variability is largely influenced by the primary underlying genetic mutation, with the recessive forms of the disease tending to be most severe. This does not account for all of the variability, however, given that multiple affected individuals within the same family who carry the same genetic mutation may have symptoms of varying severity. The effects of modifying genes or environmental factors may contribute to this additional variability.

Anemia

The red blood cell membrane has increased fragility in HS. Therefore, red cells are more easily broken down, a symptom called hemolytic anemia, which occurs primarily in the spleen. The spleen filters out old and abnormal red blood cells and fights infection from bacteria, particularly the encapsulated type. Anemia can be unnoticeable or mild, or it can be rapid and severe. Rapid, acute breakdown of red blood cells can occur as a result of exposure to chemicals or medications that are known to further increase red blood cell membrane fragility. It can also occur as a result of infection that increases the hemolytic activity of the spleen or decreases red blood cell production. Acute aplastic anemia events, in which red

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Bilirubin—A yellow pigment that is the end result of hemoglobin breakdown. This pigment is metabolized in the liver and excreted from the body through the bile. Bloodstream levels are normally low; however, extensive red blood cell destruction leads to excessive bilirubin formation and jaundice.

Cytoskeleton—The network of proteins underlying and maintaining the integrity of the red blood cell membrane.

Encapsulated—Referring to bacteria that have a thick capsule protecting their cell wall.

Hemochromatosis—Accumulation of large amounts of iron in the tissues of the body.

Hemoglobin—A protein-iron compound in the blood that carries oxygen to the cells and carries carbon dioxide away from the cells.

Hemolytic—Refers to the type of anemia caused by the breakdown of red blood cells, as compared to anemia due to decreased production, for example.

Macrophage—Specialized white blood cells that play a role in breaking down old or abnormal red blood cells.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Red blood cell—A hemoglobin-containing blood cell that transports oxygen from the lungs to tissues. In the tissues, the red blood cells exchange their oxygen for carbon dioxide, which is brought back to the lungs to be exhaled.

Reticulocyte—Immature red blood cells.

Spherocytes—Red blood cells that are spherical in shape, as compared to the normal biconcave shape. Spherocytes are more rigid, and their membranes are more fragile than normally shaped red blood cells.

Spleen—An organ located in the upper abdominal cavity that filters out old red blood cells and helps fight bacterial infections. It is responsible for breaking down spherocytes at a rapid rate.

blood cell production halts, can occur with deficient folate levels or following infection by a specific virus called parvovirus.

According to a recent study by Yale physicians, a novel mutation in the gene that encodes alpha-spectrin, a protein that is essential for normal red blood cell membranes, is responsible for many cases of recessive hereditary spherocytosis (rHS), the most severe form of the disease. Alpha-spectrin provides both strength and flexibility to red blood cell membranes, helping cells maintain their shape and integrity while making their circuit through the body. Cells without sufficient alpha-spectrin in their membranes suffer membrane damage and will lose strength and flexibility. These damaged, alpha-spectrin-deficient red blood cells are then trapped and destroyed by the spleen. The excessive removal of damaged red blood cells leads to anemia, which in some cases is life-threatening. The clinical implication for this finding is that it will update commercially available diagnostic gene panels used to screen DNA for HS mutations. These improved gene panels can assist providers in selecting the most effective treatment options, as splenectomy sometimes fails in patients with rHS, who may

instead require a hematopoietic stem cell transplant. Finally, better gene panels will allow for more accurate genetic counseling for prospective parents with family histories of HS.

Jaundice

Jaundice occurs when the level of bilirubin, a breakdown product of hemoglobin, increases. As red blood cells break down rapidly, the liver may not be able to keep up with the increased need to metabolize bilirubin, which can deposit in the skin and eyes, causing a yellowish discoloration.

Gallstones

Bilirubin levels can also be increased in the bile, which is the fluid secreted by the liver into the intestine. Bile reaches the intestine by passing through the gallbladder and bile duct. Excess bilirubin can form stones in the gallbladder early in life.

Hemochromatosis

Hemochromatosis, or high iron levels, is characteristic of HS. Iron overload can lead to dysfunction of organ

QUESTIONS TO ASK YOUR DOCTOR

- If I suspect that hereditary spherocytosis may be somewhat common in our family, should I see a genetic counselor about being tested for the disorder?
- Under what circumstances would a splenectomy be indicated for the treatment of hereditary spherocytosis?
- What is the prognosis for hereditary spherocytosis?
- Is it necessary for a person with hereditary spherocytosis to monitor the status of his or her disease on a regular basis, and if so, what kind of tests or treatments are recommended?

systems, including the endocrine system, which directs hormone levels.

Other complications

Leg ulcers are seen in HS, and acute kidney failure due to hemolytic anemia is a rare complication. Rarely, HS can be seen within a syndrome as one symptom in combination with other complications such as neurological problems and other congenital physical differences. Such syndromes may be caused by the deletion of a portion of a chromosome including a gene known to be associated with HS, among other genes.

Diagnosis

HS must be distinguished from other causes of hemolytic anemia that can resemble HS. These include immune hemolytic anemia, G6PD deficiency, unstable hemoglobin traits or diseases, Wilson disease, and spherocytosis due to burn injury or toxin exposure (e.g., clostridia—bee, spider, or snake venom). Routine blood tests are typically sufficient to diagnose HS, particularly if an individual is showing symptoms. A peripheral blood smear, which is a slide preparation of a blood sample, will show the presence of a number of spherocytes that are uniform in appearance. Bilirubin levels tend to be elevated. A complete blood count will show several abnormalities. Hemoglobin levels tend to be decreased. Reticulocytes, which are immature red blood cells, tend to be increased. Red blood cells tend to be smaller than normal, marked by a decreased mean cell volume (MCV). The mean cell hemoglobin concentration (MCHC) tends to be high, which is a reflection of the

overall decrease in the cell volume. Ektacytometry is a specialized test that can demonstrate the fragility of the red blood cell membrane by placing the cells under stress and identifying increased levels and specific patterns of hemolysis. Another specialized test, called the rapid flow cytometric test, has recently been developed. This test can determine differences in fluorescent staining patterns that distinguish normal red blood cells from those that are characteristic of HS. It is highly sensitive and specific for HS and should aid in its rapid diagnosis.

Treatment and management

Most individuals with HS do not have symptoms that are severe enough to require treatment. For those with the more severe forms, blood transfusion therapy can effectively improve symptoms until a child is old enough for total or partial removal of the spleen, the organ responsible for most of the red blood cell destruction. Splenectomy most often eliminates HS complications. Some risk remains for ongoing chronic anemia or acute anemic events, particularly those caused by viruses and other factors that can temporarily halt red blood cell production. Splenectomy can lead to an increased risk for blood clots as well as life-threatening bacterial infection, given the spleen's role in fighting bacterial infections. Studies have shown that partial, as distinguished from total, splenectomy can be effective at ameliorating HS symptoms while also maintaining the bacterial-fighting capacity of the spleen and decreasing the chance for blood clots. Prophylactic antibiotics (e.g., penicillin) and additional vaccinations for common bacterial infections play roles in decreasing negative side effects of partial or total splenectomy. Surgery may be needed to remove gallstones that become symptomatic, which usually will not occur until after age 10.

Prognosis

Prognosis is very good for all types of HS, particularly the milder forms. Treatment is very effective for the more severe forms. There are only a small number of affected individuals who still experience anemia and other symptoms following splenectomy.

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ORGANIZATIONS

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Hermansky-Pudlak syndrome

Definition

Hermansky-Pudlak syndrome (HPS) is a rare inherited disorder of melanin production. Melanin is the pigment that gives color to the skin, hair, and eyes. A lack or decrease of pigment in the skin and eyes is called oculocutaneous albinism. HPS is a specific type of oculocutaneous albinism that includes a bleeding tendency and the storage of ceroid, the by-product of cell membrane breakdown, in the body’s cells.

Description

In 1959, Drs. F. Hermansky and P. Pudlak reported two unrelated people with oculocutaneous albinism who had lifelong bleeding problems. The female died at age

33, and at that time large amounts of pigment were discovered in the walls of her small blood vessels.

Genetic profile

HPS is an autosomal recessive disorder. This means that the disease manifests itself when a person has inherited one nonworking copy of the *HPS* gene from each parent. Parents who carry the gene for HPS are healthy and have typical skin pigmentation. However, each time they have a child, the chance for the child to have HPS is 25%, or 1 in 4. Unless someone in the family has HPS, most couples are unaware of their risk.

Researchers mapped the *HPS1* gene to the long arm of chromosome 10 in 1995 and identified its exact location in 1996. The protein produced by the *HPS* gene helps organelles (specialized parts) of the cell’s cytoplasm (portion of the cell between the membrane and nucleus) to develop and function normally.

In 1999, another group of researchers identified a mutation, or gene change, in the *AP3B1* gene located on chromosome 5 as another cause of HPS. This gene makes AP3, a molecule that helps to sort proteins within the body’s cells.

As of 2014, at least nine genes had been identified as being associated with HPS, all of which code for proteins associated with the movement and function of lysosome-related organelles (LRO), which are complexes involved in producing melanocytes, platelets, and lung cells. The nine genes affected are *HPS1*, *HPS3–HPS6*, *AP3B1*, *BLOC1S3*, *BLOC1S6*, and *DTNBP1*, all of which play a role in the structure and function of LRO, and three of which are associated with pulmonary fibrosis (a lung disease). The variations of signs and symptoms of the genes affected are widespread, and a 2013 study even determined that a mutation of the *HPS4* gene has a clinical correlation with schizophrenia. Another study associated a gene mutation of *AP3B1* with lymphoma.

Demographics

In northwest Puerto Rico, HPS is a common inherited disorder, 75% of cases of which are linked to a mutation in the *HPS1* gene and 25% of cases of which are linked to a mutation in the *HPS3* gene. More than 300 persons are affected. The carrier rate is about 1 in 21. Intermarriage accounts for the high frequency. Researchers have traced the origin of HPS to southern Spain. Cases have also been reported in the Dutch, Swiss, and Japanese. Both sexes are equally affected. However, females have more lung symptoms than males. Throughout the rest of the world, 45% of cases have mutations in *HPS1*, 20% in *HPS3*, and the remaining 35% associated with the other seven identified genes affiliated with HPS.



A woman, who suffers from albinism, holds her daughter at her parents' home in Puerto Rico. Puerto Rico has one of the world's highest rates of Type 1 Hermansky-Pudlak syndrome, a rare and fatal form of albinism that causes a deadly lung disease. (AP Images/Brennan Linsley)

Signs and symptoms

People with HPS have a broad range of skin color from tan to white, reflecting the partial absence of pigmentation. Hair color ranges from brown to white, reflecting how much pigmentation is present.

Poor vision and eye abnormalities are common in people with HPS. Visual acuity can approach 20/200. Nystagmus, an irregular rapid back-and-forth movement of the eyes, is also common. The eyes can have an improper muscle balance called strabismus. Sensitivity to bright light and glare, known as photophobia, is a frequent complaint of people with HPS. These visual problems all result from abnormal development of the eye due to the lack of pigment. Just as skin and hair color vary, so will eye color. Red, brown, hazel, and violet eyes have been reported.

A bleeding tendency distinguishes HPS from other types of albinism. People with HPS bruise easily and bleed for an extended time after dental extractions and surgical procedures. Platelets are the disc-shaped structures in the blood that cause clotting. In people with

HPS, the platelets are missing certain internal components that cause them to clump together during the clotting process.

The third finding of HPS is the accumulation of ceroid in certain cells of the body such as bone marrow and the lung. As ceroid collects in the lungs, it makes the affected individual prone to respiratory infections and progressive lung disease that restricts breathing. Some people also complain of colitis (an inflammation of the colon) and diarrhea (loose, watery stools).

Diagnosis

Diagnosis of HPS can be made by specialized platelet testing and molecular testing for the known gene mutations. Very few laboratories are equipped to perform these tests. A person who is suspected to have HPS should consult with a geneticist or genetic counselor to arrange for the appropriate tests. Molecular testing is available for Puerto Rican families who usually have a specific detectable gene alteration, which is a duplication of a small segment of the gene.

KEY TERMS

Bioptics—Glasses that have small telescopes fitted in the lens.

Ceroid—The by-product of cell membrane breakdown.

Colitis—Inflammation of the colon.

Cytoplasm—The substance within a cell, including the organelles and the fluid surrounding the nucleus.

Diarrhea—Loose, watery stool.

Melanin—Pigments normally produced by the body that give color to the skin and hair.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Nystagmus—Involuntary, rhythmic movement of the eye.

Oculocutaneous albinism—Inherited lack of pigment in the skin, eyes, and hair.

Organelle—Small, subcellular structures that carry out different functions necessary for cellular survival and proper cellular functioning.

Photophobia—An extreme sensitivity to light.

Sputum—A mixture of saliva and mucus from the lungs.

Strabismus—An improper muscle balance of the ocular muscles resulting in crossed or divergent eyes.

Analysis of the person's platelets will determine if he or she is lacking the critical internal parts, called dense bodies, that help to clot blood. If dense bodies are not present, then HPS is the diagnosis.

For affected people of Puerto Rican ancestry, one unique gene mutation is present. Several other mutations can also be detected, but the lack of a gene mutation does not mean a person does not have HPS, since all mutations have not been identified.

For some families with an affected child, prenatal diagnosis may be possible for future pregnancies. Parents should consult with a genetics specialist when planning a pregnancy.

Treatment and management

For the individual with HPS, vision problems are always present. Many people will meet the legal

QUESTIONS TO ASK YOUR DOCTOR

- What are the chances that I will go completely blind?
- How can I prevent future eye or skin damage?
- How often should I be evaluated for lung disease, and what are the early symptoms of it?
- What is the maximum amount of time I should spend in the sun?
- Are there any pharmaceuticals I can take to help me with my blood clotting?

definition of blindness but still have enough vision for reading and other activities. Other affected people may be farsighted or nearsighted.

An ophthalmologist, a specialist for the eyes, can help those individuals who have strabismus, a muscle imbalance in the eyes. They can have corrective surgery that will not only improve their physical appearance but also expand their visual field. Surgery cannot restore pigment to the eyes or correct the optic nerve pathways leading from the brain to the eyes.

Many optical aids can help a person with HPS function better in daily life. Aids like hand-held magnifiers, strong reading glasses, and glasses that have small telescopes fitted in the lens called bioptics can make hobbies, jobs, and other activities easier.

Protection from excessive sunlight is crucial for people with HPS. Sunscreens of the highest rating should be used to decrease the chance for fatal skin cancers. By wearing clothing that blocks as much sunlight as possible, people with HPS can enjoy outdoor activities. A dermatologist, a specialist in skin disorders, can examine the affected person if any changes in skin color or appearance occur. Annual skin check-ups are important.

As people with HPS reach their 30s, they begin to develop lung disease. The first sign is difficulty in breathing, followed by a cough that does not bring up sputum, a mixture of saliva and mucus, from the lungs. Gradually, the lungs develop a tough, fibrous tissue that further limits breathing. The inability to breathe is the most common cause of death for people with HPS. A lung transplant may be an option for a person with end-stage lung disease.

Prolonged bleeding after tooth extraction, nosebleed, or surgery occurs regularly in people with HPS. Before any surgery, treatment with desmopressin, a drug that

stimulates clotting activity, can be effective. Individuals with HPS should avoid aspirin because it makes blood less likely to clot.

Prognosis

Many people with HPS may have concerns about their physical appearance and decreased vision. Education about the disorder is important to prevent isolation and stigmatization. Once the visual difficulties are addressed, people with albinism can participate in most activities.

Although many preventive efforts can improve the quality of life for a person with HPS, the progressive lung disease cannot be halted. The inability to breathe generally becomes fatal when the affected person is 40–50 years old.

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ORGANIZATIONS

Hermansky-Pudlak Syndrome Network, 1 South Rd., Oyster Bay, NY 11771-1905, (800) 789-9HPS, (516) 624-0640, info@hpsnetwork.org, <https://www.hpsnetwork.org>

National Organization for Albinism and Hypopigmentation, PO Box 959, East Hampstead, NH 03826-0959, (603) 887-2310 or (800) 473-2310, (800) 648-2310, info@albinism.org, <http://www.albinism.org>

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High-density hypoprotein deficiency see

Tangier disease

Hirschsprung disease

Definition

Hirschsprung disease, also known as congenital megacolon or aganglionic megacolon, is an abnormality in which certain nerve fibers are absent in segments of the bowel, resulting in severe bowel obstruction.

Description

Hirschsprung disease is caused when certain nerve cells (called parasympathetic ganglion cells) in the wall of the large intestine (colon) do not develop before birth. Without these nerves, the affected segment of the colon lacks the ability to relax and move bowel contents along. This condition is referred to as “aganglionosis,” and it causes a constriction in a segment of the bowel. The section above the constricted area dilates due to stool becoming trapped, producing megacolon (dilation of the colon). The disease can affect varying lengths of bowel segment, most often involving the region around the rectum. In up to 10% of children, however, the entire colon and part of the small intestine are involved. The length of the affected intestine accordingly classifies the disease: The most common form of the disease (approximately 80% of patients) is called short-segment Hirschsprung disease (S-HSCR), where the aganglionosis does not extend beyond the sigmoid colon. Approximately 20% of the patients are diagnosed with the long-segment variant (L-HSCR), in which the aganglionosis extends further.

Genetic profile

There is a variety of evidence showing that Hirschsprung disease is caused by genetic factors. Hirschsprung disease occurs early in fetal development when there is either failure of ganglion cell development, failure of nerve cell migration, or arrest in nerve cell development in a segment of bowel. The absence of these nerve fibers, which help control the movement of bowel contents, is what results in intestinal obstruction accompanied by other symptoms.

A complex genetic pattern is emerging and mutations in at least eight different genes have been implicated in causing Hirschsprung disease. The genes are *RET*, *GNDF*, *NRTN*, *EDNRB*, *EDN3*, *ECE1*, *SOX10*, and *ZFHX1B/SMADIP*; they are thought to be important for the healthy development of the gut. When they are not working correctly, it may lead to disease. For example, the *RET* gene codes for producing a protein that is involved in signaling within cells. This protein appears to be essential for the normal development of several

KEY TERMS

Aganglionosis—Section of bowel in which the normal enteric nerves are absent.

Anus—The opening at the end of the intestine that carries waste out of the body.

Barium enema x-ray—A procedure that involves the administration of barium into the intestines by a tube inserted into the rectum. Barium is a chalky substance that enhances the visualization of the gastrointestinal tract on x-ray.

Chromosomal deletion—Loss of a segment of DNA from a chromosome.

Colostomy—The creation of an artificial opening into the colon through the skin for the purpose of removing bodily waste. Colostomies are usually required because key portions of the intestine have been removed.

Down syndrome—Chromosomal disorder caused by the presence of all or part of an extra chromosome 21.

Endoscopic mucosal resection—Removal of the mucosa during endoscopy.

Enterocolitis—Severe inflammation of the intestines that affects the intestinal lining, muscle, nerves, and blood vessels.

Manometry—A balloon study of internal anal sphincter pressure and relaxation.

Meconium—The first waste products to be discharged from the body in a newborn infant, usually greenish in color and consisting of mucus, bile, and so forth.

Megacolon—Dilation of the colon.

Mucosa—Mucus-secreting membrane lining all body cavities or passages that communicate with the exterior.

Parasympathetic ganglion cell—Type of nerve cell normally found in the wall of the colon.

Rectal suction biopsy—The removal and examination of a sample of rectum tissue for diagnostic purposes.

kinds of nerve cells, including nerves in the intestine. *RET* mutations result in a nonfunctional version of the *RET* protein that cannot interact with growth factors or transmit signals within cells. Without *RET* signaling, enteric nerves do not develop properly. Because these nerves control contractions that move stool through the

intestine, their absence leads to the intestinal symptoms of Hirschsprung disease. The pattern of inheritance for L-HSCR is autosomal dominant whereas the inheritance of the much more common S-HSCR is believed to be multifactorial.

A chromosomal abnormality is present in approximately 12% of individuals with Hirschsprung disease. The most common chromosomal abnormality associated with the disease is Down syndrome (trisomy 21), which occurs in 2%–10% of all individuals with Hirschsprung disease. Although individuals with Down syndrome are at a 100-fold higher risk for Hirschsprung disease than the general population, none of the identified Hirschsprung single genes reside on chromosome 21; thus, the association between Down syndrome and Hirschsprung disease remains unknown. Other chromosomal abnormalities associated with Hirschsprung disease include deletions that encompass Hirschsprung-associated genes. For example, del13q22 (*EDNRB*), del10q11.2 (*RET*), and del2q22 (*ZFHX1B*) have been identified.

Demographics

The overall incidence of Hirschsprung disease in the United States is about 1 in about 5,000 live births. The incidence varies significantly among ethnic groups with 1.0, 1.5, 2.1, and 2.8 per 10,000 live births in Hispanics, Caucasian Americans, African Americans, and Asians, respectively. It is about four to five times more common in males than in females. Prevalence may also vary by region and has been shown to be as high as 1 per 3,000 live births in the Federated States of Micronesia. Nearly all children with Hirschsprung disease are diagnosed before age two. Approximately 50% of children affected with this disease are diagnosed before age one. A small number of children with Hirschsprung disease are not diagnosed until much later in childhood or adulthood.

Signs and symptoms

The initial symptom is usually severe, continuous constipation. A newborn may fail to pass meconium (the first stool) within 24 hours of birth, may repeatedly vomit yellow- or green-colored bile, and may have a distended (swollen, uncomfortable) abdomen. Occasionally, infants may have only mild or intermittent constipation, often with diarrhea.

While two-thirds of cases are diagnosed in the first three months of life, Hirschsprung disease may be diagnosed later in infancy or childhood. Occasionally, even adults are diagnosed with a variation of the disease. In older infants, symptoms and signs may include anorexia (lack of appetite or inability to eat), lack of the urge to move the bowels or empty the rectum on physical

QUESTIONS TO ASK YOUR DOCTOR

- What are the signs and symptoms of Hirschsprung disease, and how is the condition distinguished from other kinds of bowel disease?
- At what point after diagnosis for Hirschsprung disease should surgery be considered for our child?
- What portion of the child's bowel is affected by the disorder, and how does this affect the program of treatment planned for our child?

examination, distended abdomen, and a mass in the colon that can be felt by the physician during examination. It should be suspected in older children with abnormal bowel habits, especially a history of constipation dating back to infancy and ribbon-like stools.

Occasionally, the presenting symptom may be a severe intestinal infection called enterocolitis, which is life threatening. The symptoms are usually explosive, watery stools and fever in a very ill-appearing infant. It is important to diagnose the condition before the intestinal obstruction causes an overgrowth of bacteria that evolves into a medical emergency. Enterocolitis can lead to severe diarrhea and massive fluid loss, which can cause death from dehydration unless surgery is done immediately to relieve the obstruction.

Diagnosis

Hirschsprung disease in the newborn must be distinguished from other causes of intestinal obstruction. The diagnosis is suspected by the child's medical history and physical examination, especially the rectal exam. The diagnosis can be confirmed by a barium enema x-ray, an imaging technique that shows a picture of the bowel. The x-ray will indicate if a segment of bowel is constricted, causing dilation and obstruction. A rectal suction biopsy can also be performed. In this technique, a small piece of the lining of the rectum is taken off. Then this tissue is looked at very closely under a microscope (biopsy) to see if it is normal. Rectal suction biopsy is done using a tube the size of a rectal thermometer. Adults may also undergo manometry, a balloon study (device used to enlarge the anus for the procedure) of internal anal sphincter pressure and relaxation.

Treatment and management

Hirschsprung disease is first treated by rectal irrigation to decrease bowel distention. Eventually, surgery is

performed to remove the diseased, nonfunctioning segment of the bowel and restore bowel function. This is often done in two stages. The first stage relieves the intestinal obstruction by performing a colostomy. This is the creation of an opening in the abdomen (stoma) through which bowel contents can be discharged into a waste bag. When the child's weight, age, or condition is deemed appropriate, surgeons close the stoma, remove the diseased portion of bowel, and perform a "pull-through" procedure, which repairs the colon by connecting functional bowel to the anus. This usually establishes fairly normal bowel function. Hirschsprung disease is a congenital abnormality that has no known means of prevention. It is important to diagnose the condition early in order to prevent the development of enterocolitis. Genetic counseling can be offered to a couple with a previous child with the disease or to an affected individual considering pregnancy to discuss recurrence risks and treatment options. Prenatal diagnosis is not available.

Clinical trials

A few clinical trials on Hirschsprung disease are currently sponsored by the National Institutes of Health (NIH) and other agencies. In 2015, the NIH reported 15 recruiting, active, or completed studies. These included the three following recruiting studies:

- The identification of genetic, immunologic, and microbial markers of Hirschsprung-associated enterocolitis in children with Hirschsprung disease (HAEC). (NCT02193685)
- A genetic study of Hirschsprung disease. (NCT00478712)
- A study of genetic mosaicism in Hirschsprung's disease. (NCT01927809)

Clinical trial information is constantly updated by the NIH and the most recent information on Hirschsprung disease trials can be found at <http://www.clinicaltrials.gov>

Prognosis

Without recognition and treatment, there is a 50% mortality rate for Hirschsprung disease. Overall, an early diagnosis results in the best prognosis, with a 2.4% mortality rate after surgery (0.5% after colostomy), resulting from complications. Most infants with Hirschsprung disease achieve good bowel control after surgery, but a small percentage of children may have lingering problems with soilage or constipation. These infants are also at higher risk for an overgrowth of bacteria in the intestines, including subsequent episodes of enterocolitis, and should be closely followed by a physician.

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ORGANIZATIONS

International Foundation for Functional Gastrointestinal Disorders (IFFGD), 700 W. Virginia St., No. 201, Milwaukee, WI 53204, (888) 964-2001 or (414) 964-1799, (414) 964-7176, iffgd@iffgd.org, <http://www.iffgd.org>

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 9000 Rockville Pike, Bethesda, MD 20892-2560, (301) 496-3583, <http://www.niddk.nih.gov>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Pull-thru Network, 1705 Wintergreen Parkway, Normal, IL 61761, pullthrunetwork@gmail.com, <http://www.pullthrunetwork.org>

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HLA region see **Major histocompatibility complex**

Holoprosencephaly

Definition

Holoprosencephaly is a disorder in which there is a failure of the front part of the brain to properly separate into what is commonly known as the right and left half of the brain. This lack of separation is often accompanied by abnormalities of the face and skull. Holoprosencephaly may occur individually or as a component of a larger disorder.

Description

Types of holoprosencephaly

There are three different types of holoprosencephaly: alobar, semilobar, and lobar. Each of these classifications is based on the amount of separation between what is commonly known as the left and right halves of the brain. Alobar holoprosencephaly is considered to be the most severe form of the disease, in which the separation between the two halves, or hemispheres, completely fails to develop. Semilobar holoprosencephaly represents holoprosencephaly of the moderate type, in which some separation between the hemispheres has occurred. Lobar holoprosencephaly represents the least severe type of holoprosencephaly, in which the hemispheres are almost, but not completely, divided.

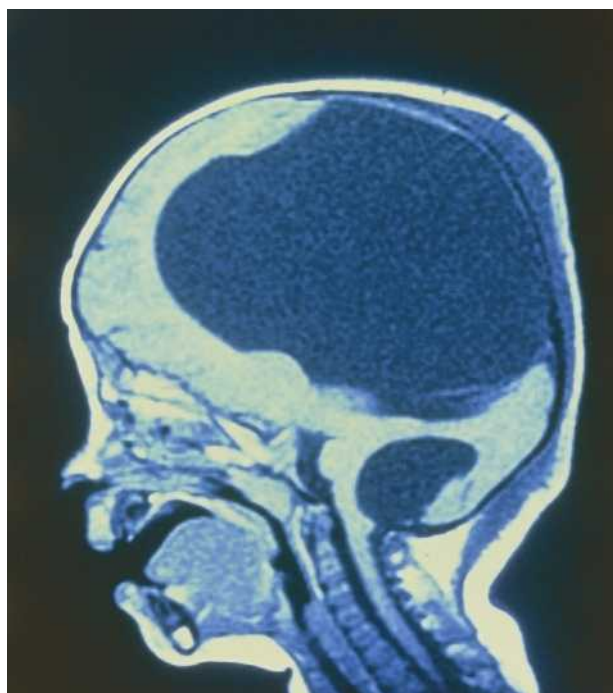
The severity of the effect of the disease on the brain is often reflected in craniofacial abnormalities (abnormalities of the face and skull). This has led to many health-care professionals utilizing the phrase "the face predicts the brain." This phrase is generally, but not always, accurate. Children may have severe craniofacial abnormalities with mild (lobar) holoprosencephaly, or children may have severe (alobar) holoprosencephaly with mild facial changes. Since the development of the face, skull, and the front of the brain are interconnected, the changes in the face often, but do not always, correspond with changes in the brain. Finally, the designation of these disorders from least severe to most severe can be mildly misleading, since the best predictor of the severity of the disease, is how well the brain functions, not its appearance. The alobar, semilobar, and lobar categories are universally utilized and give an indication of the severity of the disease, so knowledge of these categories and what they represent is useful.

Other brain abnormalities in holoprosencephaly

All patients with holoprosencephaly lack a sense of smell through the first cranial nerve (the olfactory nerve). Interestingly enough, one has a partial sense of smell through the sense of taste, which is governed by the seventh cranial nerve. The term "smell" and what it means in a conventional and strictly neurological sense differ, so it may be useful to think of persons with holoprosencephaly as lacking a portion of what is commonly referred to as "smell." This deficiency in smell can be detected by testing. One other important structural abnormality should be mentioned. The corpus callosum, which is the part of the brain that connects the right and left hemispheres with each other, is absent or deficient in persons with holoprosencephaly.

Synonyms for holoprosencephaly

Arrhinencephaly and familial alobar holoprosencephaly are synonyms for this disorder.



MRI of a 20-month-old girl with holoprosencephaly. The dark area represents the abnormally large fluid-filled ventricle typical of this disorder. (SPL/Science Source)

Genetic profile

Genetic causes of holoprosencephaly

Holoprosencephaly is a feature frequently found in many different syndromes including, but not limited to, trisomy 13, trisomy 18, triploidy, pseudotrisomy 13, Smith-Lemli-Opitz syndrome, Pallister-Hall syndrome, Fryns syndrome, CHARGE association, Goldenhar syndrome, frontonasal dysplasia, Meckel-Gruber syndrome, velocardiofacial syndrome, Genoa syndrome, Lambotte syndrome, Martin syndrome, and Steinfeld syndrome, as well as several teratogenic syndromes such as diabetic embryopathy, accutane embryopathy, and fetal alcohol syndrome. Holoprosencephaly has been linked to at least 12 different loci on 11 different chromosomes. Some candidate genes are Sonic hedgehog (abbreviated *SHH* and located at 7q36), *SIX3* (located at 2p21), and *ZIC2* (located on chromosome 13). The gene causing Smith-Lemli-Opitz syndrome, which affects cholesterol synthesis, is also a candidate to cause holoprosencephaly.

SHH, cholesterol, the prechordal plate, and the cause of holoprosencephaly

Holoprosencephaly probably arises in one of two ways (suggested by experiments in animal models). Early in the life of an embryo, an area called the prechordal plate forms. The prechordal plate is an area of the embryo that is

important for the formation of the brain. The prechordal plate is said to induce brain formation. One can think of the induction process in the following way. If you take a sponge, wet it, and then place a paper towel on top of it, the paper towel will absorb some of the water. In the same way, a signal (the water) goes from the sponge (prechordal plate) to the paper towel (future brain tissue). If the water does not hit the paper towel, brain tissue will not form. This is an extremely simplified version of how the process works, for many reasons. One is that the prechordal plate is not the only “sponge.” The notochord is another sponge, which sends out the signal (water) of *SHH* to form brain and spinal cord and other nervous tissue. Of course, *SHH* has already been mentioned as a candidate for a gene that causes holoprosencephaly. As it turns out, it is better than a candidate, because mutations in *SHH* have been found in some familial forms of holoprosencephaly. Further evidence that *SHH* plays a role in holoprosencephaly comes from *SHH* in mice and fish, which both result in holoprosencephaly. Thus, it would be a clear-cut picture if mutations in *SHH* and *SHH* alone led to holoprosencephaly, because *SHH* mutations lead to holoprosencephaly in other animals and *SHH* is already known to be involved in the formation of neural tissue.

However, *SHH* is not the only answer. Many persons with holoprosencephaly have perfectly normal *SHH* genes, and, as previously mentioned, a number of genes have been linked to holoprosencephaly, including genes involved in cholesterol synthesis. So why are so many genes involved?

One possible answer stems from the connection between cholesterol and the *SHH* signaling pathway. When *SHH* travels from one tissue to another tissue, there are a number of other genes involved before *SHH* has its final effect. This process is called signal transduction, and the genes that make it up are part of a signaling pathway. Signal transduction can be compared to a shot in the game of pool. When shooting pool, one must take the cue (*SHH*) and hit the cue ball (another gene; for *SHH* this would be the gene *Patched*). The cue ball goes on to hit the ball that one is interested in sinking (in this case, sinking the ball means making a normal brain). Thus, each step depends on the previous step and the next step. If one does not have the stick or the cue ball, one cannot sink the ball in the pocket. Thus, a number of mutations in genes in the *SHH* signaling pathway, and not just *SHH*, could cause holoprosencephaly. Other genes involved in cholesterol biosynthesis can have effects on genes in the *SHH* signaling pathway. Cholesterol appears to affect the function of the gene *Patched*. In the pool example, a lack of cholesterol would not mean the cue ball is gone, but maybe that the cue ball has a big lump on one side, so the shot is likely to miss.

KEY TERMS

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

Craniofacial—Relating to or involving both the head and the face.

Induction—Process where one tissue (the prechordal plate, for example) changes another tissue (for example, changes tissue into neural tissue).

Neural—Regarding any tissue with nerves, including the brain, the spinal cord, and other nerves.

Another possible answer comes from studies on bone morphogenetic proteins (BMPs) in chickens. The presence of too much BMP in a chick embryo after the time neural tissue is formed can cause holoprosencephaly. It appears that there are two stages that can be interfered with—one that occurs at the time of neural tissue formation involving *SHH* and another that occurs later, involving BMPs. Increased levels of BMPs may cause important neural cells to die. It has been speculated that holoprosencephaly is either a failure to grow neural cells due to failure in the *SHH* pathway, or an excess of neural cells dying, possibly as a result of increased levels of BMPs. Both may end up being true, with some *SHH* signaling defects early and BMP mutations later.

Teratogens also cause holoprosencephaly

A teratogen is any environmental influence that adversely affects the normal development of the fetus. Teratogens can be skin creams, drugs, or alcohol. Alcohol, when ingested in sufficient amounts during the second week of pregnancy, is thought to lead to some cases of holoprosencephaly. Cytomegalovirus infections in the mother during pregnancy have been associated with holoprosencephaly. Additionally, in animals, drugs inhibiting cholesterol synthesis have been shown to cause cases of holoprosencephaly. Finally, the drug cyclopamine, which affects the *SHH* pathway, also causes holoprosencephaly in animals. Cyclopamine was discovered when an abnormally large number of sheep were found to have holoprosencephaly. A local shepherd and scientists determined the drug was found in a fungus called *Veratrum californicum*.

Demographics

Holoprosencephaly affects males and females at the same rate. Estimates vary on the frequency of the disorder

in children with normal chromosomes. The estimates range from one case in every 11,363 births to one case in 53,394 births. It is important to note that this rate of incidence excludes those cases caused by chromosomal abnormalities, like trisomy 13.

Signs and symptoms

In holoprosencephaly alone, symptoms involve the brain and/or the face and bones of the face and skull. Facial abnormalities exhibit a wide range. In the most severe cases, persons with holoprosencephaly lack eyes and may lack a nose. Less severe is cyclopia, or the presence of a single eye in the middle of the face above the possibly deformed or absent nose. Even less severe are ethmocephaly and cebocephaly, in which the eyes are set close together and the nose is abnormal. In premaxillary agenesis, the patient has a midline cleft lip and cleft palate and close-set eyes. If the face is very abnormal, the patient is likely to have alobar holoprosencephaly, the most severe type. In addition to abnormalities of the face, children with alobar holoprosencephaly have small brains (less than 100 grams). These children also have small heads unless they have excess cerebrospinal fluid. Excess cerebrospinal fluid can cause the head to be abnormally large.

Persons with holoprosencephaly experience many problems due to brain malformations, including *in utero* or neonatal death. Survivors may experience seizures, problems with muscle control and muscle tone, a delay in growth, problems feeding (choking and gagging or slowness, pauses, and a lack of interest), intestinal gas, constipation, hormone deficiencies from the pituitary, breathing irregularities, and heart rhythm and heart rate abnormalities. These problems are usually least severe in lobar holoprosencephaly and most severe in alobar. Children with holoprosencephaly also experience severe deficiencies in their ability to speak and in their motor skills. An ominous sign that children with holoprosencephaly may exhibit is a sustained (lasting many hours or days) period of irregular breathing and heart rate. This may precede death. Episodes lasting only minutes are usually followed by a full recovery.

Diagnosis

Prenatal ultrasound and computerized tomography can be used to determine whether the fetus has holoprosencephaly and its severity. After birth, physical appearance and/or imaging of the brain can determine a diagnosis of holoprosencephaly. Once a diagnosis of holoprosencephaly has been made, syndromes of which holoprosencephaly is a part must be considered. Forty-one percent of holoprosencephaly cases are thought to

have a chromosomal abnormality as the primary cause. Holoprosencephaly is estimated to be found in the context of a larger syndrome in 25% of the remaining patients.

Treatment and management

Although no treatment exists for the underlying disease, symptomatic treatment can reduce the amount of fluid surrounding the brain and assist in feeding. Medical intervention can reduce or eliminate seizures and hormonal deficiencies. However, few treatments exist for the most serious aspects of the disease—breathing and heart arrhythmias (irregular heart rate)—or for the problems associated with developmental delay and poor muscle control. One important aspect of treatment is to help parents understand the effects of the disease and what may be expected from the child. Support groups may be important for this purpose. Parents should be prepared to deal with a large number of healthcare professionals based on their child's particular needs.

Prognosis

About half of the children born with alobar holoprosencephaly die before the age of four to five months, but a much longer survival time is possible, up to at least 11 years. Children with semilobar and lobar holoprosencephaly may live for any length of time. Depending on the severity of the holoprosencephaly, however, parents should be prepared for differences in their child. For example, children with alobar holoprosencephaly and semilobar holoprosencephaly learn to speak very little, if at all, and children with alobar holoprosencephaly have difficulty even mastering the simple task of reaching and grasping an object. On the other end of the spectrum, children may develop much more normally. It is very important to understand the severity of the disorder to understand the child's abilities and possibilities.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Michael V. Zuck, PhD

Holt-Oram syndrome

Definition

Holt-Oram syndrome (HOS) is one of several hereditary conditions characterized by abnormalities of the heart and hands at birth.

Description

HOS involves variable abnormalities of the heart and the hands or the hands and the arms. The heart abnormalities may range from disturbances in the electrical conduction pattern of the heart to severe structural defects requiring surgical intervention for survival. The abnormalities of the upper limbs are usually bilateral (occurring on both sides) and asymmetric (not identical from side to side). The severity of the upper limb changes may range from minor signs, such as clinodactyly (inward curvature of the fingers), to disabling defects, such as small or missing bones resulting in very short arms.

Some individuals with HOS are so mildly affected, they do not require any special care or treatment. Other individuals are severely affected and may have significant disability resulting from abnormalities of the arms or may have limited lifespans due to serious heart abnormalities. The signs of HOS are usually limited to the heart and skeleton. HOS does not cause intellectual disability.

Some references may use the alternative name of hand-heart syndrome. However, Holt-Oram syndrome is one of many hereditary hand-heart syndromes, so the two names are not truly interchangeable.

Genetic profile

HOS is inherited as an autosomal dominant condition, with variable expressivity (meaning that different individuals with HOS may have very different signs of the condition) and complete penetrance (meaning that every individual that has the genetic change causing the condition has some physical symptoms). An autosomal dominant condition requires the presence of only one

abnormal gene on a non-sex-linked chromosome for the disorder to occur. Some researchers have observed families with incomplete penetrance (meaning that not every individual with the gene abnormality shows symptoms) as well.

In some individuals and families, HOS is caused by mutations in the *TBX5* gene located on the long arm of chromosome 12. The *TBX5* gene encodes a transcription factor that helps regulate DNA expression. Other families with HOS do not show mutations in the *TBX5* gene, indicating that mutations in other genes can also cause HOS. HOS families that have *TBX5* mutations do not appear to differ significantly from those that do not.

Some patients with HOS have inherited it from an affected parent, whereas others have it as the result of a new change in a gene. The proportion of patients with HOS resulting from new mutations ranges from 8% to 85%. Regardless of where the gene came from, an affected individual has a 50% chance of passing on the gene and the condition to each child. It is difficult to pre-determine the severity of symptoms a child may have.

Demographics

Since HOS was first described in 1960, more than 200 cases have been reported in individuals of diverse ethnicity. The incidence of the condition has been estimated as 1 in 100,000 live births.

Signs and symptoms

All individuals with HOS have some degree of upper limb abnormality, and most (approximately 95% in familial cases) have defects or dysfunction of the heart. Other body parts and systems are usually not significantly affected by HOS.

Defects of the upper limbs

The limb abnormalities in HOS primarily affect the radial side (the inner or thumb side of the arm/hand). Involvement of the ulnar side (the outer side of the arm/hand, opposite the thumb) may also occur to a lesser degree. In some individuals, the abnormality of the upper limb may be very mild, such as hypoplasia (underdevelopment) of the muscle at the base of the thumb; limited rotation of the arm; or narrow, sloping shoulders. Rarely, severe abnormalities of the upper limbs may be present, resulting in extremely short, “flipper-like” arms. Abnormalities of the upper limb are always bilateral and usually asymmetric. In 90% of patients, the left side is more severely affected.

The thumb is the most commonly affected part of the upper limb in HOS and is affected in some way in 84% of

patients. Some individuals have three phalanges (or bones) in the thumb, resulting in a thumb that can bend in three places, like a finger. In other cases, the thumb may be hypoplastic (underdeveloped). Syndactyly (or skin webbing) may occur between the thumb and index finger.

Abnormalities of the fingers may include hypoplasia, underdevelopment, or absence of one or more fingers. Clinodactyly (inward curvature) of the fifth or “pinky” finger is also common. In some patients, polydactyly (extra fingers) has been reported.

The bones of the arms may also be affected by HOS. The radius (the inner bone of the forearm, adjacent to the thumb) may be hypoplastic or even missing. Such patients may have a lesser degree of hypoplasia of the ulna (outer bone of the forearm, opposite the thumb). The upper arm may be short. In rare cases, the bones of the arm are dramatically shortened, resulting in a tiny arm.

Individuals with HOS often appear to have narrow, sloping shoulders. This likely results from some degree of hypoplasia of the clavicles (collarbones), as well as decreased musculature that occurs secondarily to bone hypoplasia.

Defects and dysfunction of the heart

The vast majority (95%) of individuals with HOS who have inherited it from an affected parent have heart involvement. Most have a defect in the structure of the heart. In some patients, there is no structural defect in the heart, but abnormalities are present in the pattern of electrical conduction in the heart.

The most common heart abnormalities in people with HOS are septal defects, or holes in the heart. A hole may occur in the wall separating the atria of the heart (atrioseptal defect or ASD) or the wall separating the ventricles of the heart (ventriculoseptal defect or VSD). In rare cases, more severe and complex heart defects may occur, such as hypoplastic left heart (in which the chambers of the left side of the heart are too small to function normally) or tetralogy of fallot (a specific combination of four heart defects). In the case of severe defects, surgical correction is necessary for survival. However, most persons with HOS do not require surgical intervention.

Some individuals with HOS have a cardiac conduction defect, or an abnormal electrical pattern in the heart. The complex motion of the heart requires a system of electrical impulses for coordinated contraction of the muscle fibers. In people with cardiac conduction defects, these electrical impulses may not occur in the normal pattern, resulting in an abnormal heartbeat. In rare cases, this can result in sudden death.

KEY TERMS

Atria—The two chambers at the top of the heart, where blood from the lungs or body pools before entering one of the ventricles.

Polydactyly—The presence of extra fingers or toes.

Radius—One of the two bones of the forearm, the one adjacent to the base of the thumb.

Septal defect—A hole in the heart.

Syndactyly—Abnormal webbing of the skin between the fingers or toes.

Ulna—One of the two bones of the forearm, the one opposite the thumb.

Ventricles—The chambers (small cavities) of the heart through which blood circulates. The heart is divided into the right and left ventricle.

Other defects

Additional skeletal abnormalities occasionally reported in patients with HOS include scoliosis, vertebral abnormalities, and minor deformities of the rib cage. Some patients may have abnormalities unrelated to the cardiac or skeletal systems, such as minor eye defects and various birthmarks. It is not clear whether these additional findings are coincidental or part of HOS.

Diagnosis

The diagnosis of HOS is made on the basis of clinical judgment by a specialist physician, usually a geneticist, following physical examination and review of pertinent tests or studies. Diagnostic criteria may be employed to guide this decision. One commonly used set of criteria for the diagnosis of HOS requires that there be defect(s) of the radial side of the hand/arm, as well as septal defect(s) or conduction abnormality of the heart, within one individual or family.

X-rays may be necessary to determine involvement of the bones of the upper limb. Diagnosis of structural defects of the heart requires echocardiography, or ultrasound visualization of the heart. Conduction defects of the heart are identified via electrocardiography (EKG). This test involves measuring the electrical activity of the heart and charting the electrical impulses associated with each heartbeat.

Testing to identify changes in the *TBX5* gene may be offered but is not necessary for a diagnosis of HOS. Identification of a change or alteration in the *TBX5* gene could provide confirmation of the clinical diagnosis, prenatal

diagnosis, or assist in the diagnosis of at-risk family members who are minimally affected. Prenatal screening in a pregnancy at risk for HOS may be attempted by fetal ultrasonography targeted toward the fetal arms and heart. However, a normal ultrasound examination does not eliminate the possibility of HOS in the unborn baby.

Treatment and management

There is no specific treatment for HOS. Surgery or other treatment may be recommended for cardiac abnormalities. Referral for genetic counseling should be considered for families in which HOS has been diagnosed.

Some patients with HOS have life-threatening heart defects that require surgical correction for survival. The most complex heart defects may require multiple surgeries. However, many individuals have asymptomatic or no heart abnormalities. When life-threatening irregularities are present in the heartbeat, a pacemaker device is inserted. These devices correct the abnormal electrical patterns that cause the irregularities and stimulate the heart to beat normally.

Because eye abnormalities have been occasionally reported in HOS, an eye examination may be recommended at the time of diagnosis.

Prognosis

The prognosis for individuals with HOS depends on the severity of associated birth defects, which varies considerably. Positive correlation has been reported between the severity of upper limb and heart defects. In other words, individuals who have more severe hand or arm involvement may be more likely to have a symptomatic heart defect. People who have HOS resulting from new mutations are more likely to have severe defects than those who have inherited it from a parent.

In some cases, HOS may lead to death in early infancy due to multiple septal defects or other complex structural abnormalities of the heart. Severe and unrecognized disturbances of the cardiac conduction system can lead to sudden death. In other cases, heart involvement is limited to asymptomatic irregular heartbeat requiring no treatment.

Several unusual findings have been described with respect to the severity of HOS in families. Affected women have been reported to have a higher chance of having a severely affected child than do affected men. The severity of defects associated with HOS has also been reported to increase with successive generations. The possible explanations for these observations are not known.

QUESTIONS TO ASK YOUR DOCTOR

- What are the most common symptoms associated with Holt-Oram syndrome?
- Is there a genetic test that I can take to see if my children will be at risk for Holt-Oram syndrome?
- How is it possible to predict the course of Holt-Oram syndrome in a child who is diagnosed with the disorder as an infant?
- Are there other medical conditions with which a diagnosis of Holt-Oram syndrome might be confused and, if so, how is it possible to distinguish among these conditions?

Resources

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ORGANIZATIONS

American Society for Surgery of the Hand, 822 W. Washington Blvd., Chicago, IL 60607, (312) 880-1900, info@assh.org, <http://www.assh.org>

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Homocystinuria

Definition

The term "homocystinuria" is actually a description of a biochemical abnormality, as opposed to the name of a particular disease, although many refer to

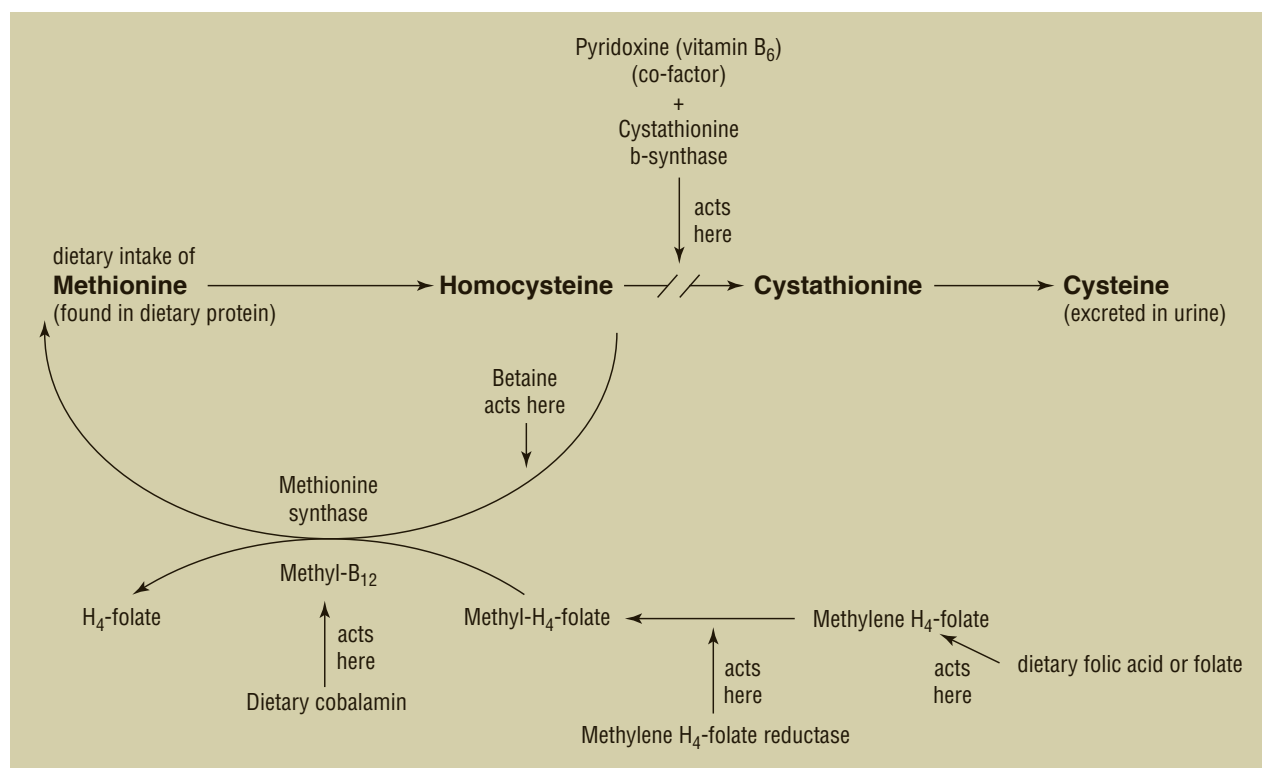
homocystinuria as a disease. Homocystinuria refers to elevated levels of homocysteine in the urine. This can be caused by different biochemical abnormalities, and, in fact, there are at least eight different gene changes that are known to cause excretion of too much homocysteine in the urine. The best known and most common cause of homocystinuria is the lack of cystathionine β -synthase. Classical homocystinuria is caused by cystathionine β -synthase deficiency (CBS deficiency).

Description

In Northern Ireland in the early 1960s, homocystinuria was described in individuals who were intellectually disabled. Soon after that, it was shown that the cause of the homocystinuria was a deficiency of the enzyme cystathionine β -synthase. This condition is an inborn error of metabolism, meaning that the cause for this condition is present from birth and it affects metabolism.

Metabolism is the sum of all of the chemical processes that take place in the body. Metabolism includes both construction (anabolism) and breakdown (catabolism) of important components. For example, amino acids are the building blocks for proteins and are converted to proteins through many steps in the process of anabolism. In contrast, proteins can also be broken down into amino acids through many steps in the process of catabolism. These processes require multiple steps that involve different substances called enzymes. These enzymes are proteins that temporarily combine with reactants and, in the process, allow these chemical processes to occur quickly. Since practically all of the reactions in the body use enzymes, they are essential for life. At any point along the way, if an enzyme is missing, the particular process that requires that enzyme would not be able to be completed as usual. Such a situation can lead to disease.

Homocysteine is involved with the catabolism of methionine. Methionine is an essential amino acid. Amino acids are the building blocks of proteins. Over 100 amino acids are found in nature, but only 22 are found in humans. Of these 22 amino acids, eight are essential for human life, including methionine. Methionine comes from dietary protein. Generally, the amount of methionine that is consumed is more than the body needs. Excess methionine is converted to homocysteine, which is then metabolized into cystathionine; cystathionine is then converted to cysteine. The cysteine is excreted in the urine. Each step along this pathway is carried out by a specific enzyme and that enzyme may even require help from vitamin co-factors to be able to complete the job. For example, the conversion of homocysteine to cystathionine by cystathionine β -synthase requires vitamin B₆ (pyridoxine). If cystathionine β -synthase is



Flow chart for the chemical processes involved in the breakdown of methionine, an essential amino acid found in dietary protein. Homocystinuria results when the enzyme cystathionine β -synthase is missing and does not break down homocysteine, a converted form of excess methionine. The elevated levels of methionine and homocysteine that result from the failure of homocysteine to break down into cystathionine and cysteine causes a disease state that affects multiple body systems. (Gale)

missing, then homocysteine cannot be broken down into cystathionine and cysteine and, instead, homocysteine accumulates and elevated levels of homocysteine and methionine can be found in the blood. Also, decreased levels of cysteine can be found in the blood. Elevated levels of homocysteine lead to a disease state that, if untreated, affects multiple systems, including the central nervous system, the eyes, the skeleton, and the vascular system.

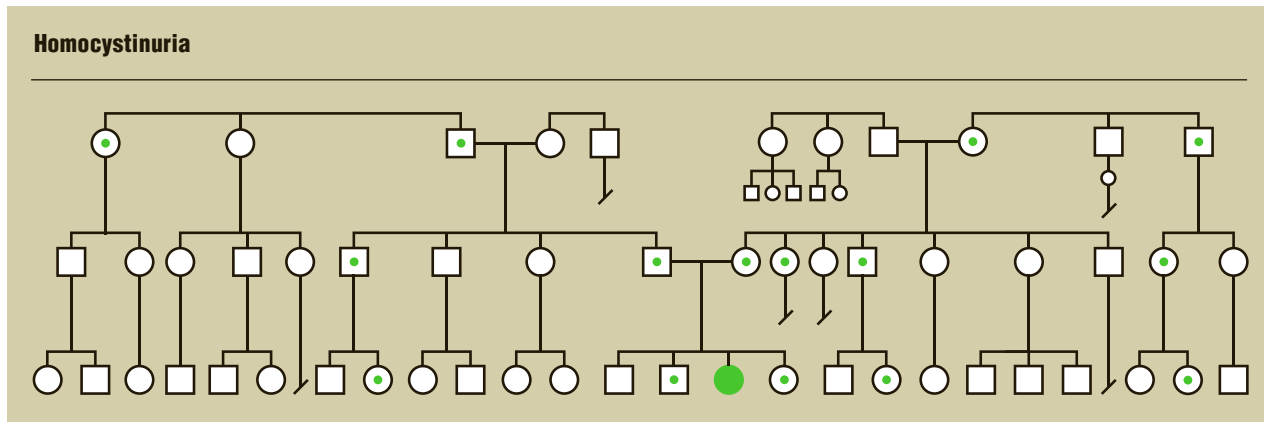
Genetic profile

Classical homocystinuria or cystathionine β -synthase (CBS) deficiency is an autosomal recessive condition. This means that in order to have the condition, an individual must inherit one copy of the gene for CBS deficiency from each parent. An individual who has only one copy of the gene is called a carrier for the condition. In most cases of autosomal recessive inheritance, a carrier for a condition does not have any signs, symptoms, or effects of the condition. This is not necessarily the case with CBS deficiency. Individuals who are carriers for CBS deficiency may have levels of homocysteine that are elevated enough to increase the risk for thromboembolic

events. So, although carriers may not exhibit obvious physical signs or symptoms of the condition, they may have clinical effects of elevated levels of homocysteine, such as vascular or cardiovascular disease. A carrier for CBS deficiency can have vascular complications, especially if they are also carriers for other clotting disorders such as factor V Leiden thrombophilia.

When two parents are carriers for CBS deficiency, there is a 1 in 4 (or 25%) chance, with each pregnancy, for having a child with CBS deficiency. They have a 1 in 2 (or 50%) chance for having a child who is a carrier for the condition, and a 1 in 4 (or 25%) chance for having a child who is neither affected nor a carrier for CBS deficiency.

The gene for CBS has been mapped to the long arm of chromosome 21, specifically at 21q22.3. Approximately 160 different disease-associated gene changes or alterations of the CBS gene have been identified. The two most frequently encountered gene changes are *I278T* and *G307S*. *G307S* is the most common cause of CBS deficiency in Irish patients, and the *I278T* gene is the most common cause of CBS deficiency in Italian patients.



Homocystinuria: pedigree analysis chart. (Gale)

Demographics

The worldwide frequency of individuals with CBS deficiency who are identified through newborn screening and clinical detection is approximately 1 in 344,000; however, newborn screening may be missing half of affected patients, and thus, the worldwide incidence may be as high as 1 in 180,000. One study showed that by lowering the cutoff level of methionine from 2 milligrams per deciliter to 1 milligram per deciliter in newborn screening, detection of the deficiency increased from 1 in 275,000 to 1 in 157,000. The incidence of CBS deficiency in the U.S. population is 1 in 58,000. In the Irish population, it is estimated to be 1 in 65,000; in the Italian population it is 1 in 55,000; and in the Japanese population, it is 1 in 889,000. CBS deficiency has been seen in persons of many different ethnic origins living in the United States.

Signs and symptoms

Individuals who have CBS deficiency tend to be tall and thin with thinning and lengthening of the bones. They tend to have a long, narrow face and a high, arched palate (roof of the mouth). The thinning and lengthening of the long bones causes individuals to be tall and thin by the time they reach late childhood. Their fingers tend to be long and thin as well (referred to as arachnodactyly). They can have curvature of the spine, called scoliosis. Their chest can be sunken in (pectus excavatum), or it may protrude out (pectus carinatum). Osteoporosis may occur. Also, they tend to have stiff joints. CBS deficiency affects the eyes, causing dislocated lenses and nearsightedness (myopia). Untreated individuals or those individuals who do not respond to treatment develop intellectual disabilities or learning disabilities. Affected individuals may also develop psychiatric problems. These psychiatric problems may include depression,

chronic behavior problems, chronic obsessive-compulsive disorder, and personality disorders. The most frequent cause of death associated with CBS deficiency is blood clots that form in veins and arteries. These are known as thromboembolisms and include deep vein thrombosis (blood clots that form in the deep veins of the legs, etc.), pulmonary embolus (blood clots that form in the lungs), and strokes. Thromboembolism can occur even in childhood. When thromboembolism does occur in childhood, CBS deficiency should always be considered as a cause for the thromboembolic events. These thromboembolic events can occur in any part of the body. Lastly, another complication of CBS deficiency is severe premature arteriosclerosis (hardening of the arteries).

Diagnosis

Approximately 50% of individuals who have CBS deficiency are diagnosed by newborn screening because they have an elevated level of methionine in their blood. Newborn screening is performed so that infants affected with genetic disorders can be identified early enough to be treated. The screening is done by collecting blood from a pin-prick on the baby's heel prior to leaving the hospital but at least 24 hours after birth. For CBS deficiency, the screening test checks for elevated levels of methionine. If the levels are elevated, then follow-up testing to verify the diagnosis is performed. There are other disorders of methionine metabolism, and follow-up testing determines the underlying cause of the positive newborn screening.

If not identified at newborn screening, diagnosis is made by identifying low levels of cysteine in blood and urine. Measurements of the amount of methionine and homocysteine produced by cultured blood cells (lymphoblasts) or cultured skin cells (fibroblasts) also can confirm the diagnosis of CBS deficiency.

DNA testing is available for families in which a gene alteration is identified. Potentially, this makes prenatal diagnosis by chorionic villus sampling (CVS) and amniocentesis available for families who have had a previously affected child and in which two identifiable gene alterations for CBS deficiency have been detected. Prenatal diagnosis is also possible by measuring the amount of enzyme activity in cultured cells grown from amniotic fluid.

CBS deficiency has several features in common with Marfan syndrome, including the tall, thin build with long limbs and long, thin fingers (arachnodactyly); a sunken-in chest (pectus excavatum); and dislocated lenses. The dislocated lens in Marfan syndrome tends to be dislocated upward; the tendency for the lens dislocation is to be downward in CBS deficiency. Also, individuals who have Marfan syndrome tend to have lens dislocation from birth (congenital), whereas individuals who have CBS deficiency have not been identified to have lens dislocation before two years of age.

Treatment and management

The first choice of therapy for patients with CBS deficiency is administration of pyridoxine (vitamin B₆). Vitamin B₆ is the cofactor for the cystathionine β -synthase reaction. Potentially, some individuals who have CBS deficiency are not missing the enzyme, but rather have an enzyme that is unable to perform its job. The addition of pyridoxine can help to push the reaction along and help to reduce the levels of homocysteine and methionine in the blood. Information suggests that approximately 50% of patients with CBS deficiency respond to high doses of pyridoxine (pyridoxine responsive) and show a significant reduction in levels of homocysteine in the blood. Patients who do not respond to pyridoxine treatment (pyridoxine non responsive) tend to be more severely affected than the patients who do respond. Those nonresponding patients are treated with combinations of folic acid, hydroxycobalamin, and betaine, which stimulate the conversion of homocysteine back to methionine. The addition of folic acid can help because within the methylene H₄-folate molecule (MTHFR), there is a molecule known as flavin adenine dinucleotide (FAD). The FAD molecule binds to the MTHFR molecule and helps with the conversion of homocysteine to methionine. Increased levels of folate help bind FAD more tightly to MTHFR, protecting the enzyme against heat inactivation and allowing the homocysteine-to-methionine-conversion pathway to proceed. Betaine and cobalamin also help in the conversion of homocysteine to methionine by acting as cofactors. The rationale behind this method of treatment is that although the methionine levels are raised, the net

drop in homocysteine is beneficial, as it appears that the elevated levels of homocysteine are what cause ectopia lentis, osteoporosis, mental deficiency, and thromboembolic events.

It appears that the addition of dietary betaine in B₆-responsive patients is also beneficial. Homocysteine that is not metabolized to cysteine is converted back to methionine in a reaction that uses betaine, so the addition of betaine may help to make this reaction occur and thus reduce the levels of homocysteine.

Other treatments include protein restriction, specifically a low-methionine diet with the addition of extra cysteine. Dietary treatment includes avoidance of all high-protein foods throughout life, with the use of a nutritional supplement. Special formulas for infants are available. The reasoning behind this is to reduce the methionine and homocysteine levels that accumulate and supplement the low levels of cysteine.

The occurrence of clinically apparent thromboembolism depends upon the age of the affected individual and whether or not he/she responds to pyridoxine treatment. In one study, untreated pyridoxine-responsive patients were at little risk for a thromboembolic event until age 12. After age 12, the risk for thromboembolism increased. By age 20, patients who would have been responsive to pyridoxine had a 25% cumulative risk for a thromboembolic event. In comparison, individuals with CBS deficiency who were untreated and not responsive to pyridoxine treatment had a similar cumulative risk for a thromboembolic event by age 15.

In reference to the two common CBS gene alterations, CBS deficiency caused by the *I278T* gene change is pyridoxine responsive. CBS deficiency caused by the *G307S* gene tends to be pyridoxine nonresponsive; however, this is not always the case, as some individuals with the *G307S* gene change are pyridoxine responsive.

Very little is known about the risks to an unborn child of a mother with pyridoxine nonresponsive CBS deficiency. There have been numerous reports of healthy children born to women and men who have pyridoxine-responsive CBS deficiency; however, only two reports of children born to pyridoxine nonresponsive women have been reported, and one had multiple birth defects that may have been related to the mother's condition. Potentially, the mother's elevated levels of homocysteine can cause problems for a developing baby. This could be similar to the process by which infants of mothers who have phenylketonuria are affected by the elevated levels of phenylalanine if their mothers are not being treated with dietary restriction during pregnancy.

KEY TERMS

Anabolism—The energy-using process of building up complex chemical compounds from simpler ones in the body.

Catabolism—The energy-releasing process of breaking down complex chemical compounds into simpler ones in the body.

Marfan syndrome—A syndrome characterized by skeletal changes (arachnodactyly, long limbs, lax joints), ectopia lentis, and vascular defects.

Thrombophilia—A disorder in which there is a greater tendency for thrombosis (clot in blood vessel).

Prognosis

Untreated CBS deficiency leads to intellectual disability, lens dislocation, and a decreased life expectancy because of complications associated with blood clots. If untreated from early infancy, approximately 20% of affected patients will have seizures. If treated from birth, prevention or long-term delay of the complications of CBS deficiency can be expected.

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National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Homogentisic acid oxidase deficiency see
Alkaptonuria

Human Genome Project

Definition

The Human Genome Project (HGP) was an international project to sequence the DNA of the human genome. The sequencing work was conducted in many laboratories around the world, but the majority of the work was done by five institutions: the Whitehead Institute for Medical Research (WIMR) in Massachusetts, the Baylor College of Medicine in Texas, the Washington University, the Joint Genome Institute in California, and the Sanger Centre near Cambridge in the United Kingdom. Most of the funding for these centers was provided by the U.S. National Institutes of Health and Department of Energy, and the Wellcome Trust, a charitable foundation in the United Kingdom.

Description

Completely sequencing the human genome was first suggested at a conference in Alta, Utah, in 1984. The conference was convened by the U.S. Department of Energy, which was concerned with measuring the mutation rate of human DNA when exposed to low-level radiation, similar to conditions after an attack by nuclear weapons. The technology to make such measurements did not exist at the time, and the sequence of the genome was one step required for this aim to become possible. The genome was estimated to be 3,000Mb long, however, and sequencing it seemed an arduous task, especially using the sequencing technology of the time. If most of the DNA was "junk" (not coding for genes), scientists assumed that they could speed the process along by targeting specific genes for sequencing. This could be done by sequencing complementary DNA (cDNA), which are derived from mRNA used to code for proteins in the cell. Despite several advocates for this method, it was decided that the whole genome would be sequenced, with a 2005 target completion date. Goals for the HGP included identifying all of the approximately 20,000–25,000 genes in human DNA; determining the sequence of the three billion base pairs that make up human DNA; storing this information in retrievable databases; and addressing the ethical, legal, and social issues that would inevitably arise from the project. The HGP quickly became the world's premier science project for biology, involving large factory-like laboratories rather than small laboratories of independent geneticists.

The strategy employed by the HGP involved three stages and is termed hierarchical shotgun sequencing. The first stage involved generating physical and genetic

maps of the human genome. The second stage was placing clones from a genomic library onto these maps. The third stage was fragmenting these genomic clones into smaller overlapping clones (shotgun cloning), which were a more suitable size for sequencing. Then, the complete sequence of each chromosome could be reconstructed by assembling the fragments of sequence that overlapped with each other to generate the sequence of the genomic clone. The sequence of each genomic clone could then be fitted together using the assembly (contig) of genomic clones on the genetic and physical map.

Although the ultimate aim was a high-quality sequence of the human genome, it was recognized that the genetic and physical maps generated by the first stage of the HGP would be by themselves very useful for genetic research. The first-generation physical map was constructed by screening a yeast artificial chromosome (YAC) genomic library to isolate YACs, and overlaps were identified by restriction enzyme digest “fingerprints” and STS content mapping. These STSs were sequenced around the highly polymorphic CA-repeat markers (microsatellites) that were used to generate the genetic map. Genetic maps were also constructed. These use recombination between markers in families to deduce the distance separating and order of these markers. The first human genetic map used restriction fragment-length polymorphisms (RFLPs) as markers, which have only two alleles per marker, but common microsatellites were used to create a high-resolution genetic map.

The second stage of human genome sequencing was made simpler by the development of bacterial artificial chromosomes (BACs), cloning vectors that could carry up to 150kb of DNA. Before then, it was assumed that a contig of YACs and cosmids, carrying up to 2Mb and 40kb of DNA, respectively, would be assembled. These two types of genomic clones were found to be liable to rearrangement; the DNA in the vector could be in chunks that were not necessarily in the same order as in the genome. The BAC vector did not rearrange DNA and could carry more DNA than many other types of genomic clone.

The third stage was made easier by development of high-throughput DNA sequencing and affordable computing power to enable reassembly of the sequence fragments. It was these developments that led to the idea of whole-genome shotgun sequencing of the human genome. In contrast to the HGP plan involving the use of genetic contigs and physical maps as a framework for genomic clones and sequence, scientists suggested that the whole genome could be fragmented into small chunks for sequencing and then reassembled using overlap

between fragment sequences (whole-genome shotgun sequencing). This required large amounts of computing power to generate the correct assembly but was considerably faster than the HGP approach. Many scientists did not believe that this method would assemble the genome properly and suggested that overlap between small fragments could not be the only guide to assembly, because the genome contained many repeated DNA sequences. American biochemist J. Craig Venter believed the method could work and formed Celera, a private company that would sequence the human genome before the HGP.

Celera demonstrated that the whole-genome shotgun method would work by sequencing the genome of a model organism, the fruit fly *Drosophila melanogaster*. Despite the successful sequencing of the fly, many people were still skeptical that the method would be successful for the bigger human genome. The publicly funded HGP, in light of Celera’s competition, decided to concentrate, like Celera, on a draft of the human genome sequence (3× coverage—that is, each nucleotide has been sequenced an average of three times) before generating a more accurate map of 8× coverage. Celera had an advantage because the HGP had agreed to release all its data as it was generated onto a freely accessible database, as part of the Bermuda rules (named after the location of a series of meetings during the early stages of the HGP). This allowed Celera to use HGP data to link its sequence fragments with the BAC contigs and genetic/physical maps.

The human genome draft sequence of both groups were published in February 2001 by Celera and the HGP consortium in the journals *Science* and *Nature*, respectively. Celera had imposed restrictions on access to its genomic data, and this was a source of disagreement between the private company and the HGP. Celera scientists argue that their methods are cheaper and quicker than the HGP framework method, but HGP scientists, in turn, argue that Celera’s assembly would not have been possible without the HGP data. No matter who eventually takes credit, the finalized complete sequence was completed in 2003.

For human geneticists in general, and medical researchers in particular, the genome sequence is abundantly useful. The ability to identify genes, single-nucleotide polymorphisms, from a database search speeds up research. Previously, mapping and finding (positional cloning) a gene would take several years of research, a task that now takes several minutes. The investment in the sequencing centers continue to be of use, with a mouse sequencing project underway and many genomes of pathogenic bacteria sequenced.

This study of genomes and parts of genomes has been called genomics. The medical benefits of genomics were emphasized throughout the project, partly to ensure continuing government support. These benefits are not likely to be immediate or direct, but the genome sequence will have a significant effect on pharmacogenomics, which studies how genetic variants affect how well a drug can treat a disease. In addition, through pharmacogenomics it is hoped that there will be a substantial increase in the design of more effective drugs with lower toxicity by tailoring drug treatment to a patient's individual genetically determined drug metabolism.

The HGP has also given scientists more powerful tools in elucidating the determinants of cancer susceptibility. In many ways, cancer can be considered as a complex genetic trait, where the interaction between a person's genes and environment interact in such a way to confer a variable degree of risk of developing cancer. Through information gained from the HGP, a significant amount of information has been gleaned about high-penetrance genes that are responsible for some familial aggregations of cancer, such as the BRCA mutations and their association with breast cancer.

The impact on nonscientists has been substantial, with the HGP suggested to be the ultimate in self-knowledge.

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ORGANIZATIONS

National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Dr., MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152,

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Huntington's disease

Definition

Huntington's disease (HD) is a progressive, neurodegenerative disease causing uncontrolled physical movements and mental and emotional deterioration, as well as personality changes. Many people with this diagnosis die early but not directly from the disease itself. Instead, many die from choking, injuries from falls, or infections such as pneumonia. The disease was first discovered in 1872 by George Huntington of Pomeroy, Ohio, who described this hereditary movement disorder. The gene causing Huntington's disease was discovered in 1993 by James Gusella and colleagues after ten years of exhaustive research. HD is rare, and according to experts P. McCloghan and S.J. Tabrizi, the prevalence is about 11 to 14 individuals for every 100,000 people.

Description

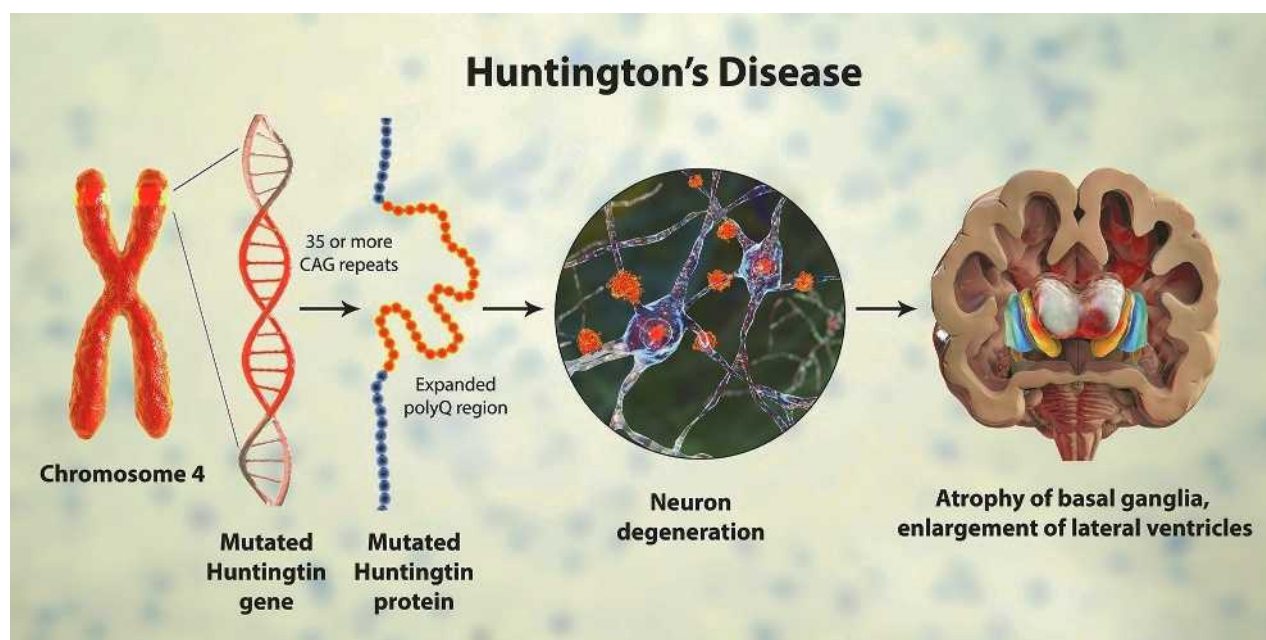
Huntington's disease is also called Huntington's chorea, from the Greek word for "dance," referring to the involuntary movements that develop as the disease progresses. It is occasionally referred to as "Woody Guthrie's disease" for the American folk singer who died from it. HD affects the basal ganglia and cerebral cortex, areas of the brain responsible for some aspects of movement control and mental functioning, causing a progressive loss of cells in those areas. A person with HD gradually develops abnormal movements and changes in cognition, behavior, and personality.

Demographics

The onset of symptoms usually occurs between the ages of 30 and 50, although in 10% of cases, the onset is in late childhood or early adolescence. In a study of subjects carrying the gene for Huntington's disease, Jordan L. Schultz, PharmD and colleagues compared "premanifest" participants (who did not yet have symptoms although they carried the gene for Huntington's disease) to those with symptoms, and they found a significant relationship between hypertension and an earlier diagnosis of Huntington's disease. In contrast, patients who had the HD gene but who had normal blood pressure had a significantly lower risk of receiving an early diagnosis of HD. Further research is needed, but if this study is validated, this may mean that keeping blood pressure to normal levels may delay the onset of symptoms in patients with the genetic mutation for Huntington's disease.

Genetic profile

Huntington's disease is caused by a change in the *HTT* gene located on chromosome 4 at 4p16.3. This gene



Molecular genesis of Huntington's disease. Expansion of the CAG trinucleotide sequence in the *htt* gene causes production of mutated Huntingtin protein leading to neurodegeneration, atrophy of brain basal ganglia, involuntary movements, and dementia. (Kateryna Kon/Science Source)

contains the coding for producing a protein called huntingtin (not a misspelling). While the full function of the huntingtin protein is not understood, researchers know that it is involved in the production and/or maintenance of neurons (nerve cells) in the brain. The gene for Huntington's disease is present at birth, but symptoms usually do not occur until middle age; however, rarely children may develop early symptoms, which is referred to as juvenile Huntington's disease. If the mutated gene is present, then symptoms will inevitably develop at some point.

The mutation in the *HTT* gene responsible for HD is found in the nucleotide coding region known as the CAG trinucleotide repeat. Normally, this section repeats 10 to 35 times; however, in individuals with HD, this section contains anywhere from 36 to over 120 repeats. The extra building blocks in the *HTT* gene cause the protein that is made from it to contain an extra section as well. It is currently thought that this extra protein section, or portion, interacts with other proteins in brain cells where it ultimately leads to cell death.

The *HTT* gene mutation is inherited in an autosomal dominant gene, meaning that only one copy of it is needed to in order develop the disease. HD affects both males and females. The mutation may be inherited from either parent, who will also be affected by the disease. A parent with the *HTT* gene mutation has a 50% chance of passing it on to each offspring. The chances of passing

on the *HTT* gene mutation are not affected by the results of previous pregnancies.

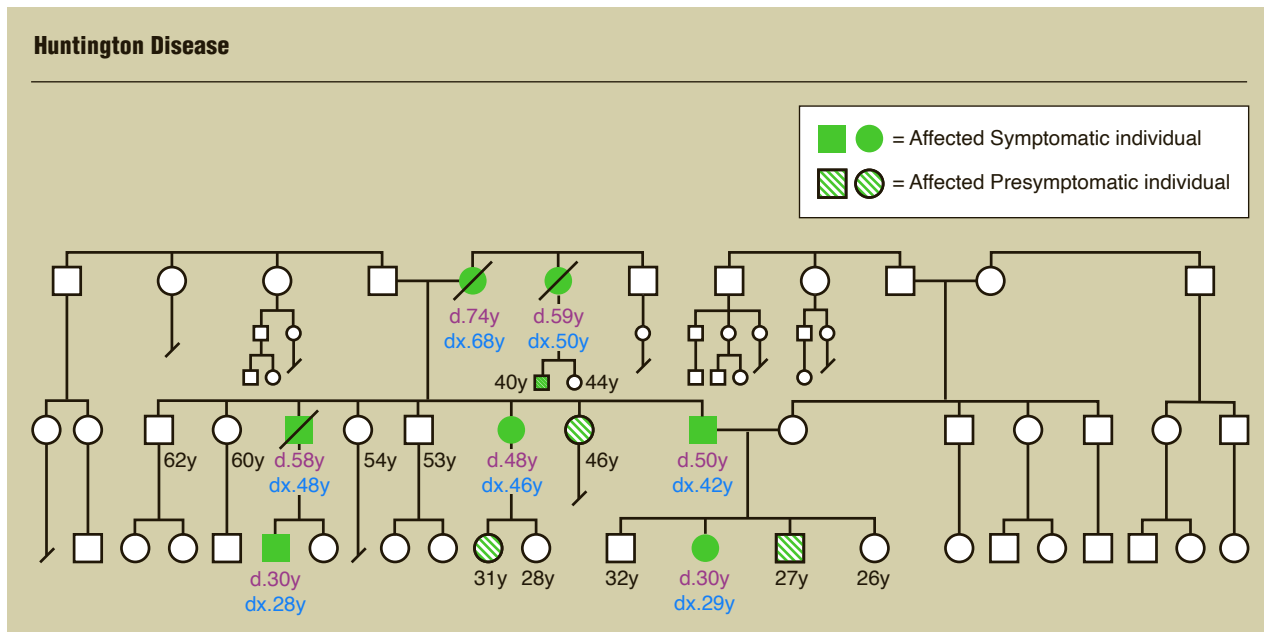
Signs and symptoms

The symptoms of HD fall into three categories: motor or movement symptoms, personality and behavioral changes, and cognitive decline. The severity and rate of progression of each type of symptom can vary from person to person.

Early motor symptoms include restlessness, twitching, and a desire to move about. Handwriting may become less controlled, and coordination may decline.

Later symptoms of HD include:

- Dystonia or sustained abnormal postures, including facial grimaces, a twisted neck, or an arched back.
- Chorea, in which involuntary jerking, twisting, or writhing motions become pronounced.
- Slowness of voluntary movements, inability to regulate the speed or force of movements, inability to initiate movement, and slowed reactions.
- Slurred speech and difficulty speaking and swallowing due to involvement of the throat muscles.
- Localized or generalized weakness and impaired balance ability.
- Rigidity, especially in late-stage disease.



Huntington's Disease: pedigree analysis chart. (Gale)

- Personality and behavioral changes, including depression, irritability, anxiety, and apathy. The person with HD may become impulsive, aggressive, or socially withdrawn.
- Cognitive changes, including loss of ability to plan and execute routine tasks, slowed thought, and impaired or inappropriate judgment.
- Short-term memory loss usually occurs, although long-term memory is usually not affected. The person with late-stage HD usually retains knowledge of his environment and recognizes family members or other loved ones, despite severe cognitive decline.

Diagnosis

Diagnosis of HD begins with a detailed medical history and a thorough physical and neurological exam. Family medical history is very important. Magnetic resonance imaging (MRI) or computed tomography (CT) scan imaging may be performed to look for degeneration in the basal ganglia and cortex, the brain regions most affected by HD.

A genetic test is available for confirmation of the clinical diagnosis. In this test, a small blood sample is taken, and DNA from it is analyzed to determine the CAG repeat number. A person with a repeat number of 30 or below will not develop HD. A person with a repeat number between 35 and 40 might not develop the disease within their normal lifespan. A person with a very high

number of repeats (70 or above) is likely to develop the juvenile-onset form. One important part of genetic testing is extensive genetic counseling.

Prenatal testing is available. A person who is at risk for HD (such as the adult child of an affected person) may obtain fetal testing without determining whether the adult carries the gene. This test, also called a linkage test, examines the pattern of DNA near the gene in both parent and fetus but does not analyze for the triple nucleotide repeat (CAG). If the DNA patterns do not match, the fetus can be assumed not to have inherited the HD gene, even if it is present in the parent. A pattern match indicates that the fetus probably has the same genetic makeup of the at-risk parent.

Treatment and management

There is no cure for HD or any treatment that can slow the rate of progression, although researchers are actively seeking new therapies and treatments. Treatment is aimed at reducing the disability caused by the motor impairments and treating behavioral and emotional symptoms.

Physical therapy is used to maintain strength and compensate for lost strength and balance. Stretching and range-of-motion exercises help to minimize contracture, or muscle shortening, a result of weakness and disuse. A physical therapist can advise on the use of mobility aids such as walkers or wheelchairs.

KEY TERMS

Basal ganglia—The region of the base of the brain that controls involuntary movement.

Cerebral cortex—The outer layer of the brain, also called the gray matter, that is responsible for thinking and functions related to language.

Chorea—An involuntary movement disorder characterized by short, jerky motions of the body.

Computed tomography (CT) scan—An imaging test that uses computers and x-rays to produce detailed images of the body.

Dystonia—An involuntary movement disorder in which muscle contractions cause parts of the body to twist.

Magnetic resonance imaging (MRI)—An imaging test that uses computers and magnetic fields to produce detailed images of the body.

Nucleotide—The building blocks of DNA and RNA.

Motor symptoms may be treated with drugs, although some studies suggest that antichorea treatment rarely improves function. Chorea (movements caused by abnormal muscle contractions) can be suppressed with drugs that deplete dopamine, an important brain chemical that regulates movement. As HD progresses, natural dopamine levels fall, leading to loss of chorea and an increase in rigidity and movement slowness. Treatment with L-dopa (which resupplies dopamine) may be useful. Frequent reassessment of the effectiveness and appropriateness of any drug therapy is necessary. Individuals with HD may also be treated with antipsychotic medications to decrease the chorea symptoms as well as to manage delusions, hallucinations, and violent behavior. Antidepressants may be used to treat depression.

Occupational therapy is used to design compensatory strategies for lost abilities in the activities of daily living, such as eating, dressing, and grooming. The occupational therapist advises on modifications to the home that improve safety, accessibility, and comfort.

Difficulty swallowing may be lessened by preparation of softer foods, blending food in an electric blender, and taking care to eat slowly and carefully. Use of a straw for all liquids can help. The potential for choking on food is a concern, especially late in the disease progression. Caregivers should learn the use of the Heimlich maneuver. In addition, passage of food into the airways increases the risk for pneumonia. A gastric feeding tube

QUESTIONS TO ASK YOUR DOCTOR

- What kinds of examinations and diagnostic tests will be performed to determine whether I have Huntington's?
- Can my baby be tested for Huntington's?
- What do these exams and tests involve?
- How should I prepare for these exams and tests?
- Will other members of my family be tested? Why or why not?

may be needed if swallowing becomes too difficult or dangerous.

Speech difficulties may be partially compensated by using picture boards or other augmentative communication devices. Loss of cognitive ability affects both speech production and understanding. A speech-language pathologist can work with the family to develop simplified and more directed communication strategies, including speaking slowly, using simple words, and repeating sentences exactly.

Early behavioral changes, including depression and anxiety, may respond to drug therapy. Maintaining a calm, familiar, and secure environment is useful as the disease progresses. Support groups for patients and caregivers form an important part of treatment.

Gene therapy to treat HD holds great promise, and there are clinical trials underway. For example, the experimental drug AMT-130 reduces the amount of the mutated huntingtin (*HTT*) gene, the toxic fragments of which cause the symptoms of HD. This trial began in 2019 and is designed to follow 26 subjects with HD for five years.

Prognosis

The person with Huntington's disease may be able to maintain a job for several years after diagnosis, despite the increase in disability. Loss of cognitive functions and increase in motor and behavioral symptoms eventually prevent the person with HD from continuing employment. Ultimately, severe motor symptoms prevent mobility. Death usually occurs 15 to 20 years after disease onset. Progressive weakness of respiratory and swallowing muscles leads to increased risk of respiratory infection and choking, the most common causes of death in persons with HD. Future research in this area is currently focusing on nerve cell transplantation.

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ORGANIZATIONS

- Huntington's Disease Society of America, 505 Eighth Avenue, Suite 902, New York, NY 10018, (800) 345-HDSA, hdsainfo@hdsa.org, <http://hdsa.org>

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Huntington chorea see **Huntington's disease**

Hutchinson-Gilford progeria syndrome

Definition

Hutchinson-Gilford progeria syndrome (HGPS), formerly known as progeria syndrome, is an extremely rare genetic disorder of unknown origin that manifests as premature aging in children. HGPS affects many parts of the body including the skin, bones, and arteries.

Description

Dr. Jonathan Hutchinson in 1886 and Dr. Hastings Gilford in 1904 first described this syndrome. The word "progeria" is from the Greek word "geras," which means "old age." HGPS is also known as progeria syndrome or Gilford syndrome.

Most patients with this genetic abnormality appear normal at birth. Signs and symptoms usually begin to develop within the first one to two years of life. Changes in skin and failure to thrive (failure to gain weight) are usually evident first, the exception being four reported cases of possible neonatal progeria. All four infants died before 20 months of age. Death in these cases appears to be related to intrauterine growth retardation and presentation of HGPS signs and symptoms at birth. The neonatal cases did not exhibit the development of arteriosclerosis (hardening of the arteries). Arteriosclerosis is the most serious complication of HGPS. Complications secondary to arteriosclerosis in childhood, adolescence, or adulthood are the leading cause of death.

Patients with HGPS develop many other signs and symptoms that present a classical appearance. The majority of patients with HGPS resemble each other. Common external findings include aging at an accelerated rate, alopecia (hair loss), prominent scalp veins, absence of fat under the skin (subcutaneous fat), scleroderma (thickening of the skin), a pinched nose, small face and jaw (micrognathia) relative to head size (bird face), delayed tooth formation, high pitched voice, and impaired or absence of sexual development. Patients are also known to experience stiffening of various joints, bone structure abnormalities, and the development of arteriosclerosis. Patients with HGPS experience average intelligence, and their cognitive abilities are usually not affected.

Genetic profile

The gene mutation responsible for HGPS is the *LMNA* gene located on the short arm of chromosome 1. The mutation is typically due to a point mutation of the coding of this gene. The *LMNA* gene codes for the protein lamin-A, which determines the shape of the nucleus of cells. The alteration in this protein, named progerin, helps derive the name of the syndrome. The shape of the nucleus is extremely important for the correct replication of cells; therefore, it is necessary for the proper growth, development, and repair of the cells of the human body. When this protein is not coded properly, as seen in HGPS, the body will not develop properly and will lead to premature death of the cell, resulting in the typical signs and symptoms of HGPS. HGPS is passed on in an autosomal dominant new mutation fashion. The disorder is transmitted to children by autosomal dominant



Photo of Ontlametse Phalatse of South Africa, shown here at age 12, was at the time the only known black female born with the extremely rare premature aging disease. Phalatse died at age 18 in 2017. (AP Images/Denis Farrell)

inheritance. This means that either affected parent (father or mother) has a 50% chance of having a child (regardless of gender) with the disorder. New mutation refers to the chance change in the structure of a gene, resulting in alterations in its function. This new mutation is believed to happen at conception sporadically and permanently (since neither parent is affected). New mutations occur as a result of both genetic and environmental factors. They can be either chromosomal abnormalities or point mutations (specific alterations in the building blocks of genes called nucleotides). Research is ongoing to identify a more specific genetic mutation that causes HGPS.

Demographics

Occurrence of HGPS is sporadic and rare, although studies suggest frequency may be related to increased parental age and increased average difference in age of parents. Approximately 200 cases have been reported to date in the world, with the estimated prevalence being 1 in 4 to 8 million.

Signs and symptoms

HGPS is progressive. The following signs develop over time:

- **General**—Patients are short and weigh less than is appropriate for height. Patients usually do not grow taller than 3.7 ft. (1.15 m) or weigh over 40 lb (15 kg). Patients with HGPS do not usually exhibit mental impairment.
- **Skin**—Skin is usually thin, dry, and wrinkled. The skin in the hands and feet is pushed inward. The skin also exhibits color (pigmentation) changes, which present clinically as yellow-brownish spots. Patients also have a decrease in fat below the skin (subcutaneous) except in

KEY TERMS

Arteriosclerosis—Hardening of the arteries that often results in decreased ability of blood to flow smoothly.

Failure to thrive—Significantly reduced or delayed physical growth.

Progeria—Genetic abnormality that presents initially as premature aging and failure to thrive in children.

Scleroderma—A relatively rare autoimmune disease affecting blood vessels and connective tissue that makes skin appear thickened.

the area below the navel. The nails of patients with HGPS are small, thin, and poorly developed. Patients experience alopecia (hair loss) of the scalp, eyelashes, and eyebrows. Scalp veins become visible and prominent as hair loss progresses.

- **Bones**—There are several abnormalities in the skeletal structure.
- **Eyes**—Patients often appear to have prominent eyes. This is in part secondary to the alterations in bone structure of the face. Patients also may experience farsightedness (hyperopia) and astigmatism. Astigmatism is the changes in the structure of the lens and cornea (parts of the internal structure of the eyes) that alter the eyes' ability to focus incoming visual images.

Diagnosis

Diagnosis is based upon physical appearance. It is usually made within the first two years of life when patients develop skin changes and fail to grow.

Patients with HGPS eventually develop skeletal system (bone and joint) changes. Patients show characteristic radiographic (x-ray) findings. In general the skeleton is hypoplastic (underdeveloped). Patients have persistent anterior fontanelles (soft spots of skull in newborn children). Patients with HGPS may also develop deterioration of the collarbone and ends of the fingers. Hip joints are affected because of alteration in the bone structure of the femur (the bone that extends from the knee upward to the pelvis). This causes the femur to sit in more of a straight-line relationship to the hip joint. This is abnormal and causes a wide-based gait (walking) and the appearance of a horse-riding stance. It is described as coxa valga. Some patients also show an increase in the amount of hyaluronic acid secreted in the urine. Hyaluronic acid is a substance in the body that is found in tissues such

QUESTIONS TO ASK YOUR DOCTOR

- What are the symptoms and signs by which HGPS can be recognized?
- What do scientists know about the genetic basis of HGPS?
- Are there medications or other treatments that can be used to alter the rate at which HGPS progresses?
- What organizations provide additional information and/or support services for parents of children with HGPS?

as cartilage. Cartilage is a flexible connective tissue that works as a joint stabilizer.

Treatment and management

There is no cure for HGPS. Treatment is symptomatic and aimed at providing psychological support. Palliative measures such as wearing a wig may be beneficial. Relief from chest pain due to changes in arteries can be accomplished by nitroglycerin, which is a medication that relaxes muscle fibers in blood vessels, causing them to expand or dilate. This permits proper blood flow to affected areas, which enables cells and tissues to receive adequate amounts of the oxygen necessary for cell maintenance.

Experimental research management

Recent evidence suggests the benefit of giving nutritional therapy and growth hormone supplementation. The combination treatment of nutritional therapy and growth hormone supplementation demonstrated an increase in growth of HGPS patients, an increase in growth factors (chemicals that promote formation) within the blood, and a decrease in the patients' basal metabolic rates. Basal metabolic rate is the minimum amount of energy (calories) that an individual needs to ingest on a daily basis in order to execute normal activities and tasks. Cruciferous vegetables may also be a utilized nutritional therapy, as sulforaphane (SFN), an antioxidant found in these leafy greens, have been shown to clear progerin buildup in cells and decrease signs and symptoms of the syndrome. This finding may lead to increased therapies with sulforaphane itself as well.

Testing for drug treatment of this disease and even reversal of the disorder *in vitro* is currently ongoing. This treatment includes the use of statins and

farnesyltransferase inhibitors to decrease the amount of progerin in the body. These drugs have reduced the amount of changes to the nuclear rim of cells, increasing the lifespan of individuals with HGPS and also decreasing the severity of the symptoms. These drugs are not yet approved by the FDA.

Arteriosclerosis is most prominent in coronary (heart) arteries and the aorta (the largest artery in the body, which has many branches supplying oxygen-filled blood to cells and tissues). Research indicates successful outcome from aggressive treatment of arteriosclerosis utilizing techniques such as coronary artery bypass (reconstruction of the heart arteries) or coronary artery balloon dilation (stretching the heart arteries in an attempt to allow increased blood flow).

Prognosis

Age of death ranges from 7 to 27 years. One documented case reports an individual living to be 45 years of age. Death is usually secondary to arteriosclerosis complications such as heart failure, myocardial infarction (heart attack), or coronary thrombosis (when a clot from the heart moves to another location, cutting the flow of blood to the new location).

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ORGANIZATIONS

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Hydrocephalus

Definition

Hydrocephalus is an abnormal expansion of cavities (ventricles) within the brain that is caused by the accumulation of cerebrospinal fluid. Hydrocephalus comes from two Greek words: *hydros* means “water” and *cephalus* means “head.”

There are two main varieties of hydrocephalus: congenital and acquired. An obstruction of the cerebral aqueduct (aqueductal stenosis) is the most frequent cause of congenital hydrocephalus. Acquired hydrocephalus may result from spina bifida, intraventricular hemorrhage, meningitis, head trauma, tumors, and cysts.

Description

Hydrocephalus is the result of an imbalance between the formation and drainage of cerebrospinal fluid (CSF). Approximately 500 milliliters (1 pint) of CSF is formed within the brain each day, by ependymal cells in structures collectively called the choroid plexus. These cells line chambers called ventricles that are located within the brain. There are four ventricles in a human brain. Once formed, CSF usually circulates among all the ventricles before it is absorbed and returned to the circulatory system. The normal adult volume of circulating CSF is 150 milliliters. The CSF turnover rate is more than three times per day. Because production is independent of absorption, reduced absorption causes CSF to accumulate within the ventricles.

Hydrocephalus may be present at birth (congenital) or acquired. Congenital hydrocephalus may be caused by events that occur during fetal development or by genetic abnormalities. Acquired hydrocephalus develops at the time of birth or at some point afterward. It can affect persons of all ages and may be caused by injury or disease. Hydrocephalus is usually described as “communicating” or “noncommunicating.” Noncommunicating hydrocephalus is the most common variety, caused by reduced CSF absorption that occurs when one or more passages connecting the ventricles become blocked. This prevents the movement of CSF to its drainage sites in the subarachnoid space just inside the skull. In communicating hydrocephalus, a reduction in the CSF absorption rate is caused by damage to the absorptive tissue.

Both types of hydrocephalus lead to an elevation of the CSF pressure within the brain. The increased pressure pushes aside the soft tissues of the brain. This squeezes and distorts them. This process also results in damage to these tissues. In infants whose skull bones have not yet fused, the intracranial pressure is partly relieved by

expansion of the skull so that symptoms may not be as dramatic. Both types of elevated-pressure hydrocephalus may occur from infancy to adulthood.

There are two other types of hydrocephalus that primarily affect adults: normal-pressure hydrocephalus and hydrocephalus ex-vacuo. Normal-pressure hydrocephalus is characterized by ventricle enlargement without an apparent increase in CSF pressure. This type affects mainly the elderly. Hydrocephalus ex-vacuo occurs when stroke or traumatic injury damage the brain.

Hydrocephalus has a variety of causes including the following:

- congenital brain defects
- hemorrhage, either into the ventricles or the subarachnoid space
- infection of the central nervous system (syphilis, herpes, meningitis, encephalitis, or mumps)
- tumor

Genetic profile

A growing body of evidence suggests that genetic factors play a major role in congenital hydrocephalus. Genetic studies in animal models have helped understand the underlying pathology of the condition. At least 43 mutants/loci linked to hydrocephalus have been identified in animal models and humans. In animal models, nine genes associated with hydrocephalus have been identified. Molecular genetic studies have shown that the responsible gene for human congenital hydrocephalus is located at Xq28 encoding for *LICAM* (L1 cell adhesion molecule).

The *LICAM* gene provides instructions for producing the L1 protein, found throughout the nervous system on the surface of neurons. It is a trans-membrane protein, meaning that it spans across the cell membrane and plays an important role in the development and organization of neurons, the formation of the protective sheath (myelin) that surrounds nerve fibers, and the formation of junctions between nerve cells (synapses) that allow cell-to-cell communication. Some 200 mutations of this gene have been associated with L1 syndrome, a disorder characterized by muscle stiffness (spasticity) of the lower limbs, intellectual disability, hydrocephalus, and thumbs bent toward the palm (adducted thumbs).

Demographics

The incidence of hydrocephalus is difficult to establish since there is no national registry or database of people with the condition. According to the National Institute of Neurological Disorders and Stroke (NINDS), hydrocephalus is believed to occur in approximately 1 of every



Transillumination of the head of an infant suffering from hydrocephalus. Yellow areas show fluid accumulation inside the skull that has caused enlargement of the baby's head. To prevent brain damage, the fluid must be drained by means of a tube (shunt) inserted through a hole in the skull; surgery is usually successful. (Alfred Benjamin/Science Source)

500 live births. The incidence of adult-onset hydrocephalus is not known.

Signs and symptoms

Signs and symptoms of elevated-pressure hydrocephalus include the following:

- headache
- nausea and vomiting, especially in the morning
- lethargy
- disturbances in walking (gait)
- double vision
- subtle difficulties in learning and memory
- delay in children achieving developmental milestones

Irritability is the most common sign of hydrocephalus in infants. If this is not treated, it may lead to lethargy. Bulging of the fontanelles, or the soft spots between the skull bones, may also be an early sign. When hydrocephalus occurs in infants, fusion of the skull bones is prevented. This leads to abnormal expansion of the skull.

Symptoms of normal-pressure hydrocephalus include dementia, gait abnormalities, and incontinence (involuntary urination or bowel movements).

Diagnosis

Imaging studies—x-ray, computed tomography scan (CT scan), ultrasound, and especially magnetic resonance imaging (MRI)—are used to assess the presence and

KEY TERMS

Cerebral ventricles—Spaces in the brain that are located between portions of the brain and filled with cerebrospinal fluid.

Cerebrospinal fluid—Fluid that circulates throughout the cerebral ventricles and around the spinal cord within the spinal canal.

Choroid plexus—Specialized structures located in the ventricles of the brain that produce cerebrospinal fluid.

Fontanelle—One of several “soft spots” on the skull where the developing bones of the skull have yet to fuse.

L1 syndrome—Inherited disorder that primarily affects the nervous system caused by mutations in the *L1CAM* gene. L1 syndrome involves a variety of features including muscle stiffness (spasticity) of the lower limbs, intellectual disability, hydrocephalus, and thumbs bent toward the palm (adducted thumbs).

Neuron—A nerve cell that sends and receives electrical signals over long distances within the body.

Shunt—A small tube placed in a ventricle of the brain to direct cerebrospinal fluid away from the blockage into another part of the body.

Stenosis—The constricting or narrowing of an opening or passageway.

Subarachnoid space—The space between two membranes surrounding the brain, the arachnoid and pia mater.

location of obstructions, as well as changes in brain tissue that have occurred as a result of the hydrocephalus. Lumbar puncture (spinal tap) may be performed to aid in determining the cause when infection is suspected.

Treatment and management

The primary method of treatment for both elevated and normal-pressure hydrocephalus is surgical installation of a shunt. A shunt is a tube connecting the ventricles of the brain to an alternative drainage site, usually the abdominal cavity. A shunt contains a one-way valve to prevent reverse flow of fluid. In some cases of noncommunicating hydrocephalus, a direct connection can be made between one of the ventricles and the subarachnoid space, allowing drainage without a shunt.

QUESTIONS TO ASK YOUR DOCTOR

- Your tentative diagnosis is that our infant has hydrocephalus. On what is this diagnosis based?
- What tests are available to confirm your diagnosis?
- What treatments or procedures are available for our child's condition?
- Should my spouse and I decide to have more children, what is the risk that they will also have hydrocephalus?

Installation of a shunt requires lifelong monitoring by the recipient or family members for signs of recurring hydrocephalus due to obstruction or failure of the shunt. Other than monitoring, no other management activity is usually required.

Some drugs may postpone the need for surgery by inhibiting the production of CSF. These include acetazolamide and furosemide. Other drugs that are used to delay surgery include glycerol, digoxin, and isosorbide.

Some cases of elevated-pressure hydrocephalus may be avoided by preventing or treating the infectious diseases that precede them. Prenatal diagnosis of congenital brain malformation is often possible.

Clinical trials

Clinical trials on hydrocephalus are currently sponsored by the National Institutes of Health (NIH) and other agencies. As of 2015, there were three trials reported as under way by NIH. Examples of studies include the following:

- a study to determine which combination of tests will enable physicians to predict whether a patient with symptoms of normal-pressure hydrocephalus will improve with a shunt (NCT00613886)
- the evaluation of a new procedure, endoscopic third ventriculostomy (ETV), to treat hydrocephalus (NCT00652470)
- the Core Data Project, which aims to obtain data about all neurosurgical hydrocephalus events from a network of clinical centers to help investigators understand the variability, progression, and current treatment practices for hydrocephalus in children, with an ultimate goal of better guiding and assessing therapeutic intervention and

providing recommendations on patient care (NCT00670735)

- the evaluation of an ultrasonic flow sensor to accurately measure flow in hydrocephalic shunts (NCT00652197)

Clinical trial information is constantly updated by NIH and the most recent information on hydrocephalus trials can be found at <http://www.clinicaltrials.gov>

Prognosis

The prognosis for elevated-pressure hydrocephalus depends on a wide variety of factors, including the cause, age of onset, and the timing of surgery. Studies indicate that about half of all children who receive appropriate treatment and follow-up will develop IQs greater than 85. Those with hydrocephalus at birth do better than those with later onset due to meningitis. For individuals with normal-pressure hydrocephalus, approximately half will benefit from the installation of a shunt.

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ORGANIZATIONS

Hydrocephalus Association, 4340 East-West Hwy., Suite 905, Bethesda, MD 20814, (301) 202-3811 or (888) 598-3789, info@hydroassoc.org, <http://www.hydroassoc.org>

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National Institute of Neurological Disorders and Stroke (NINDS), PO Box 5801, Bethesda, MD 20824, (800) 352-9424 or (301) 496-5751, <http://www.ninds.nih.gov>

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Hydrolethalus syndrome 1 (HLS1)

Definition

Hydrolethalus syndrome 1 (HLS1) is a rare and primarily lethal disorder characterized by severe birth defects and stillbirth.

Description

HLS1 is a congenital condition characterized by multiple birth defects including hydrocephalus (excess fluid in the brain), polydactyly (extra fingers and toes), incomplete lung development, and anomalies of the brain, heart, face, lip, and palate. The birth defects are typically extreme enough to cause stillbirth or death within a few days of birth. A less common name for HLS1 is Salonen-Herva-Norio syndrome, after the Finnish researchers who first described it in 1981.

Genetic profile

HLS1 is caused by mutations in the *HYLS1* gene, which carries instructions for proteins that are contained in the cytoplasm of the cell. It is unclear how mutations in the *HYLS1* gene cause the malformations that are characteristic to HLS1.

Mutations in the *HYLS1* gene are inherited in an autosomal recessive pattern. Autosomal means that the syndrome is not carried on a sex chromosome, while recessive means that both parents must carry the gene mutation in order for their child to have the disorder. Some cases of HLS1 have been observed where the parents are related by blood (consanguineous). Parents with one child affected by HLS1 have a 25% chance that their next child will also be affected with the disease.

Each parent passes 23 chromosomes, or units of genetic information, to the infant. Structurally, each chromosome has a short segment or “arm,” called the p arm, and a long arm, called the q arm, extending from a central region called the centromere. Along each arm the chromosome is further divided by numbering the bands down the arm according to their appearance under a microscope. Each band corresponds to specific genes. Based on studies of genetic material from affected and nonaffected families, the gene location for HSL1 was determined to be 11q23-25, or somewhere between the 23rd and 25th band of the q arm of chromosome 11.

Demographics

The majority of cases of HLS1 have been reported in people of Finnish ancestry. In Finland the incidence of

KEY TERMS

Atrioventricular communis defect—A birth defect of the heart in which the canal between the upper and lower chambers of the heart does not form correctly.

Congenital—Present at birth.

Cytoplasm—The fluid inside a cell.

Foramen magnum—The round opening at the base of the skull through which the spinal cord passes to join the spine.

Sex chromosome—Genes that carry the information that determines gender.

HLS1 is estimated at 1 in every 20,000. Fewer than 20 cases have been reported outside of Finland.

HLS1 affects fetal development in the womb and is a syndrome of infants only, due to the extremely serious birth defects caused by the disorder. No cases of survival into childhood or adulthood have been reported. The syndrome appears to affect both males and females with equal probability.

Signs and symptoms

Prenatal symptoms include hydramnios, an excess of amniotic fluid in the womb. Babies with HLS1 are often delivered preterm and may be stillborn.

All or most of the following congenital anomalies are seen in HLS1:

- Hydrocephalus—Excess fluid in the brain
- Heart defects—Atrioventricular communis defect
- Pulmonary hypoplasia—Incomplete development of the lungs
- Polydactyly—Extra fingers and toes specifically, an extra big toe and an extra little finger on both hands and feet
- Club foot—Abnormally positioned, inwardly turned feet
- Cleft lip or palate—An opening in the lip and/or palate
- Micrognathia—Small lower jaw
- Hypoplastic (small) eyes
- Nose—Poorly formed
- Keyhole-shaped foramen magnum—A keyhole shaped defect at the base of the skull
- Abnormal genitalia—Abnormal sex organs

QUESTIONS TO ASK YOUR DOCTOR

- What are the chances that I will have another baby with HLS1?
- Is there a prenatal test to see whether my baby has HLS1?
- Is there a way to prevent HLS1?
- Should my partner and I have a family history screening?

Diagnosis

HLS1 can be diagnosed prenatally by ultrasound scanning in as early as the 11th week of gestation. After birth, the presence of multiple malformations, especially the extreme swelling of the skull and other brain and spinal cord defects, can confirm the diagnosis. A family history and genetic testing may be useful in making the diagnosis certain.

Treatment and management

There is no treatment for HLS1 other than management of the specific medical conditions and providing care and comfort to the infant. The severity of symptoms almost always causes death of the infant within a few days of birth, that is if the fetus survives to full term.

Genetic counseling is particularly important in the prenatal treatment and management of HLS1 and to help parents plan subsequent pregnancies.

Prognosis

The prognosis for infants with HLS1 is extremely poor. Most affected infants are stillborn or die within the first day of life. Only a handful of cases of survival past the neonatal period have been reported, and the longest survival period was 44 days.

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ORGANIZATIONS

Genetic Alliance, 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008-2369, (202) 966-5557, (202) 966-8553, info@geneticalliance.org, <http://www.geneticalliance.org>

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Hydrometrocolpos syndrome see **McKusick-Kaufman syndrome**

Hydrops fetalis

Definition

Hydrops fetalis (HF) refers to the abnormal accumulation of fluid in the skin, body cavities, umbilical cord, and placenta of an unborn baby. HF can result from many different diseases and structural defects. It is traditionally divided into two major categories: immune HF and non-immune HF. Immune HF is caused by Rh incompatibility, which was the most common cause of HF until the advent of anti-Rh antibody treatment (RhoGAM) during pregnancy. All other causes of HF are termed nonimmune HF. Nonimmune hydrops fetalis (NIHF) may be caused by chromosomal aberrations, other genetic disorders, infections, anemias, such structural birth defects as congenital heart disease, and many other conditions.

Description

HF occurs when a baby has a condition or birth defect that causes accumulation of excess fluid, known as edema, in the skin and other body cavities. Immune HF occurs when a mother's blood group is Rh-negative (this term means that she does not have the Rh factor [protein] on the surface of her blood cells) and her baby's blood group is Rh-positive (the baby has the Rh protein on its blood cells). During the pregnancy a small amount

of the baby's blood crosses into the mother's circulatory system. When this exchange happens, the mother's immune system recognizes the Rh protein on the baby's blood cells as foreign and makes antibodies to the Rh protein. The antibodies can then cross back over to the baby and attack its blood cells, destroying them and causing anemia. The anemia causes heart failure, subsequent edema, and ultimately HF. The mother's immune response becomes greater with each subsequent pregnancy in which the baby has Rh-positive blood and thus the HF becomes worse. Administration of anti-Rh antibodies during all of an Rh-negative mother's pregnancies will prevent her from ever developing an immune response to Rh-positive blood and will prevent HF.

The most common causes of nonimmune HF include heart disease (congenital malformations and arrhythmia), chromosome aberrations (Turner syndrome and Down syndrome), other genetic disorders that cause anemia (particularly alpha thalassemia), and anemia caused by other disorders (fetomaternal transfusion and twin-twin transfusion). Other causes include infections, metabolic disorders, and tumors. In all there are over 100 separate causes of nonimmune HF.

All disorders that cause HF do so by three common mechanisms that include heart failure, hypoproteinemia (low levels of protein in the bloodstream), and vascular or lymphatic obstruction. Some disorders combine two or more of these mechanisms to cause HF. Most disorders cause some degree of heart failure. Anemia causes heart failure by increasing the work of the heart so much that it fails (high-output heart failure). Isolated congenital heart disease or conditions that have congenital heart disease as a feature often develop heart failure due to a poorly functioning heart (low-output heart failure). Conditions that block the flow of blood or lymph can cause edema and HF. Examples include tumors and congenital malformations of the blood and lymphatic vessels. Conditions that lower the amount of protein in the blood can cause edema and HF by allowing fluid to easily leak out of the vessels and collect in the soft tissues and body cavities. Examples include metabolic conditions that damage the liver and prevent it from producing enough protein, such as Gaucher disease and Sly disease.

Genetic profile

Many causes of HF do not have a genetic etiology. Because the recurrence risk can range from 0% to 100% depending on the underlying cause, an accurate diagnosis is important. Infectious causes are not genetic and should not recur in subsequent pregnancies. Other causes of HF have a specific genetic profile. Immune causes are due to a difference in the antigens on the mother's and baby's blood cells, which can recur in subsequent pregnancies if

anti-Rh antibodies are not given to the mother. Recurrence can either be 50% or 100% depending on the father's Rh-antigen status.

If HF is caused by a chromosome aberration, the risk of recurrence is about 1%, as most of these conditions occur sporadically and are not inherited.

Malformations causing HF, such as congenital heart disease, are most commonly inherited as multifactorial traits. This type of inheritance pattern is caused by multiple genes and environmental factors working in combination. The recurrence risk for a multifactorial trait is about 3%–5% with each subsequent pregnancy.

Higher risk of recurrence occurs when a single gene condition is the cause of HF. Such autosomal recessive conditions as alpha thalassemia major, Gaucher disease, and Sly disease have a recurrence risk of 25% with each subsequent pregnancy. The X-linked recessive disorder G-6-P-deficiency has a recurrence risk of 50% with each additional male child and 0% with each additional female child.

Some dominant conditions can cause HF; these are often lethal and usually represent a new mutation in that child. In these cases the recurrence risk is about 1%. Other dominant conditions such as myotonic dystrophy and lymphedema distichiasis are variable; recurrence may be 50% with each child.

Demographics

The incidence of common HF in the United States is estimated at 1 in 600 to 1 in 4,000 pregnancies. The incidence of immune hydrops has significantly decreased with the wide use of passive immunization using Rh immunoglobulin for Rh-negative mothers at 28 weeks gestation and postpartum. This program has resulted in a decline in the incidence of Rh-hemolytic disease of the fetus or newborn, from 65 in 10,000 births in the United States in 1960 to 6.7 in 10,000 births in 2002.

HF is much more common in Southeast Asia and North Africa. In Thailand, the expected frequency of hydrops from homozygous alpha thalassemia or Bart's hydrops alone is 1 in 500 to 1 in 1,500 pregnancies. Bart's hydrops, also known as Hb Bart's syndrome, is the most severe form of alpha thalassemia and is marked by frequent miscarriage of the affected pregnancy or the death of the baby shortly after birth. Accurate reports from the Mediterranean region are lacking; however, the commonness of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and of defects in alpha-chain hemoglobin production in several populations from this region suggest that the incidence of HF is higher than it is in the United States. The single exception is California, which

KEY TERMS

Alpha thalassemia—A genetic disorder in which mutations in the *HBA1* and *HBA2* genes on chromosome 16 lead to impaired production of a subtype of hemoglobin known as alpha globin. The severity of the disorder depends on how many of the four alpha globin chains are affected by mutations.

Autosomal dominant—A pattern of genetic inheritance in which only one abnormal gene is needed to display the trait or disease.

Edema—An abnormal accumulation of fluid beneath the skin and in the cavities of the body.

G-6-P deficiency—An X-linked genetic disorder that predisposes patients to the spontaneous destruction of red blood cells in response to certain triggers that include certain foods, medications, and illnesses. It is caused by a mutation on the X chromosome at Xq28.

Gaucher disease—A genetic disorder characterized by the accumulation of fatty substances in certain cells and organs. It is caused by a mutation in a gene on chromosome 1 and is inherited in an autosomal recessive pattern. It is named for the French physician Philippe Gaucher, who first described it in 1882.

Hb Bart's syndrome—The form of alpha thalassemia most likely to cause hydrops fetalis in the fetus. The name of the syndrome refers to a defective type of hemoglobin (Hb) that has almost no ability to carry oxygen to the fetus's tissues and to the hospital in London (St. Bartholomew's, or Bart's) where the syndrome was first identified.

Indirect Coombs test—A test given to pregnant women to detect the presence of circulating antibodies against red blood cells.

Lymphedema distichiasis—A genetic syndrome caused by a mutation in the *FOXC2* gene on chromosome 16 and characterized by localized fluid

retention and swelling of the limbs (lymphedema) and a double row of eyelashes (distichiasis).

Myotonic dystrophy—A chronic progressive multi-system disease characterized by general muscular weakness, cataracts, and changes in the endocrine system. It is inherited in an autosomal dominant pattern and is caused by mutations in either the *DMPK* gene on chromosome 19 or the *ZNF9* gene on chromosome 3.

Rh factor—An inherited trait that refers to a protein found on the surface of red blood cells. A person whose blood cells have the protein is said to be Rh-positive; a person whose blood cells lack the protein is Rh-negative. "Rh" stands for Rhesus, the species of monkey used in the medical research that led to the discovery of the Rh factor.

RhoGAM—The trade name of a medication given by intramuscular injection to a pregnant woman to prevent Rh disease in the newborn. Its generic name is Rho (D) immune globulin.

Sly disease—Also called Sly syndrome, an autosomal recessive lysosomal storage disease caused by a mutation in a gene on chromosome 7. It is named for William Sly, the American biochemist who discovered it.

Toxemia of pregnancy—A condition characterized by high blood pressure and large amounts of protein in the urine. It is also called pre-eclampsia. If left untreated, it may result in the breakdown of red blood cells, liver and kidney dysfunction, and seizures.

Turner syndrome—A genetic disorder in which a female has only one normal X chromosome due to a chromosomal abnormality in which all or part of the second X chromosome is missing.

has experienced a high rate of immigration from Southeast Asia and North Africa in recent years.

Signs and symptoms

All babies with HF have edema of the skin, soft tissues, and placenta. Often the body cavities (including the abdominal cavity [ascites], pleural cavity, and pericardial cavity) will show fluid collections. The back of the neck is particularly prone to fluid collections and can sometimes contain so much fluid that it appears as a large cystic mass called a cystic hygroma. Such internal organs as the liver, spleen, and heart can become enlarged with

accumulated fluid. All of these signs may be seen in the newborn or before birth using ultrasonography.

Other signs of HF are variable and often depend on the underlying cause. Common to most causes of HF are decreased movements during the pregnancy, respiratory distress from poor lung development due to compression of the lungs by accumulated fluid, and heart failure.

Diagnosis

HF is easily diagnosed at birth by the swollen appearance of an affected baby, but the diagnosis is often

QUESTIONS TO ASK YOUR DOCTOR

- How common are the various forms of nonimmune HF in the general American population?
- How early during pregnancy can nonimmune HF be detected?
- Should I or other family members consider genetic testing for alpha thalassemia or the other genetic syndromes associated with HF?
- Can you recommend a nearby medical center with special expertise in delivering infants diagnosed with HF?

made during the pregnancy by ultrasonography. Determining the cause of the HF is more challenging, but necessary, for possible treatment and recurrence risk assessment. The Society for Maternal-Fetal Medicine (SMFM) recommends first administering an antibody screen known as an indirect Coombs test to determine whether the HF is nonimmune. Testing the mother for infections such as toxoplasmosis, rubella, cytomegalovirus (CMV), herpes, syphilis, and parvovirus B19 can rule out most infectious causes of HF. A high-resolution ultrasound will help determine if a baby has any major structural malformations or tumors that could cause HF. At the same time as the ultrasound, a percutaneous umbilical artery blood sampling (PUBS) procedure can be done. This procedure consists of passing a needle through the mother's abdomen into the uterine cavity and then into the baby's umbilical cord to withdraw a small amount of blood. This blood is then used to test for Rh antibodies, anemia, chromosome aberrations, and other suspected conditions. Molecular genetic testing for Hb Bart's syndrome is available at the molecular diagnostics laboratory at the University of California, San Francisco. These diagnostic steps determine the cause of the HF in many cases, but sometimes the cause remains unknown.

Treatment and management

Immune HF is easily prevented by administration of anti-Rh antibodies to Rh-negative pregnant women. Most nonimmune HF causes have no specific treatment other than early delivery and supportive care. The SMFM recommends delivery at a specialized facility with experience in stabilizing and treating critically ill newborns. HF associated with alpha thalassemia is often treated by termination of the pregnancy, as the fetus is unlikely to survive until birth and the mother is at risk for severe complications of the pregnancy, including toxemia of pregnancy (pre-eclampsia). HF caused by some types of

anemia can be treated by a blood transfusion via a PUBS procedure. Fetal arrhythmia can often be treated by antiarrhythmic medications taken by the mother. Fetal operations are indicated for HF caused by sacrococcygeal teratomas (a type of tumor seen in newborns) and some other structural malformations.

Prognosis

The prognosis of HF is poor. A baby who is diagnosed by ultrasonography before birth has a less than 30% chance of survival. Babies who are born alive have a 50% chance of survival. The specific cause of HF influences the chances of survival, with chromosome aberrations and alpha thalassemia having a higher mortality rate, and infectious etiologies having a lower mortality rate.

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ORGANIZATIONS

- American Congress of Obstetricians and Gynecologists (ACOG), PO Box 70620, Washington, DC 20004-2188, (202) 638-5577 or (800) 673-8444, <http://www.acog.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>
- Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

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Hyperactivity of childhood see **Attention deficit hyperactivity disorder**

Hyperglycemia with ketoacidosis and lactic acidosis (propionic type) see **Propionic acidemia**

Hyperlipoproteinemia

Definition

Hyperlipoproteinemia refers to a group of acquired and inherited disorders whose common denominator is excessive levels of lipids (fats) in the blood caused by a metabolic disorder. It is also referred to as hyperlipidemia. The condition is a major cause of coronary heart disease (CHD).

Description

The acquired form of hyperlipoproteinemia occurs as a condition secondary to another disease, such as diabetes mellitus, hypothyroidism, or nephrosis. The hereditary, or inherited, form of hyperlipoproteinemia is classified into five major types.

Lipids are an essential part of human metabolism and are a primary source of energy for the body. Lipids are produced by cells in the body and, along with carbohydrates and proteins, are components of all life. Lipids are essentially oil-based and as such do not mix with a water-based liquid such as blood. Yet both must be carried through the body's circulatory system. So to get around this obstacle, lipids attach themselves to proteins. This combination of lipids and proteins is called lipoproteins, which are water-soluble particles that can be carried through the bloodstream.

Some of the chemicals in the lipoproteins are fatty nutrients that are absorbed by the intestines for use in other parts of the body. Cholesterol is carried by lipoproteins through the bloodstream to the liver and ultimately to the bowel for excretion. If the substances in the lipoproteins are not properly balanced, cholesterol will stay in the tissues instead of being excreted. It can also build up in blood vessels, eventually restricting and even blocking blood flow.

There are five different densities of lipoproteins, each containing triglycerides, cholesterol, phospholipids (lipids with phosphorus attached), and special proteins. The lipoproteins are high-density lipoproteins (HDL), low-density lipoproteins (LDL), intermediate-density lipoproteins, very low-density lipoproteins (VLDL), and chylomicrons. HDL is commonly called "good" cholesterol and LDL "bad" cholesterol. The two major lipoprotein groups are HDL and LDL.

HDL helps prevent fat buildup throughout the body by carrying cholesterol from the arteries to the liver, where it is disposed of. Abnormally low levels of HDL, fewer than 30 milligrams per deciliter (mg/dL) of blood, are associated with a greater risk for coronary heart disease and stroke. LDL carries most of the cholesterol in

the body, so an excess of LDL, usually 160 mg/dL of blood, can clog the arteries with cholesterol buildup. This can lead to atherosclerosis, commonly referred to as hardening of the arteries, or acute myocardial infarction (heart attack).

The five types of inherited hyperlipoproteinemia are as follows:

- Type I, characterized by high levels of chylomicrons and triglycerides and a deficiency of lipoprotein lipase, an enzyme that accelerates the breakdown of lipoproteins. Disease onset is usually in infancy.
- Type II, broken into two subtypes, type II-a and type II-b. Both subtypes display high levels of blood cholesterol. People with type II-b also have high levels of triglycerides in their blood. Disease onset is usually after age 20.
- Type III, also called broad beta disease, is characterized by high blood levels of cholesterol and triglycerides and the presence of a lipoprotein called apolipoprotein E (ApoE) genotype E2/E2. Disease onset is usually in adults.
- Type IV, characterized only by high triglyceride levels in the blood. Disease onset is usually during puberty or early adulthood.
- Type V, characterized by increased blood levels of chylomicrons and triglycerides and low levels of LDL and HDL. Disease onset is usually in children or adults.

Genetic profile

As of 2015, type I hyperlipoproteinemia was considered to be due to a mutation in the *LPL* and *APOC-II* genes, as opposed to an autosomal dominant disorder as previously thought. These genes have a role in the activity of cholesterol and the removal of visceral fat.

Type III hyperlipoproteinemia is an autosomal recessive disorder that affects males and females. "Autosomal" means that the gene does not reside on the sex chromosome. People with only one abnormal gene are carriers, but since the gene is recessive, they do not have the disorder. Their children could be carriers of the disorder but not show symptoms of the disease. Both parents must have one of the abnormal genes for a child to have symptoms of type III hyperlipoproteinemia. When both parents have the abnormal gene, there is a 25% chance that each child will inherit both abnormal genes and have the disease. There is a 50% chance that each child will inherit one abnormal gene and become a carrier of the disorder but not have the disease itself. There is a 25% chance that each child will inherit neither abnormal gene and not have the disease or be a carrier.

KEY TERMS

Cholesterol—A steroid alcohol $C_{27}H_{45}OH$ present in animal cells and body fluids that regulates membrane fluidity, functions as a precursor molecule in various metabolic pathways, and functions as a constituent of LDL; it may cause arteriosclerosis.

Hyperlipoproteinemia—An increase in the amount of lipoproteins in the body.

Lipids—Any of various substances that are soluble in nonpolar organic solvents (as chloroform and ether) that with proteins and carbohydrates constitute the principal structural components of living cells, and that include fats, waxes, phospholipids, cerebroside, and related and derived compounds.

Lipoprotein—A complex protein that carries lipids throughout the body.

Type III hyperlipoproteinemia is a mutation in the production of *ApoE*, an apolipoprotein that has a role in the uptake of types of fat in the liver. The *ApoE* gene is located on the long arm of chromosome 19. When this protein is not functioning correctly, it will not remove the fat from the liver, hence a buildup of cholesterol in the body.

The other types of hyperlipoproteinemia are autosomal dominant. This means that they occur when an abnormal gene from one parent is capable of causing the disease even though the matching gene from the other parent is normal. The abnormal gene dominates the outcome of the gene pair. This means that there is a 50% chance that each child of the couple will have the disease. Consequently, there is a 50% chance that each child will not inherit the defective gene and will not have the disease.

Demographics

Hyperlipoproteinemia can affect people regardless of age, gender, race, or ethnicity; however, hyperlipoproteinemia III is known to affect males more than females. All adults, starting at age 20, should be tested for hyperlipoproteinemia at least once every five years, as recommended by the National Cholesterol Education Program (NCEP) of the National Institutes of Health (NIH). People considered to be high risk for hyperlipoproteinemia should be tested more often and include those with a diet high in fat and cholesterol, who have a family history of the disorder, who use oral contraceptives or take estrogen, or who have diabetes mellitus, hypothyroidism,

nephrosis, or alcoholism. Ethnic groups that have a higher risk of developing hyperlipoproteinemia include Latinos, Native Americans, African Americans, and Pacific Islanders.

Signs and symptoms

It is very common for people with hyperlipoproteinemia to show no outward signs of the disorder. However, there are several general signs that may indicate a person has the disorder, including obesity; yellowish skin; fatty yellow patches or nodules on the skin, especially the eyelids, neck, and back; inflamed tendons; an enlarged spleen; an inflamed pancreas; nausea and vomiting; or abdominal pain. However, these are also symptoms of a variety of other conditions, so for hyperlipoproteinemia to be diagnosed, blood tests are needed.

Diagnosis

Diagnosis involves a series of blood tests to measure lipid levels and determine the type of hyperlipoproteinemia. Blood tests, usually taken after a 12-hour fast, include measurement of total serum cholesterol, HDL, LDL, VLDL, and triglycerides, as well as measurement for the presence of apolipoprotein E. When hyperlipoproteinemia secondary to another disorder has been excluded and inherited hyperlipoproteinemia seems likely, first-degree relatives should be tested. These include parents, children, and siblings. The diagnosis for type I is made when at least three of the following criteria are met:

- clinical presentation of phenotype
- an apoprotein to B/LDL-C ration of less than 1.0 or the presence of small, dense LDLs
- secondary hyperlipidemia from another disease or disorder ruled out
- one or more immediate relatives diagnosed with types of hyperlipoproteinemia

The diagnosis for type III hyperlipoproteinemia is made with major criteria of increased serum cholesterol and serum TG levels, a change in the pattern of LDL and VLDL as seen on electrophoresis, abnormalities in *ApoE* as seen on electrophoresis with or without xanthoma, increased serum *ApoE*, a change in the ratio of VLDL to serum TG, a decreased level of LDL-C, and/or a diagnosis of cardiovascular disease(s).

Treatment and management

Hyperlipoproteinemia treatment is usually based on a threefold attack: diet, exercise, and lipid-lowering medications. People who are overweight should begin a program to slowly but consistently lose weight until they are at or near the recommended weight for their height

QUESTIONS TO ASK YOUR DOCTOR

- How often should I get bloodwork to check my levels?
- What type do I have, and what are the chances my children will be diagnosed with it as well?
- What dietary changes should I make?
- How long will I need to be on a diet?
- What complications should I be on the lookout for?
- How much exercise should I be doing daily/weekly, and what kind?
- Is there a prescription that is best for me?
- Is it possible for me to control this disorder without pharmaceuticals?

and body frame. It is essential to eat a diet low in fat. “Bad” cholesterol is found only in animal products, so eating a diet very low in meat, especially avoiding cow and pig products, and unhealthy oils, especially in fried foods, is extremely important. Exercise also plays a vital role. A minimum of 20 minutes of aerobic exercise three times a week is beneficial, and 30 minutes or more daily is ideal. The exercise can take the form of running, jogging, cycling, swimming, cardiovascular machines, or even walking briskly.

Eating healthy and exercising regularly, while extremely beneficial, are not always enough to bring lipid levels to the desired range. Prescription medications are often required. There is a wide range of medications available to manage lipid levels. The most prescribed are HMG-CoA-reductase inhibitors, commonly called “statins,” which hinder the body’s production of cholesterol. Statins include cerivastatin (Baycol), fluvastatin (Lescol), lovastatin (Mevacor), pravastatin (Pravachol), atorvastatin (Lipitor), and simvastatin (Zocor). Other first-line medications include bile acid sequestrants, cholestyramine (Questran), colesevelam (Welchol), and colestipol (Colestid). Also, probucol (Lorelco) is sometimes used.

The type of drug prescribed may vary, depending on the lipid test results and the type of hyperlipoproteinemia that is diagnosed. For example, people with type III of the disorder respond better when prescribed fibric acid derivatives such as gemfibrozil (Lopid), clofibrate (Atromid-S), and fenofibrate (Tricor) or nicotinic acid (niacin).

Case studies published as of 2015 reported that another form of treatment for hyperlipoproteinemia and prevention of cardiovascular disease have been

conclusive. This form of treatment is known as lipoprotein apheresis (LA). LA is a form of therapy in which blood is removed from the body and passed through a filter system that removes lipids and puts back in the clean blood. LA has been shown to be highly effective in the treatment and management of hyperlipoproteinemia and the prevention of cardiac events.

Other factors that have a negative effect on hyperlipoproteinemia include smoking, excessive alcohol consumption, and stress. It is important to treat underlying conditions, such as diabetes, heart disease, pancreatitis (inflamed pancreas), and thyroid problems.

Prognosis

The prognosis is good for type I hyperlipoproteinemia with treatment. For type II, the prognosis is good for II-b and fair for II-a with early diagnosis and treatment. The prognosis for type III is good when the prescribed diet is strictly followed. The prognosis is uncertain for types IV and V, due to the risk of developing premature coronary artery disease in type IV and pancreatitis in type V.

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ORGANIZATIONS

- National Heart, Lung, and Blood Institute, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbiinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov>

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Hypermobility syndrome see **Larsen syndrome**

Hyperoxaluria

Definition

Hyperoxaluria occurs when a person's urine contains too much of a salt known as oxalate. Symptoms can range from kidney stones to kidney failure.

Description

Individuals with hyperoxaluria have an excess of oxalate in their urine. Oxalate is a salt of oxalic acid, which is found in many plants, such as spinach, soy beans, and coffee. The excess oxalate can have several causes, including its overproduction by the liver. The excess oxalate does not readily dissolve; instead, it combines with calcium in the urine to produce a compound called calcium oxalate. These calcium oxalate deposits can become kidney stones in the urinary tract.

For some patients, having kidney stones is the main and sometimes only symptom of hyperoxaluria. One-fifth to one-third of patients with recurring kidney stones have excess oxalate in their urine. In other patients, the concentration of oxalate is especially high and can lead to kidney damage and eventually kidney failure. When patients experience such kidney failure, they develop a condition known as oxalosis in which the overload of oxalate begins to gather elsewhere in the body, including the eyes, bones and muscles, circulatory system, and other organs, where it can cause damage. There are four main types of hyperoxaluria: primary hyperoxaluria (types, I, II, and III), enteric hyperoxaluria, dietary hyperoxaluria, and idiopathic or mild hyperoxaluria.

Individuals who have excess oxalate due to overproduction by the liver are said to have primary hyperoxaluria. Primary hyperoxaluria is a rare genetic disorder that causes the liver to make insufficient enzymes, which in turn causes the excess production of oxalate. In this form of hyperoxaluria, oxalate levels can be very high (200 mg/d or more). Primary hyperoxaluria occurs in three types: Type I primary hyperoxaluria, in which the liver makes too little of the enzyme known as alanine-glyoxylate aminotransferase (AGT); Type II primary hyperoxaluria, in which the liver is lacking the enzyme known as glyoxylate reductase/hydroxypyruvate reductase, or GR/HPR; and Type III primary hyperoxaluria, a less severe form of hyperoxaluria than primary type I or II that may be completely asymptomatic or limited to stone formation only. Primary type III may even improve over time, unlike primary hyperoxaluria type I or II.

The other types of hyperoxaluria include enteric hyperoxaluria, which is typically associated with chronic diarrhea, dietary hyperoxaluria, which is caused by a diet

heavy in oxalate-rich foods and animal proteins (such as meat), and idiopathic or mild hyperoxaluria, which may be related to diet or to unknown causes.

Genetic profile

Primary hyperoxaluria is the only type of hyperoxaluria with a known genetic origin. It is caused by mutations in the *AGXT* and *GRHPR* genes. Located on chromosome 2, the *AGXT* gene carries the blueprint for making the liver enzyme AGT. Scientists have identified over 50 mutations of this gene associated with type I primary hyperoxaluria. Mutations of the *AGXT* gene cause reduced production of AGT. Low levels of AGT lead to the accumulation of glyoxylate, which then converts to oxalate. Excess oxalate combines with calcium to form calcium oxalate and leads to the symptoms of primary hyperoxaluria type I, such as kidney stones, kidney damage, and kidney failure, and may possibly damage other organs as well.

The *GRHPR* gene is located on chromosome 9. It carries the blueprint for making the liver and kidney enzyme GR/HPR. Scientists have identified at least a dozen *AGXT* mutations associated with type II primary hyperoxaluria. Individuals who have inherited the mutated GR/HPR gene make insufficient GR/HPR. As with mutations on the *AGXT* gene, mutations in the *GRHPR* cause glyoxylate to build up and convert into excess oxalate, leading to the symptoms of primary hyperoxaluria type II.

Primary hyperoxaluria types I and II are inherited in an autosomal recessive pattern. For someone to be affected with an autosomal recessive disease, he or she must inherit two copies of an abnormal or mutated gene, one from each parent. A parent who has only one gene associated with an autosomal recessive condition is not affected by the disease and is known as a carrier of the disease. Two carriers of autosomal recessive mutated gene have a 25% chance of having a child affected with the disorder in each pregnancy.

Demographics

Primary hyperoxaluria is a rare genetic disorder. Both type I and type II are autosomal recessive disorders. According to the National Institutes of Health, Type I hyperoxaluria affects about one to three million people worldwide, with the highest incidence in Tunisia and some other Mediterranean countries. Most individuals with type I experience symptoms in late childhood to early adolescence, although some have their first symptoms soon after birth (this is sometimes called infantile type I), while others have their first symptoms in their mid-20s.

KEY TERMS

Biopsy—A medical procedure in which a small piece of tissue is removed so that it may be tested or examined.

Enzyme—Proteins within the body that cause chemical changes.

Kidney stones—Mineral depots that form inside the kidney.

Molecular genetic testing (gene tests)—Medical test that examines single genes or short lengths of DNA to identify changes or mutations that cause genetic disorders.

Oxalate—A naturally occurring molecule in the human body and in nature, too much of which can cause kidney stones.

Oxalosis—A metabolic process in the body that happens in patients with primary hyperoxaluria whose kidneys fail. When the body stops removing extra oxalate, it accumulates in the blood and organs and leads to serious complications.

Type II is even rarer than type I, although no estimate has been made of the number of people it affects. Symptoms typically first appear during the childhood years.

Signs and symptoms

Individuals with type I primary hyperoxaluria may begin to experience symptoms soon after birth or later in life, usually by about 25 years of age. About 1 in 10 develop symptoms before they are six months old, and they typically experience severe health problems including the following:

- Nephrocalcinosis, a disorder in which the concentration of calcium in the kidneys is too high
- Anemia, a disorder resulting from insufficient red blood cells or hemoglobin in the blood
- Metabolic acidosis, which is an unusually high acidity in the blood

The first symptoms of the remaining majority of individuals with type I primary hyperoxaluria typically are recurrent kidney stones. If left untreated, individuals with type I primary hyperoxaluria typically experience a continued decline in kidney function and eventual kidney failure with progression to oxalosis, possibly culminating with death from end-stage kidney disease.

Individuals with type II primary hyperoxaluria typically experience recurring kidney stones in childhood. If untreated, the disease progresses as it does with many type I patients: recurring kidney stones, decline in kidney function, eventual kidney failure, oxalosis, and death from end-stage kidney disease.

Diagnosis

Hyperoxaluria is diagnosed through the following methods.

Examination

Doctors may suspect primary hyperoxaluria if a patient, especially one younger than 25 years of age, experiences recurring kidney stones. To make a diagnosis, the doctor will order tests.

Tests

A doctor will order a urine and/or blood test to check for a high concentration of oxalate in the urine and or the blood plasma.

Procedures

In addition, a doctor may perform a liver biopsy to check for activity of the GR/HPR or AGT enzymes. The doctor may order molecular genetic testing, which scans the patient's DNA for the presence of the *GRHPR* or *AGXT* gene mutations.

Treatment and management

Treatment varies with the severity of the disorder.

Drugs

The doctor may prescribe regular, daily, high dosages of pyridoxine (vitamin B₆) to help reduce the amount of oxalate produced by the liver. The doctor may also recommend neutral phosphates, citrate, and/or magnesium to diminish kidney stone formation.

Dietary modifications

Patients may be advised to limit fats as well as certain foods that contain high levels of oxalate.

Other

The doctor may suggest that some patients—not those with kidney failure—drink ample fluids to help reduce kidney-stone formation. For patients with painful kidney stones or stones that are affecting urine flow, doctors may recommend a visit to a qualified medical professional who will remove them or break them up by a procedure called lithotripsy. In severe cases, the patient

QUESTIONS TO ASK YOUR DOCTOR

- What type of hyperoxaluria do I have?
- Is there a cure for hyperoxaluria?
- Is there a diet that will help reduce my symptoms?
- Are there foods I should avoid?
- What is the best treatment for my type of hyperoxaluria?
- Should I or my family members have genetic testing?

may require kidney dialysis. According to the Oxalosis and Hyperoxaluria Foundation, while dialysis can remove oxalate from the blood, it typically cannot keep pace with the very large amount of oxalate produced in patients with primary hyperoxaluria. For them, the only definitive treatment of kidney failure and oxalosis is transplantation.

There is no way to prevent hyperoxaluria in a given individual. It is an inherited disorder.

Adults who are carriers may wish to undergo genetic counseling before deciding to have children so in order to better understand the risks. Parents of children born with hyperoxaluria may want to have genetic testing to determine whether they are carriers of genetic mutations in the *AGXT* or *GRHPR* genes. The siblings of an affected child may also want to be tested. Brothers and sisters of a child with the disorder have a 25% chance of having the disorder themselves and a 50% chance of being a carrier for the disorder.

Prognosis

Some patients with hyperoxaluria experience kidney stones but no other health problems. Others, especially those with primary hyperoxaluria, have far more severe effects. According to the Oxalosis and Hyperoxaluria Foundation, about one-half of the individuals with primary hyperoxaluria experience kidney failure by age 15 and about 80% by age 30.

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ORGANIZATIONS

Oxalosis and Hyperoxaluria Foundation, 201 East 19th St., 12E, New York, NY 10003, (800) OHF-8699, info@ohf.org, <http://ohf.org>

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Hyperphenylalaninemia

Definition

Hyperphenylalaninemia (HPA) is elevated levels of phenylalanine in the blood. It is an inherited metabolic disorder caused by an inability to effectively break down or metabolize dietary phenylalanine that may lead to intellectual impairment if left untreated. This disorder is distinguished from phenylketonuria by lower levels of phenylalanine in the blood and increased tolerance of dietary phenylalanine.

Description

Hyperphenylalaninemia is broadly defined as an increased level of phenylalanine in the blood. However, there are two disorders that fall under this broad category: phenylketonuria (PKU) and mild hyperphenylalaninemia. These disorders are differentiated from one another by the level of phenylalanine present in the blood. Phenylalanine levels above 20 mg/dL indicate phenylketonuria. Levels between 2 and 20 mg/dL are considered mild hyperphenylalaninemia.

Elevated blood phenylalanine levels of more than 12 mg/dL cause damage to the nervous system, resulting in intellectual impairment or intellectual disability. A protein-restricted diet and supplementation with phenylalanine-free foods are used to decrease the blood phenylalanine levels of people with mild hyperphenylalaninemia.

Genetic profile

Mild hyperphenylalaninemia is a genetic disorder caused by mutations in the *PAH* gene, which provides the instructions for the enzyme phenylalanine hydroxylase.

KEY TERMS

Amino acids—Organic compounds that form the building blocks of protein. There are 20 types of amino acids (eight are “essential amino acids” that the body cannot make and that must be obtained from food).

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Mutation—An inherited or *de novo* change in the DNA sequence of the genome.

Phenylalanine (Phe)—An essential amino acid that must be obtained from food since the human body cannot manufacture it.

Phenylalanine hydroxylase—The enzyme responsible for converting dietary phenylalanine to tyrosine. If phenylalanine hydroxylase is not working efficiently, phenylalanine levels in the blood increase.

Phenylketonuria (PKU)—An inherited inability to metabolize dietary phenylalanine, resulting in blood phenylalanine levels above 20 mg/dL. If left untreated, elevated blood phenylalanine levels can result in damage to the nervous system, including severe cognitive impairment, often referred to as intellectual disability.

Protein—Molecules made of amino acids that are found in various types of food such as meat and dairy products. People with mild hyperphenylalaninemia may have to limit the amount of protein that they eat.

This enzyme, located in the liver, is responsible for breaking down phenylalanine. Enzymes are molecules used by the body to digest food, and when they are not working properly, the result is metabolic disease.

Mild hyperphenylalaninemia is an inherited, autosomal recessive disorder. “Autosomal” simply means that the gene responsible for this disorder is not located on one of the sex chromosomes. “Recessive” refers to the fact that both of a person’s *PAH* genes are mutated. Genes come in pairs and provide the instructions for how an enzyme forms.

Since genes come in pairs, the parents of a person with mild hyperphenylalaninemia have one normal and one mutated *PAH* gene. When they have children, they pass on one of these genes. If their child inherits two

copies of the mutated gene (one from each parent), he or she will have hyperphenylalaninemia. When both parents are carriers of mutated *PAH* genes, they have a 25% chance that each of their children will have hyperphenylalaninemia.

Mutations of the *PAH* gene that cause mild hyperphenylalaninemia are not as harmful to enzyme function as the mutations that cause PKU. Different mutations affect enzyme activity differently. More serious mutations cause a greater loss of enzyme activity, leading to a greater buildup of phenylalanine in the blood. The mutations responsible for mild hyperphenylalaninemia cause less enzyme activity loss and less buildup of phenylalanine in the blood.

GTP-cyclohydrolase I deficiency (14q22.1-q22.2) is one cause of HPA. It is caused by a tetrahydrobiopterin deficiency that affects transmission of nerve impulses in the brain.

Demographics

Mild hyperphenylalaninemia occurs in 15 to 75 people per 1 million and is rarer than classic phenylketonuria, which occurs in about 1 in 15,000 births. It occurs in all races equally and affects both men and women.

Signs and symptoms

In the United States and Puerto Rico, all newborns are screened for HPA. If unscreened, mild to moderate intellectual deficits will be noted as the child grows up. A special diet until the late teens to mid-20s can prevent the detrimental effects of PKU buildup in the central nervous system and the subsequent damage. If left untreated, intellectual impairment, seizures, and dystonia (muscle weakness) can result.

Diagnosis

Tests

The diagnosis of hyperphenylalaninemia is usually made through a newborn screening test performed at birth. The United States and Puerto Rico have newborn screening programs, and the test is required by law. A blood sample is collected from the infant with a prick of the heel (heelstick), and the level of phenylalanine and other amino acids are quantitated using a technology called tandem mass spectrometry or MS/MS. If the initial newborn screening tests show an elevated phenylalanine level, then follow-up confirmatory blood tests are ordered to determine if the elevated phenylalanine level is due to phenylketonuria (PKU), mild hyperphenylalaninemia, or another reason. It is not uncommon for infants with

QUESTIONS TO ASK YOUR DOCTOR

- What is my baby's phenylalanine level?
- Does my baby need to be on a special diet?
- Can I still breastfeed my baby?

initially elevated phenylalanine levels on a newborn screening test to have normal follow-up tests.

If an infant's follow-up test indicates a persistently elevated phenylalanine level, further confirmatory testing will be done to determine if the infant has phenylketonuria or mild hyperphenylalaninemia. The diagnosis of mild hyperphenylalaninemia is made if the blood phenylalanine level is between 2 and 20 mg/dL on an unrestricted diet.

Treatment and management

Traditional

Dietary restriction of protein, which contains phenylalanine, is the main treatment for hyperphenylalaninemia. Mild hyperphenylalaninemia may or may not require treatment depending on the phenylalanine level. Individuals with phenylalanine levels greater than 2 mg/dL but less than 6 mg/dL do not generally require treatment. Dietary treatment is controversial in people with serum phenylalanine levels greater than 7 mg/dL but less than 11 mg/dL, with some studies showing a benefit while others do not. Dietary treatment is recommended in people with serum phenylalanine levels greater than 12 mg/dL. The treatment of mild hyperphenylalaninemia is usually handled by a team of medical professionals, including a geneticist and metabolic nutritionist.

Untreated mild hyperphenylalaninemia can lead to a decrease in IQ. Elevated serum levels of phenylalanine are directly related to IQ levels. The goal of dietary treatment is to keep serum phenylalanine levels below 10 mg/dL.

It is usually possible to breastfeed infants with mild hyperphenylalaninemia. The use of the artificial sweetener aspartame may be restricted, as phenylalanine is the primary component of this sweetener.

Drugs

The brand name drug Kuvan is a synthetic form of a cofactor for phenylalanine hydroxylase. This cofactor increases the efficiency of phenylalanine hydroxylase and

can decrease blood phenylalanine levels in some patients. It is used in conjunction with a phenylalanine-restricted diet. People with mild hyperphenylalaninemia may also use special foods and formula that are specially formulated and do not contain phenylalanine.

Prognosis

The prognosis for individuals with mild hyperphenylalaninemia is excellent. With early detection through newborn screening and dietary management when necessary, people affected with mild hyperphenylalaninemia are expected to have a normal life expectancy and normal intelligence quotient (IQ).

Women with blood phenylalanine levels above 6 mg/dL during pregnancy are at increased risk of having children with birth defects such as microcephaly or heart defects. Women with mild hyperphenylalaninemia should be seen in a metabolic center prior to pregnancy to aid in management of phenylalanine levels during pregnancy.

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ORGANIZATIONS

- Children's PKU Network, 3306 Bumann Rd., Encinitas, CA 92024, (858) 756-0079, (858) 756-1059, pkunetwork@aol.com, <http://www.pkunetwork.org>
- New England Connection for PKU and Allied Disorders, PO Box 3235, Woburn, MA 01888-2135, <http://www.necpad.org/index.php>

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Hypochondrogenesis

Definition

Hypochondrogenesis is a lethal genetic skeletal dysplasia caused by a mutation in the *COL2A1* gene. This condition is characterized by a severe limb and trunk shortening with a disproportionately large head. Infants with this disorder usually die of respiratory failure soon after birth.

Description

Hypochondrogenesis is a rare form of skeletal dysplasia (or dwarfing syndrome) caused by mutations in the *COL2A1* gene. The *COL2A1* gene provides the instruction for the formation of collagen type II, which is a major building block of cartilage, a major component of bone. Because of these mutations, infants with hypochondrogenesis have defects in their bone formation that cause them to have severely shortened limbs (arms and legs) and a small chest with short ribs. Because infants with hypochondrogenesis have small chests and abnormal ribs, their lungs are underdeveloped, which leads to respiratory (breathing) difficulties at birth. In addition, the vertebrae or spinal bones in the neck and part of the sacrum (pelvis) do not harden, or ossify, properly. The face of an infant with hypochondrogenesis is flat and oval-shaped, with widely spaced eyes, a small chin, and, in some cases, an opening in the roof of the mouth called a cleft palate. Rarely, fetuses with hypochondrogenesis can develop a condition called hydrops fetalis in which excess fluid builds up in the abdomen and body before birth. One report has suggested that some infants with hypochondrogenesis may also have heart defects.

There are many causes for impaired growth or dwarfism, including hormone imbalances, metabolic problems, genetic disorders, and problems with bone growth. Hypochondrogenesis belongs to a class of dwarfism referred to as a chondrodystrophy or skeletal dysplasia and results from a problem with bone growth. All skeletal dysplasias are the result of a problem with bone formation or growth. There are more than 100 different types of skeletal dysplasias. Hypochondrogenesis is also sometimes referred to as a collagenopathy because the specific abnormality in hypochondrogenesis is a problem in the formation of collagen.

The collagenopathies are a group of disorders that affect connective tissue, the tissue that supports the body's joints and organs. Collagenopathies, as a group, are caused by defects in either type II or type IX collagen. Hypochondrogenesis is caused by a defect in the formation of type II collagen. Collagen is a complex protein molecule that provides structure, strength, and elasticity to connective tissue.

There are other skeletal dysplasias that have features very similar to hypochondrogenesis and are associated with mutations in the same gene. Consequently, hypochondrogenesis is considered by most specialists to belong to a spectrum, or continuum, of skeletal dysplasias that vary in severity. This spectrum includes achondrogenesis type II at the severe end and spondyloepiphyseal dysplasia congenita (SEDC) at the milder end. Infants with achondrogenesis type II have the same spinal changes as seen in hypochondrogenesis, but the condition is generally more severe and is invariably lethal. Infants with spondyloepiphyseal dysplasia congenita have the same findings as an infant with hypochondrogenesis, but their condition tends to be milder. Infants with SEDC can survive into adult life, but they generally have many complications due to their severe skeletal problems.

Genetic profile

Hypochondrogenesis is caused by a mutation, or change, in the *COL2A1* gene located on the long arm of chromosome 12 (12q13.11-q13.2). Hypochondrogenesis has autosomal dominant inheritance; however, there is usually no prior history of the condition in the family. In an autosomal dominant disorder, only one gene has to have a mutation for the person to have the disorder. All individuals have two *COL2A1* genes: one from their father and one from their mother. However, all infants with hypochondrogenesis are born to average-stature parents. The infant's hypochondrogenesis is the result of a *de novo*, or new, mutation. The occurrence of hypochondrogenesis is almost always due to a *de novo* mutation that typically occurs in one of the *type II collagen* genes from an average-sized parent. The cause of *de novo* mutations is unknown. Because infants with hypochondrogenesis do not survive to reproductive age, there is no risk of their passing on this mutated gene to the next generation. Because most *de novo* mutations occur sporadically, the recurrence risk is small.

Several different types of mutations in the *COL2A1* gene are responsible for hypochondrogenesis. These mutations may include small deletions, or missing pieces, of the *COL2A1* gene, missense mutations that lead to the substitution of one amino acid for another, and other changes that leave out important parts of the protein. All of these changes interfere with the formation of mature triple-stranded type II collagen molecules, which results in hypochondrogenesis by affecting tissues that are rich in type II collagen.

Demographics

Hypochondrogenesis occurs equally in males and females and is found with equal frequency in all races

and ethnic groups. There is no exact prevalence data for hypochondrogenesis, but collectively, collagenopathies are found in about 1 in 10,000 people. Because achondrogenesis and hypochondrogenesis can be difficult to tell apart, the incidence data reflect the incidence of both disorders. Hypochondrogenesis and achondrogenesis type II together occur in approximately 1 in 40,000–60,000 births. With the advent of DNA testing and the ability to make a more definitive diagnosis, it should soon be possible to have an incidence figure for hypochondrogenesis alone.

Signs and symptoms

Physical findings

Type II collagen is a major building block of the spine, cartilage, and vitreous protein in the eye. Defects in this collagen and the cartilage that it forms cause infants with hypochondrogenesis to have micromelia (extremely short limbs), a short trunk (or body) with shortened ribs, and a head that appears large. Their flat, oval-shaped faces have a characteristic appearance with wide-set eyes (hypertelorism), small chin, and, occasionally, a cleft palate or opening on the roof of the mouth. These infants may also have heart defects.

X-ray findings

Infants with hypochondrogenesis have very characteristic or unique x-ray findings. In order to understand what these findings are, it is important to know a little bit about how x-rays work. X-rays are a form of energy that is able to pass through some objects and not others. When x-rays pass through a body, more x-rays are absorbed by the denser parts (such as teeth and bone) than by softer tissues (such as muscles and digestive organs). X-rays create a negative image on the x-ray film. Soft tissues, such as blood, muscles, and digestive organs, appear darker or do not appear at all because the x-rays pass directly through the tissues onto the film. Bones and teeth appear brighter because fewer x-rays penetrate these structures and reach the film during exposure.

When looking at the x-ray of an infant with hypochondrogenesis, the observer can easily see abnormalities in the child's bones. Because the vertebrae are underdeveloped and have not hardened, they are quite difficult to see on an x-ray; normally, they should be easy to see. Those vertebrae that can be seen are usually abnormally shaped. The ribs appear very thin. In addition to vertebral and rib abnormalities, the bones of the pelvis and, in particular, the hip socket are abnormally shaped. Hip sockets are usually curved, but in hypochondrogenesis these bones are flattened and smaller than usual.

While the findings in hypochondrogenesis are distinctly abnormal, it is important to distinguish these findings from those seen in achondrogenesis type II and those seen in spondyloepiphyseal dysplasia congenita. The x-ray findings of achondrogenesis type II are more severe than those of hypochondrogenesis, and the findings of SEDc are generally milder than those seen in hypochondrogenesis.

Diagnosis

The diagnosis of hypochondrogenesis can be made prenatally by ultrasound or shortly after birth. A number of different tests, including x-rays, biopsies, and DNA testing, is used to confirm the diagnosis. Consultation with experts in the field of skeletal dysplasias may also be helpful.

The diagnosis of hypochondrogenesis can be made prenatally (during pregnancy), either by ultrasound (sonogram) or by prenatal DNA testing. Sonograms use sound waves to provide an image of a fetus. The structural abnormalities of hypochondrogenesis, including severely shortened limbs, shortened trunk with abnormal ribs, and unossified vertebral bones, can be observed during the second trimester of pregnancy. Because of overlapping features with other skeletal dysplasias, it can be very difficult to definitively diagnose hypochondrogenesis by sonogram. DNA testing can have a role in clarifying ambiguous ultrasound findings.

The neonatal diagnosis in infants is made by physical examination shortly after birth. Severe shortening of the limbs, a small trunk, abnormal facial features, and a cleft palate are often seen and raise the suspicion of the diagnosis of hypochondrogenesis. The diagnosis cannot be made by physical examination alone because hypochondrogenesis and numerous other skeletal dysplasias look very similar.

X-rays are often helpful in establishing the diagnosis of hypochondrogenesis. X-ray findings include underossified vertebra, abnormally thin ribs, and abnormally shaped hip bones. The x-ray findings of achondrogenesis type II are generally more severe, and the findings of SEDc are less severe.

Biopsies are the collection of tissue that can then be examined under a microscope. In hypochondrogenesis, a skin biopsy may be done to obtain skin cells for DNA analysis. Biopsies of the connective tissue may also be collected so that the collagen and other connective tissues can be examined microscopically.

DNA testing can be performed on a blood or skin sample. The presence of a mutation in the *COL2A1* gene would confirm the diagnosis of hypochondrogenesis. It is estimated that DNA testing will detect greater than

KEY TERMS

Achondrogenesis—A genetic disorder of skeletal development with three subtypes, one of which (achondrogenesis type II) is caused by mutations in the same gene as hypochondrogenesis.

Autosomal dominant—A pattern of genetic inheritance in which only one abnormal gene is needed to display the trait or disease.

Chondrodystrophy—A general term for any of several disorders of the skeleton caused by mutations that affect the normal development of cartilage.

Collagen—The main structural protein found in the various types of connective tissue in humans and other animals. It is found in skin, ligaments, tendons, cartilage, and the intervertebral disks in the spine. Disorders of collagen are called collagenopathies.

De novo mutation—A genetic mutation that is not inherited from either parent. The Latin phrase means “new.”

Dysplasia—A general term used to refer to abnormalities of growth or development.

Hydrops fetalis—The abnormal accumulation of fluid in the skin, body cavities, and placenta of an unborn baby.

Hypertelorism—Abnormally widely spaced eyes.

Micromelia—Abnormal shortness or smallness of the limbs.

Neonatologist—A pediatrician who specializes in the care of newborns, particularly sick or premature newborns.

Skeletal dysplasias—A group of syndromes consisting of abnormal prenatal bone development and growth.

Spondyloepiphyseal dysplasia congenita—A subtype of collagenopathy, types II and IX, with symptoms that are similar to but milder than those of hypochondrogenesis and achondrogenesis type II.

90% of mutations in the *COL2A1* gene. Because scientists have not yet found all of the mutations in this gene, the absence of a detectable mutation does not completely rule out the diagnosis. The *COL2A1* gene is a large gene with many possible mutations. Because of this complexity, the results of DNA testing may take four to six weeks.

Prenatal testing can also be done using DNA technology. A sample of tissue from a fetus is obtained by either chorionic villus sampling (CVS) or by amniocentesis. CVS is generally done between 10 and 12 weeks of pregnancy, and amniocentesis is done between 14 and 18 weeks of pregnancy. CVS involves removing a small amount of tissue from the developing placenta. The tissue in the placenta contains the same DNA as the fetus. Amniocentesis involves removing a small amount of fluid from around the fetus. This fluid contains some fetal skin cells from which DNA can be isolated. The fetal DNA is then tested to determine whether there are any mutations in the *COL2A1* gene. This test is not done in low-risk couples and may be available only if a specific mutation has already been characterized in a family. Molecular genetic testing for hypochondrogenesis was available in three genetic testing laboratories in the United States as of 2015.

Because hypochondrogenesis is such a rare disorder and has a great deal of overlap with other skeletal dysplasias, it can be very difficult to diagnose definitively. It can be helpful to consult with skeletal dysplasia experts who may suggest further specialized testing to help clarify the diagnosis.

Treatment and management

There is no cure or treatment for hypochondrogenesis. If the diagnosis is made prior to birth, the parents may wish to meet with a neonatologist to discuss management of the birth.

If hypochondrogenesis is detected during a pregnancy, patients have the option to terminate the pregnancy based upon the lethality of this condition. This is a very personal decision and should be made following serious counseling about the nature and outcome of this diagnosis.

Once the diagnosis has been firmly established, there is no need for resuscitation and ventilatory support for the infant given the established lethality of the condition. Infants should be provided with basic supportive care, including warmth, nourishment, and comfort.

If the diagnosis has not been confirmed prior to birth, resuscitation and ventilatory (breathing) support are appropriate to allow time for a thorough diagnostic evaluation. X-rays should be performed, and skin and connective and blood tissue should be collected.

The diagnosis of hypochondrogenesis is shocking for families. The bleak prognosis and lack of treatment can be devastating. Families should be reassured that there is nothing that they did or did not do that could have prevented the outcome. The family needs time to process the information about the diagnosis and should be

QUESTIONS TO ASK YOUR DOCTOR

- How common are mutations in the *COL2A1* gene?
- Are there steps that we should take to prepare for the poor prognosis of this disorder?
- Should other family members be tested for possible *de novo* mutations in the *COL2A1* gene?
- What research is being done to improve understanding of hypochondrogenesis and related disorders?

provided emotional support. The neonatal staff can aid in collecting reminders of the baby, including footprints, photographs, and locks of hair, that can help the family as they deal with the crisis. In addition to providing emotional support, it is equally important to make sure that the parents understand the genetic diagnosis and its implications for future pregnancies. They need to understand the sporadic nature of this diagnosis and that it is unlikely to recur in a future pregnancy. Because the interpretation of some of the test results are complicated, it is best that the family be referred to a genetics center for counseling following the diagnosis of hypochondrogenesis.

Prognosis

The prognosis for an infant with hypochondrogenesis is poor. Some infants are stillborn, and those that are born alive die shortly after birth due to respiratory failure. Survival can range from a few days to a few weeks. If an infant with suspected hypochondrogenesis does survive the newborn period, it is assumed that he or she actually has spondyloepiphyseal dysplasia congenita. In cases in which the diagnosis is ambiguous, DNA testing can help to confirm the diagnosis and may allow for a more accurate prognosis.

Resources

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ORGANIZATIONS

- Compassionate Friends, PO Box 3696, Oak Brook, IL 60522-3696, (630) 990-0010 or (877) 969-0010, (630) 990-0010, <http://www.compassionatefriends.org>
- Greenberg Center for Skeletal Dysplasias, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21287, (410) 614-0977, (410) 502-2475, <https://igm.jhmi.edu/content/greenberg-center-skeletal-dysplasias-welcome>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Hypochondroplasia

Definition

Hypochondroplasia is an autosomal dominant mutation that results in short stature with disproportionately short arms and legs but normal head size.

Description

Hypochondroplasia is a genetic form of short stature (dwarfism) due to a problem of bone growth and development. There are many causes for short stature, including hormone imbalances, metabolic problems, and problems with bone growth. Hypochondroplasia is a common form of short stature and belongs to a class of dwarfism referred to as a chondrodystrophy or skeletal dysplasia. All skeletal dysplasias are the result of a problem with bone formation or growth. There are over 300 different types of skeletal dysplasia.

Because the features of hypochondroplasia are so mild, the disorder may go undiagnosed. Although infants with hypochondroplasia may have low birth weight, hypochondroplasia is often not evident until between two and six years of age. In general, individuals with hypochondroplasia have disproportionate short stature with an

average height of 51–57 in. (130–145 cm). The degree of disproportion of the limbs to the body is variable.

Most individuals with hypochondroplasia have a normal IQ, although some studies suggest that up to 10% of individuals with hypochondroplasia may have mild intellectual disabilities or learning disabilities. This finding is controversial, and as of 2015, more studies were underway to verify it. The motor development of infants with hypochondroplasia is normal. In rare cases, individuals with hypochondroplasia may experience neurologic problems due to spinal cord compression. The spinal canal (which holds the spinal cord) can be smaller than normal in patients with hypochondroplasia.

Genetic profile

Hypochondroplasia is caused by a mutation, or change, in the fibroblast growth factor receptor 3 gene (*FGFR3*) located on the short arm of chromosome 4.

FGFR (fibroblast growth factor receptor) genes provide the instruction for the formation of a cell receptor. Every cell in the body has an outer layer called a cell membrane that serves as a filter. Substances are transported into and out of the cells by receptors located on the surface of the cell membrane. Every cell has hundreds of different types of receptors. The fibroblast growth factor receptors transport fibroblast growth factor into a cell. Fibroblast growth factors play a role in the normal growth and development of bones. When the receptors for fibroblast growth factor do not work properly, the cells do not receive enough fibroblast growth factor, and the result is abnormal growth and development of bones.

Approximately 70% of hypochondroplasia is caused by mutations in the *FGFR3* gene. The genes (or gene) responsible for the other 30% of cases are not known. The *FGFR3* gene consists of 2,520 bases. In a normal (nonmutated) gene, base number 1,620 codes for the amino acid asparagine. In most individuals with hypochondroplasia, a mutation changes the asparagine to the amino acid lysine. Two specific mutations account for approximately 70% of hypochondroplasia. These small substitutions change the amino acid that affects the protein structure. Both of these small substitutions cause a change in the *FGFR* that affects the function of this receptor.

The remaining 30% of patients diagnosed with hypochondroplasia do not show *FGFR3* gene mutations. It has not yet been made clear if these patients have a different gene abnormality, an unrecognized *FGFR3* gene mutation, or are normal variants. Another possibility is that

these individuals actually have another disorder in which short stature results.

Mutations in the *FGFR3* gene are inherited in an autosomal dominant manner. Individuals have two *FGFR3* genes—one from their father and one from their mother. In an autosomal dominant disorder, only one gene has to have a mutation for a person to have the disorder. An individual with hypochondroplasia has a 50% chance of passing on his or her changed (mutated) gene to offspring. An individual can inherit a mutated gene from one parent or the mutation can occur for the first time in the individual. Mutations that arise for the first time in affected individuals are called *de novo* mutations. The causes of mutations are not known.

Demographics

Because hypochondroplasia has such a wide range of variability, many people mildly affected with hypochondroplasia may never be diagnosed. Thus, the true incidence of hypochondroplasia is unknown. Experts believe that hypochondroplasia may be as common as achondroplasia, which occurs in 1 out of every 15,000 to 40,000 births. As of 2015, there were more than 200 diagnosed cases of hypochondroplasia worldwide.

Signs and symptoms

Individuals with hypochondroplasia have disproportionate short stature, limb abnormalities, and rhizomelic shortening of the limbs. Rhizomelic shortening of the limbs means that those segments of a limb closest to the body (the root of the limb) are more severely affected. In individuals with hypochondroplasia, the upper arms are shorter than the forearms and the upper leg (thigh) is shorter than the lower leg. In general, the upper limbs are more affected than the lower limbs in individuals with hypochondroplasia.

In addition to shortened limbs, individuals with hypochondroplasia have other characteristic limb differences such as a limited ability to rotate and extend their elbows. They can develop bowed legs, a finding that usually improves as they get older. Their hands and feet are short and broad, as are their fingers and toes. Their final adult height is usually 51–57 in. (130–145 cm). Their body habitus or shape is described as thick and stocky with a relatively long trunk. They may have lumbar lordosis (curved back), giving them a swayed back appearance.

Diagnosis

The diagnosis of hypochondroplasia can be extremely difficult to make for a number of reasons. There is no one physical feature or x-ray finding specific to hypochondroplasia, and there is a great deal of overlap between

KEY TERMS

Fibroblast growth factor receptor gene—A type of gene that codes for a cell membrane receptor involved in normal bone growth and development.

Rhizomelic—Disproportionate shortening of the upper part of a limb compared to the lower part of the limb.

individuals with hypochondroplasia and individuals in the general population. Many of the physical findings of hypochondroplasia (short stature, bowed legs, and a stocky build) are seen in individuals without hypochondroplasia. The same is true for the “typical” x-ray findings. All of the possible x-ray findings associated with hypochondroplasia can also be seen in unaffected individuals. There is no consensus on specific criteria necessary for diagnosis; however, it is usually made based on a combination of physical and x-ray findings and is rarely made in infants.

DNA testing for hypochondroplasia is complicated because testing only detects 70% of the mutations that cause hypochondroplasia. DNA testing can be performed on blood samples from children or adults. If an individual is suspected of having hypochondroplasia and a mutation is detected, then the diagnosis is confirmed. If a mutation is not detected, then the diagnosis of hypochondroplasia has neither been confirmed nor ruled out. This individual could be one of the 30% of individuals with hypochondroplasia due to unknown mutations, or they could have short stature due to another disorder.

Prenatal testing for hypochondroplasia can be performed using DNA technology. A sample of tissue from a fetus is obtained by either chorionic villus sampling (CVS) or by amniocentesis. CVS is generally done between 10 and 12 weeks of pregnancy, and amniocentesis is done between 16 and 18 weeks of pregnancy. CVS involves removing a small amount of tissue from the developing placenta. The tissue in the placenta contains the same DNA as the fetus. Amniocentesis involves removing a small amount of fluid from around the fetus. This fluid contains some fetal skin cells. DNA can be isolated from these skin cells. The fetal DNA is then tested to determine whether it contains either of the two mutations responsible for achondroplasia.

Prenatal DNA testing for hypochondroplasia is not routinely performed in low-risk pregnancies. This type of testing is generally limited to high-risk pregnancies, such as when one parent has hypochondroplasia. This testing can only be performed if the mutation causing hypochondroplasia in the parent has been identified.

Treatment and management

There is no cure for hypochondroplasia. Because of the wide range of variability of this condition, there is no consensus on the medical management of individuals with hypochondroplasia, either. Individuals with more severe cases are the only individuals likely to need medical management. The recommendations for the medical management of individuals with hypochondroplasia have been outlined by the American Academy of Pediatrics’ Committee on Genetics and should be used as a guide for the management of individuals with severe hypochondroplasia. The potential medical complications of hypochondroplasia range from mild to moderate. Early intervention may avert some of the long-term consequences of these complications.

As children with hypochondroplasia develop, certain conditions and behaviors should be monitored. Their height, weight, and head circumference should be measured regularly and plotted on growth curves developed for children with hypochondroplasia as a guide. Neurologic problems such as lethargy, abnormal reflexes, or loss of muscle control should be seen by a neurologist to make sure that they are not experiencing compression of their spinal cord. Compression of the spinal cord is rare in individuals with hypochondroplasia but can occur because of the abnormal size of their spinal canal.

Children with hypochondroplasia should be monitored for sleep apnea. Sleep apnea occurs when an individual stops breathing during sleep. This can occur for several reasons, including obstruction of the throat by the tonsils and adenoids, spinal cord compression, and obesity. Individuals with hypochondroplasia are more prone to sleep apnea because of the changes in their spinal canal and foramen magnum. Treatment for sleep apnea depends on the cause of the sleep apnea. Obstructive sleep apnea is treated by surgically removing the tonsils and adenoids. Weight management may also play a role in the treatment of sleep apnea.

The bowed legs of children with hypochondroplasia usually improve as they get older and rarely require surgical intervention. Children with hypochondroplasia can often have an increased risk for middle ear infections, which can be treated with oral antibiotics and the surgical placement of ear tubes.

Children with visible physical differences can have difficulties in school and socially. Support groups such as Little People of America can be a source of guidance on how to deal with these issues. It is important that children with hypochondroplasia not be limited in activities that pose no danger.

Two treatments have been used to try to increase the final adult height of individuals with hypochondroplasia—limb-lengthening and growth hormone therapy. There are

QUESTIONS TO ASK YOUR DOCTOR

- My son has been diagnosed with hypochondroplasia. What causes this disorder?
- Will my son “grow out” of this condition, or is some type of treatment needed? If so, what kinds of treatments are available?
- Will growth hormone be useful in helping my son to grow normally?
- What long-term physical and mental problems is my son likely to experience as a result of this genetic disorder?

risks and benefits to both treatments and they are still considered experimental.

Limb-lengthening involves surgically attaching external rods to the long bones in the arms and legs. These rods run parallel to the bone on the outside of the body. Over a period of 18–24 months, the tension on these rods is increased, which results in the lengthening of the underlying bone. This procedure is long, costly, and has potential complications such as pain, infections, and nerve problems. Limb-lengthening can increase overall height by 12–14 in. (30.5–35.6 cm). This is an elective surgery and individuals must decide for themselves whether it would be of benefit to them. The optimal age to perform this surgery is not known.

Growth hormone therapy has been used to treat some children with hypochondroplasia. Originally, there was doubt about the effectiveness of this treatment because children with hypochondroplasia are not growth-hormone deficient. Studies have shown mixed results. Some children with hypochondroplasia show improvement in their growth rate, and others do not. It is too early to say how effective this treatment is because the children involved in this study are still growing and have not reached their final adult height.

Prognosis

The prognosis for most people with hypochondroplasia is very good. In general, they have minimal medical problems, normal IQ, and most achieve success and have a long life, regardless of their stature. The most serious medical barriers to an excellent prognosis are the neurologic complications that very rarely arise in hypochondroplasia, including mild intellectual disability and spinal cord compression.

Successful social adaptation plays an important role in the ultimate success and happiness of an individual with hypochondroplasia. It is very important that the career and life choices of individuals with hypochondroplasia not be limited by preconceived ideas about their abilities.

Resources

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- “Hypochondroplasia.” NORD. <https://rarediseases.org/rare-diseases/hypochondroplasia/> (accessed June 11, 2021).

ORGANIZATIONS

- Human Growth Foundation, 997 Glencove Ave., Suite 5, Glenhead, NY 11545, (516) 671-4055 or (800) 451-6434, hgf1@hgfound.org
- MAGIC Foundation, 6645 W. North Ave., Oak Park, IL 60302, (708) 383-0808 or (800) 362-4423, ContactUs@magicfoundation.org, <http://www.magicfoundation.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06813, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Kathleen Fergus, MS

Hypophosphatasia

Definition

Hypophosphatasia is an inherited bone disease with highly variable clinical symptoms ranging from prenatal death to a severe lack of bone mineralization to early loss of teeth in adulthood. Hypophosphatasia is caused by a mutation in the *ALPL* gene that provides instructions for producing an enzyme called tissue-nonspecific alkaline

phosphatase (TNSALP) that is required for the proper mineralization (hardening) of bones.

Description

Hypophosphatasia means “low phosphatase.” Phosphatase is an enzyme that removes phosphate molecules (PO_4^{3-}) from other molecules in the body and supplies phosphate to bone. The term “hypophosphatasia” was first used in 1948 by a Canadian pediatrician, J. C. Rathbun, to describe an infant who died of what appeared to be severe rickets, weight loss, and seizures. Rickets is caused by vitamin D deficiency, which interferes with the absorption and utilization of calcium and phosphorus, which are required for proper bone growth and development; however, this child had very low levels of alkaline phosphatase. In 1953, the clinical features of hypophosphatasia were expanded to include not only abnormal mineralization of bone but also premature loss of the permanent teeth in adulthood. Hypophosphatasia is now classified into six types, based on the severity of the disease and the age at which symptoms first appear:

- perinatal lethal hypophosphatasia
- perinatal benign hypophosphatasia
- infantile hypophosphatasia
- childhood hypophosphatasia
- adult hypophosphatasia
- odontohypophosphatasia

Alkaline phosphatase (ALP) is an enzyme that occurs in most all plants and animals. There are at least four different genes that encode different forms of ALP in humans. Hypophosphatasia is caused by a deficiency of TNSALP, the form of ALP that is particularly abundant in the liver, bones, and kidneys. TNSALP is important for mineralization of the bones of the skeleton, as well as the teeth. Thus, abnormalities in either the production or function of this enzyme have a direct effect on the formation and strength of bones and teeth. Low levels of active TNSALP result in the abnormal buildup in the body of several other substances that are normally processed by the enzyme. In particular, it is believed that the buildup of inorganic pyrophosphate results in the defective mineralization of the bones and teeth.

Genetic profile

The first report of siblings affected by hypophosphatasia was published in 1950, providing supportive evidence that this was an inherited disorder rather than an acquired disease. The gene for TNSALP is located near the tip of the short arm (p) of chromosome 1 at 1p36.12.

The most severe forms of hypophosphatasia—perinatal lethal and infantile—are inherited as an

autosomal recessive condition. This means that an affected infant must inherit two copies of a mutated *ALPL* gene, one copy from each parent. Each child of parents who both carry a mutated *ALPL* gene has a 25% (one in four) chance of being affected by perinatal lethal or infantile hypophosphatasia and a 50% chance of inheriting one mutated gene.

The milder forms of hypophosphatasia, especially the adult form and odontohypophosphatasia, are inherited as either autosomal recessive or autosomal dominant conditions, depending on the specific mutation in the *ALPL* gene. Individuals who inherit a single autosomal recessive *ALPL* gene mutation have low TNSALP enzyme activity but either have no symptoms or milder symptoms, depending on the specific mutation. There also have been reports of *de novo* autosomal recessive *ALPL* mutations that occurred in the egg or sperm cell or during early embryonic development; in such cases, neither parent carried a mutated *ALPL* gene. Individuals who inherit a single autosomal dominant *ALPL* gene have hypophosphatasia, and each of their children has a 50% risk of inheriting the pathogenic *ALPL* gene.

More than 200 different *ALPL* mutations have been associated with hypophosphatasia, and the severity of the disorder depends on the specific mutation. Mutations that do not completely eliminate the activity of TNSALP cause milder and/or later-onset forms of the disorder. Thus, even some children who inherit two mutated *ALPL* genes have only mild symptoms or no symptoms at all, depending on the specific mutations.

Demographics

The prevalence of autosomal recessive perinatal lethal and infantile hypophosphatasia in Ontario, Canada, has been estimated at 1 in 100,000. This would make the frequency of pathogenic *ALPL* mutation carriers about 1 in 150 individuals. Hypophosphatasia is especially common among Mennonite families in Manitoba, Canada, where marriages between related individuals are not unusual. The frequency of the perinatal lethal form in this population is approximately 1 in 2,500, with a corresponding carrier frequency of 1 in 25. The number of different *ALPL* mutations identified in this group is smaller than in the general population. It is difficult to estimate the frequency of milder childhood and adult hypophosphatasia and odontohypophosphatasia, but these forms are probably more common.

Hypophosphatasia has not been reported from Africa outside of North Africa. The disorder is very rare among African Americans.

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall, and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Rachitic—Pertaining to, or affected by, rickets. Examples of rachitic deformities include curved long bones with prominent ends, a prominent middle chest wall, or bony nodules at the inner ends of the ribs.

Signs and symptoms

The major symptom of hypophosphatasia is generalized impairment of skeletal mineralization, but signs and symptoms vary greatly depending on the specific ALPL mutation(s) and levels of active TNSALP. Although signs and symptoms within affected families tend to be similar, variations are observed even within families. Even some individuals with low levels of TNSALP have no signs or symptoms of the disorder.

Perinatal hypophosphatasia

Lethal perinatal hypophosphatasia is often diagnosed prenatally. The limbs are typically shortened and abnormal. Bone fractures may be present. An excessive amount of amniotic fluid (polyhydramnios) is common. Many affected infants die prior to delivery or are stillborn. Those who survive are often irritable, have a high-pitched cry, and fail to gain weight. Respiratory failure is a common cause of death, usually due to deformities of the chest and associated underdevelopment of the lungs. In contrast, benign perinatal hypophosphatasia may cause prenatal

skeletal abnormalities that eventually resolve into a milder childhood or adult form.

Infantile hypophosphatasia

Many infants with this form of the disease appear normal at birth and initially develop normally. However, difficulties such as poor feeding, slow weight gain, and soft, deformed bones begin before six months of age. Bone abnormalities of the chest, as well as an increased susceptibility to fractures, make affected infants more susceptible to pneumonia. Over 50% of affected children die during infancy, usually from severe respiratory failure. Infants who survive often have episodes of recurrent vomiting and abnormal kidney function due to excess loss of calcium from bone. Additionally, they may develop a misshapen head due to early closure of bones of the skull. However, spontaneous overall improvement sometimes occurs.

Childhood hypophosphatasia

The most common clinical feature in this form of hypophosphatasia is loss of the primary (deciduous) teeth before the age of five. This premature loss is directly related to abnormal dental cementum, the bony layer that normally establishes the connections of the teeth to the jaw. Cementum is frequently completely missing, underdeveloped, or abnormal. Symptoms of more severe cases include short stature, skeletal deformities, and bone pain and fractures.

Adult hypophosphatasia

Although affected individuals are usually diagnosed in adulthood, careful review of medical histories often reveals childhood skeletal abnormalities and/or early loss of the primary teeth, followed by relatively good health during adolescence and young adulthood. Dental and skeletal difficulties occur gradually. Age at symptom onset and symptom severity vary. Early loss of the permanent teeth is common. Other common symptoms include osteomalacia (a softening of bones similar to rickets in children), bone fractures and deformities, and chronic foot pain due to recurrent, poorly healing stress fractures. Affected adults may experience pain in the thighs and hips from zones of decalcification (pseudo-fractures). Some older adults diagnosed with osteoporosis may actually have a mild form of hypophosphatasia.

Odontohypophosphatasia

Dental disease in children or adults is the only clinical abnormality associated with this form.

Diagnosis

Prenatal diagnosis of perinatal hypophosphatasia is usually apparent on ultrasound by midpregnancy. Fetal x-rays may confirm a diagnosis. ALP activity may be measured in cultured cells obtained by chorionic villus sampling (CVS) or amniocentesis; however, it can be difficult to directly test for TNSALP. Genetic tests are available for prenatal diagnosis, especially if the family mutation(s) has been identified.

Diagnosis of hypophosphatasia after birth is based on a combination of a physical examination, x-rays, and biochemical studies. X-rays can be particularly helpful in differentiating between the more severe forms of hypophosphatasia (perinatal, infantile) and other inherited bone diseases. In the perinatal form, the skeleton generally appears severely undermineralized and occasionally is absent. Bone fractures may be present. X-ray findings for the infantile form are similar to those seen in the perinatal form but are usually much less severe.

Blood serum is tested for low levels of alkaline phosphatase activity, which primarily represents TNSALP activity. Substances such as inorganic pyrophosphate, which are normally acted upon by TNSALP, accumulate in the blood and urine and can be measured. Genetic testing can also be used for diagnosis.

Treatment and management

Children with hypophosphatasia are treated with repeated infusions of TNSALP directed to bone. As of 2015, clinical trials of this treatment were underway in adults.

Management of hypophosphatasia is directed at preventing or treating disease-related complications. Physical therapy and orthopedic management are important for preventing and treating bone complications such as fractures. Expert dental care is very important. Young children with the infantile form should be monitored carefully for increased pressure within the skull from early fusion of the bones.

Prognosis

The prognosis for each type of hypophosphatasia depends on the age of onset and severity. In general, the earlier the diagnosis, the more severe the skeletal abnormalities. Mortality from lethal perinatal or infantile hypophosphatasia ranges up to 50% in the first year of life. However, infants with benign perinatal disease may spontaneously improve. Symptoms of childhood disease may improve during adolescence but occasionally reappear in adulthood. Adult-onset hypophosphatasia is associated with ongoing orthopedic problems. Women, in particular, may suffer increased bone loss and fractures after menopause.

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- HPP-Choose Hope, 2140 W. Greenview Dr., Suite 10, Middleton, WI 53562, (888) 348-4673, info@hppchoosehope.com, <http://www.choosehope.org>
- MAGIC Foundation, 6645 W. North Ave., Oak Park, IL 60302, (708) 383-0808 or (800) 3MAGIC3 (362-4423), ContactUs@magicfoundation.org, <http://www.magicfoundation.org>
- Office of Rare Diseases Research, National Center for Advancing Translational Sciences, National Institutes of Health, 6701 Democracy Blvd., Suite 1001, MSC 4874, Bethesda, MD 29892, (301) 402-4336, (301) 480-4655, idr@nih.gov, <https://rarediseases.info.nih.gov>

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Hypophosphatemia

Definition

Hypophosphatemia is a group of inherited disorders in which there is abnormally low levels of phosphate in the blood, leading to softening of the bones. This condition can result in rickets, a childhood disease in which soft and weak bones can lead to bone deformities. While there is no cure, treatment can prevent the bone changes and allow proper growth of bones.

Description

Bone is one of the strongest tissues of the human body. As the main component of the adult skeleton, it provides support for movement, protects the brain and organs

KEY TERMS

Hydroxyapatite—A complex phosphate of calcium $\text{Ca}_5(\text{PO}_4)_3\text{OH}$ that occurs as a mineral and is the chief structural element of vertebrate bone.

Hypophosphatemia—A decrease in the blood circulation of phosphate.

Rickets—A childhood disease in which soft and weak bones can lead to the development of bone deformities.

of the chest from injury, and contains the bone marrow, where blood cells are formed. Bone is made up of several components, including a substance called hydroxyapatite. Hydroxyapatite is made of calcium and phosphate and is partially responsible for the strength of bone.

Because of the importance of hydroxyapatite, the strength of bone is dependent on the proper levels of calcium and phosphate within the body. A lack of calcium or phosphate in the diet or a failure in maintaining proper levels of calcium or phosphate in the blood can lead to abnormalities of bone growth. Another factor required for proper development of bone is vitamin D. Vitamin D is either obtained through foods in the diet or is made by the body in response to sunlight exposure. Vitamin D is converted to another substance within the body called calcitriol. Calcitriol promotes bone development by helping to absorb calcium and phosphate from the diet and by preventing the loss of calcium and phosphate in the urine.

Hypophosphatemia is a group of inherited disorders in which there is abnormally low phosphate levels in the blood because large amounts of phosphate exit the body through the urine. In some forms of the disease there may be problems in the conversion of vitamin D to calcitriol. Research suggests that inherited hypophosphatemia syndromes result from an abnormality in the way the kidney handles phosphate. Normally, the kidney prevents phosphate from leaving the body in the urine, but in hypophosphatemia, an abnormality in the way the kidney handles phosphate leads to large losses of phosphate in the urine. This results in abnormally low levels of phosphate in the blood, leading to poor hydroxyapatite formation and soft bones. Insufficient levels of phosphate for bone formation results in rickets, a childhood condition in which there is abnormal bone development, growth, and repair (when this occurs in adults, it is called osteomalacia). Inherited hypophosphatemia was first described by R. W. Winters in 1958 and has been referred to in the past as vitamin D-resistant rickets or familial hypophosphatemic rickets.

Genetic profile

Hypophosphatemia is a group of conditions that can be inherited or passed on in a family. The different types of hypophosphatemia have different causes, patterns of inheritance, and symptoms.

The most common and widely studied form of hypophosphatemia is hereditary hypophosphatemia type I, also known as X-linked hypophosphatemia (XLH). The abnormality in XLH is in a gene called *PHEX*. It is not known precisely how this gene affects phosphate handling by the kidney. Changes in other genes have been shown to cause hypophosphatemia, but the mechanism is similarly unclear. While most occurrences of hypophosphatemia are passed from parent to child, there are several examples of new genetic changes arising in a child with no relatives with hypophosphatemia.

There are different patterns of inheritance in different forms of hypophosphatemia, including autosomal dominant inheritance and X-linked dominant inheritance. In autosomal dominant inheritance, only one abnormal gene is needed to display the disease, and the chance of passing the gene to offspring is 50%.

X-linked dominant inheritance is similar to autosomal dominant inheritance in that only one abnormal gene is needed to display the disease. However, in X-linked dominant inheritance, the genetic abnormality is located on the X chromosome. Females have two X chromosomes, whereas males only have one X chromosome. Females have a 50% chance of passing the abnormal gene on to either a son or a daughter, as the mother always contributes one X chromosome to a child. On the other hand, males with the abnormal X chromosome always pass the abnormal gene to a daughter (the father will contribute the abnormal X chromosome) but never to a son (the father will contribute a normal Y chromosome, and not the abnormal X chromosome).

Demographics

Hypophosphatemia has been estimated to be present in between 1 in 10,000 and 1 in 100,000 people, but 1 in 20,000 people is the most widely quoted figure. It is not known whether this disease is present equally among different geographical areas and ethnic groups. The first reports of the condition found hypophosphatemia in a Bedouin (nomadic Arab) tribe.

Signs and symptoms

Major symptoms of hypophosphatemia include poor growth, bone pain, abnormally bowed legs, weakness, tooth abscesses, and sometimes listlessness and irritability in infants and young children. Although the disease affects

QUESTIONS TO ASK YOUR DOCTOR

- Are there any dietary restriction/additions or supplements I should take to help support my bones?
- Are there any adverse side effects of the pharmaceuticals used to treat this condition?
- Can my future children be screened for this disorder, and what are the chances they will inherit it?

all bones, the legs are more severely affected than the arms, ribs, or pelvis. The bowed legs are often noted by 12 months of age, and the altered growth increases in severity as the child grows older. Because of poor hydroxyapatite formation, people may experience fractures and subsequent abnormal healing, further contributing to growth abnormalities. As a result of poor bone development and poor healing, people with hypophosphatemia often have short stature and may have a waddling walk. Other, less common manifestations of hypophosphatemia include high blood pressure and hearing loss or deafness.

While most symptoms are the same in the different types of hypophosphatemia, there may be small changes in the severity and age at which a person will experience the symptoms.

Diagnosis

If there is no family history of hypophosphatemia, diagnosis is usually guided by physical exam and bloodwork. Obvious bowed-leg deformities will lead to x-rays of the legs and knees, which show characteristic bone abnormalities. Other studies of bone strength using radioactive tracer materials can be used, or a bone biopsy (surgical excision of a small portion of bone for inspection with a microscope) can be performed to confirm that there is less hydroxyapatite than normal.

Laboratory tests aid in determining the cause of poor bone growth and rickets. In XLH, the serum phosphorus is low and the levels of serum calcium and calcitriol are low or sometimes normal. Urine levels of phosphate are high, indicating that phosphate is being lost in the urine and that the kidney is not reabsorbing the phosphate properly. Another laboratory finding in XLH is the presence of increased alkaline phosphatase, an enzyme that breaks down bone. However, alkaline phosphatase is often elevated in growing children compared to normal adult values. Other forms of hypophosphatemia may have

other variations in laboratory findings, including normal calcitriol levels or high levels of calcium in the urine and can be used to distinguish between the different types of hypophosphatemia.

Treatment and management

There is no cure, but medical and surgical treatment can greatly improve the outcome of people with hypophosphatemia. Goals of treatment include improvement in growth; reduction in severity of bone disease, bowed legs, and activity limitations; and minimization of the complications that may develop from the treatment itself.

Medical treatment is directed toward increasing the blood phosphate levels by using phosphate salts and calcitriol, both given by mouth. However, phosphate may have to be given five times a day because it is rapidly lost in the urine, and it often causes diarrhea. Despite these drawbacks, the response to the medications is very good, and bowed legs may straighten over several years of growth. Scientific studies are also being performed to determine if growth hormone can help in achieving normal growth and height development.

Healthcare providers are able to monitor the person's ability to take the medication by checking the phosphate levels in the urine and the blood. It is recommended that these tests be performed in small children every three months to determine if they are receiving adequate amounts of phosphate. Later, the monitoring can be decreased to every four to six months. It is also recommended that childhood x-rays of the knee be performed every one to two years to see whether medication changes are needed.

Some problems may result from the medications used to treat hypophosphatemia. High levels of calcium can build up in the bloodstream, causing problems with the kidneys and the parathyroid (a gland in the neck). Because of these problems, routine calcium measurements and kidney ultrasound studies should be performed to determine if additional medications should be added or changes in medications should be made.

Treatment with medication is sometimes not enough to reverse the bone abnormalities. In cases such as these, surgery can be performed to reshape or even lengthen the bones.

Prognosis

With early diagnosis and treatment, the prognosis for people with hypophosphatemia is excellent. Adult heights of 67 in. (170 cm) may be achievable, compared to 51–65 in. (130–165 cm) without treatment. While some degree of abnormal bone growth may always be

detectable, people with hypophosphatemia generally have normal lifespans.

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ORGANIZATIONS

- XLH Network, 911 Central Ave., No. 161, Albany, NY 12206, info@xlhnetwork.org, <http://www.xlhnetwork.org>

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Hypophosphatemic rickets see **Hypophosphatemia**

Hypospadias and epispadias

Definition

Hypospadias is a congenital defect, primarily of males, in which the urethra opens on the underside (ventrum) of the penis. The corresponding defect in females is an opening of the urethra into the vagina and is rare.

Epispadias (also called bladder exstrophy) is a congenital defect of males in which the urethra opens on the upper surface (dorsum) of the penis. The corresponding defect in females is a fissure in the upper wall of the urethra and is quite rare.

Description

In a male, the external opening of the urinary tract (external meatus) is normally located at the tip of the

penis. In a female, it is normally located between the clitoris and the vaginal opening.

In males with hypospadias, the urethra opens on the inferior surface or underside of the penis. In females with hypospadias, the urethra opens into the cavity of the vagina.

In males with epispadias, the urethra opens on the superior surface or upper side of the penis. In females with epispadias, there is a crack or fissure in the wall of the urethra and out of the body through an opening in the skin above the clitoris.

During the embryological development of males, a groove of tissue folds inward and then fuses to form a tube that becomes the urethra. Hypospadias occurs when the tube does not form or does not fuse completely. Epispadias is due to a defect in the tissue that folds inward to form the urethra.

During the development of a female, similar processes occur to form the urethra. The problem is usually insufficient length of the tube that becomes the urethra. As a result, the urethra opens in an abnormal location, resulting in a hypospadias. Occasionally, fissures form in the bladder. These may extend to the surface of the abdomen and fuse with the adjacent skin. This is most often identified as a defect in the bladder although it is technically an epispadias.

Hypospadias in males generally occur alone. Female hypospadias may be associated with abnormalities of the genital tract, since the urinary and genital tracts are formed in the same embryonic process.

Because it represents incomplete development of the penis, some experts think that insufficient male hormone may be responsible for hypospadias.

Genetic profile

Hypospadias and epispadias are congenital defects of the urinary tract. This means that they occur during intra-uterine development. There is no genetic basis for the defects. Some hypospadias have been linked to manmade chemicals, but specific causes for most hypospadias are not known. This means that blood relatives do not have increased chances of developing them.

Demographics

In males, the incidence of hypospadias is approximately 1 per 250 to 300 live births. Epispadias is much less common, having an incidence of about 1 per 100,000 live male births.

In females, hypospadias is much less common than in males. It appears about once in every 500,000 live

KEY TERMS

Bladder—The organ that stores urine after it flows out of the kidneys and through the ureters.

Circumcision—The surgical removal of the foreskin of the penis.

Continence—Normal function of the urinary bladder and urethra, allowing fluid flow during urination and completely stopping flow at other times.

External meatus—The external opening through which urine and seminal fluid (in males only) leave the body.

Genital tract—The organs involved in reproduction. In a male, they include the penis, testicles, prostate, and various tubular structures to transport seminal fluid and sperm. In a female, they include the clitoris, vagina, cervix, uterus, fallopian tubes, and ovaries.

Urethra—The tubular portion of the urinary tract connecting the bladder and external meatus through which urine passes. In males, seminal fluid and sperm also pass through the urethra.

female births. Epispadias is even rarer. Reliable estimates of the prevalence of epispadias in females are not available. Epispadias in females is often diagnosed and recorded as a bladder anomaly.

Signs and symptoms

Hypospadias is usually not associated with other defects of the penis or urethra. In males, it can occur at any site along the underside of the penis. In females, the urethra exits the body in an abnormal location. This is usually due to inadequate length of the urethra.

Epispadias is associated with bladder abnormalities. In females, the front wall of the bladder does not fuse or close. The bladder fissure may extend to the external abdominal wall. In such a rare case, the front of the pelvis is also widely separated. In males, the bladder fissure extends into the urethra and simply becomes an opening somewhere along the upper surface of the penis.

Hypospadias is associated with difficulty in assigning gender to babies. This occurs when gender is not obvious at birth because of deformities in the sex organs.

Diagnosis

Male external urinary tract defects are discovered at birth during the first detailed examination of the newborn.

Female urethral defects may not be discovered for some time due to the difficulty in viewing the infant vagina.

Treatment and management

Surgery is the treatment of choice for both hypospadias and epispadias. All surgical repairs should be undertaken early and completed without delay. This minimizes psychological trauma.

In males with hypospadias, one surgery is usually sufficient to repair the defect. With more complicated hypospadias (more than one abnormally situated urethral opening), multiple surgeries may be required. In females with hypospadias, surgical repair is technically more complicated but can usually be completed in a brief interval of time.

Repairing an epispadias is more difficult. In males, this may involve other structures in the penis. Males should not be circumcised since the foreskin is often needed for the repair. Unfortunately, choices may be required that affect the ability to inseminate a female partner. Reproduction requires that the urethral meatus be close to the tip of the penis. Cosmetic appearance and urinary continence are usually the primary goals. Surgery for these defects is successful 70%–80% of the time. Modern treatment of complete male epispadias allows for an excellent genital appearance and achievement of urinary continence.

In females, repair of epispadias may require multiple surgical procedures. Urinary continence and cosmetic appearance are the usual primary considerations. Urinary continence is usually achieved, although cosmetic appearance may be somewhat compromised. Fertility is not usually affected. Repair rates that are similar or better than those for males can usually be achieved for females.

Hypospadias in both males and females is more of a nuisance and hindrance to reproduction than a threat to health. If surgery is not an option, the condition may be allowed to persist. This usually leads to an increased risk of infections in the lower urinary tract.

Prognosis

With adequate surgical repair, most males with simple hypospadias can lead normal lives with a penis that appears and functions in a normal manner. This includes fathering children. Females with simple hypospadias also have normal lives, including conceiving and bearing children.

The prognosis for epispadias depends on the extent of the defect. Most males with relatively minor epispadias lead normal lives, including fathering children. As the extent of the defect increases, surgical reconstruction is

QUESTIONS TO ASK YOUR DOCTOR

- Will my child be able to urinate normally?
- Will this condition lead to any other problems?
- How visible will the scars of the repair surgery be?

generally acceptable. However, many of these men are unable to conceive children. Most epispadias in females can be surgically repaired. The chances of residual disfigurement increase as the extent of the epispadias increases. Fertility in females is not generally affected by epispadias.

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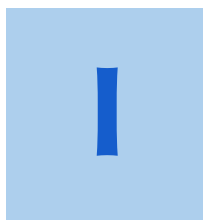
- Association for the Bladder Exstrophy Community, 6737 W. Washington St., Suite 3265, West Allis, WI 53214, <http://www.bladderexstrophy.com>
- Urology Care Foundation, 1000 Corporate Blvd., Linthicum, MD 21090, (410) 689-3700 or (800) 828-7866, (410) 689-3998, info@urologyhealth.org, <http://www.urologyhealth.org>

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Hypothalamic hamartoblastoma see
Pallister-Hall syndrome

Hypotonia-obesity-prominent incisors syndrome see **Cohen syndrome**

Hypoxanthine guanine phosphoribosyltransferase 1 (HPRT1) see **Lesch-Nyhan syndrome**



Ichthyosis-spastic neurologic oligophrenia disorder syndrome see **Sjögren-Larsson syndrome**

Ichthyosis

Definition

Derived from the Greek word meaning fish disease, ichthyosis is a congenital (present at birth) dermatological (skin) disease that is characterized by thick, scaly skin.

Description

The ichthyoses are a group of genetic skin diseases caused by an abnormality in skin growth that results in drying and scaling. It may occur as a symptom of a syndrome or as an individual skin condition. There are at least 20 types of ichthyosis. Ichthyosis can be more or less severe, sometimes accumulating thick scales and cracks that are painful and bleed. Ichthyosis is not contagious because it is inherited.

Genetic profile

Ichthyoses have been associated with mutations in many genes including *ABCA12*, *ABHD5*, *ALDH3A2*, *ALOX12B*, *ALOXE3*, *AP1S1*, *BRAF*, *CARD14*, *CLDN1*, *CSTA*, *CYP4F22*, *ERCC2*, *ERCC3*, *FLG*, *GJB2*, *GTF2H5*, *KRAS*, *KRT1*, *KRT10*, *LIPN*, *MAP2K1*, *MAP2K2*, *MBTPS2*, *MPLKIP*, *NIPAL4*, *NSDHL*, *PNPLA1*, *PNPLA2*, *POMP*, *SPINK5*, *SLC27A4*, *STS*, *SUMF1*, and *TGM1*. These genes are involved in skin production and maintenance.

Depending on the specific type of ichthyosis, the inheritance can be autosomal recessive, autosomal dominant, X-linked recessive, X-linked dominant, or sporadic. Autosomal recessive means that the altered gene for the disease or trait is located on one of the first 22 pairs of chromosomes, which are also called “autosomes.” Males

and females are equally likely to have an autosomal recessive disease or trait. Recessive means that two copies of the altered gene are necessary to express the condition. Therefore, a child inherits one copy of the altered gene from each parent, who are called carriers (because they have only one copy of the altered gene). Since carriers do not express the altered gene, parents usually do not know they carry the altered gene that causes ichthyosis until they have an affected child. Carrier parents have a one-in-four chance (or 25%) with each pregnancy to have a child with ichthyosis.

Autosomal dominant inheritance also means that both males and females are equally likely to have the disease but only one copy of the altered gene is necessary to have the condition. An individual with ichthyosis has a 50% chance of passing the condition to his or her child.

The last pair of human chromosomes, either two X (female) or one X and one Y (male) determines gender. X-linked means the altered gene causing the disease or trait is located on the X chromosome. Females have two X chromosomes while males have one X chromosome. The term “recessive” usually infers that two copies of a gene—one on each of the chromosome pair—are necessary to cause a disease or express a particular trait. X-linked recessive diseases are most often seen in males, however, because they have a single X chromosome and no “back-up.” So, if a male inherits a particular gene on the X, he expresses the altered gene, even though he has only a single copy of it. Females, on the other hand, have two X chromosomes and therefore can carry a gene on one of their X chromosomes yet not express any symptoms. (Their second X, or “back-up,” functions normally). Usually a mother carries the altered gene for X-linked recessive ichthyosis unknowingly and has a 50% chance with each pregnancy to transmit the altered gene. If the child is a male, he will have ichthyosis. If the child is a female, she will be a carrier for ichthyosis like her mother.

X-linked dominant inheritance means that only one gene from the X chromosome is necessary to produce



Ichthyosis is characterized by dry, scaly skin. (MedicImage/Alamy)

the condition. Mothers with the altered gene are affected and have a 50% chance to pass the condition to any child, who will also have ichthyosis. In some cases, X-linked dominant inheritance is lethal in males, which means that male fetuses with X-linked dominant ichthyosis are miscarried. This is true for a rare disorder called Conradi-Hunerman, in which ichthyosis is just one feature.

New mutations—alterations in the DNA of a gene—can cause disease. In these cases, neither parent has the disease-causing mutation. This may occur because the mutation in the gene happened for the first time only in the egg or sperm for that particular pregnancy. New mutations are thought to happen by chance and are therefore referred to as “sporadic,” meaning that they occur occasionally and are not predictable.

Demographics

The most common form of ichthyosis is called ichthyosis vulgaris (*vulgar* is Latin for common). It occurs in approximately 1 person in every 250 and is inherited in an autosomal dominant manner. The rarest types of ichthyosis occur in fewer than 1 person in 1 million and are inherited in an autosomal recessive

manner. Ichthyosis occurs regardless of the part of the world the child is from or the ethnic background of the parents.

Signs and symptoms

The skin is made up of several layers supported underneath by a layer of fat that is thicker or thinner depending on location. The lower layers contain blood vessels, the middle layers contain actively growing cells, and the upper layer consists of dead cells that serve as a barrier to the outside world. This barrier is nearly waterproof and highly resistant to infection. Scattered throughout the middle layers are hair follicles, oil and sweat glands, and nerve endings. The upper layer is constantly flaking off and being replaced from beneath by new tissue. In ichthyosis, the skin’s natural shedding process is slowed or inhibited, and in some types, skin cells are produced too rapidly.

The abnormality in skin growth and hydration of ichthyosis may present with symptoms at birth or in early childhood. Ichthyosis can itch relentlessly leading to complications caused by scratching such as lichen simplex (dermatitis characterized by raw patches of skin).

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman’s abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Amniotic fluid—The fluid that surrounds a developing baby during pregnancy.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Dermatologist—A physician who specializes in disorders of the skin.

Emollient—Petroleum- or lanolin-based skin lubricants.

Keratin—A tough, non-water-soluble protein found in the nails, hair, and the outermost layer of skin. Human hair is made up largely of keratin.

Keratinocytes—Skin cells.

Keratolytic—An agent that dissolves or breaks down the outer layer of skin (keratins).

Retinoids—A derivative of synthetic vitamin A.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

X-linked dominant inheritance—The inheritance of a trait by the presence of a single gene on the X chromosome in a male or female, passed from an affected female who has the gene on one of her X chromosomes.

X-linked recessive inheritance—The inheritance of a trait by the presence of a single gene on the X chromosome in a male, passed from a female who has the gene on one of her X chromosomes. She is referred to as an unaffected carrier.

Both cracked skin and itching may cause infection, discomfort, and necessitate additional treatment.

Diagnosis

A dermatologist will often make the diagnosis of ichthyosis based on a clinical exam. However, a skin

biopsy or DNA study (from a small blood sample) is necessary to confirm the diagnosis. A complete physical exam may be performed to check for additional medical conditions.

For some types of ichthyosis, the abnormal gene has been identified and prenatal testing is available. Several autosomal recessive congenital ichthyoses may be detected by prenatal testing such as:

- Lamellar ichthyosis (LI)
- Autosomal recessive lamellar ichthyosis (ARLI)
- Congenital ichthyosiform erythroderma (CIE)
- Non-bullous congenital ichthyosiform erythroderma (NBCIE)
- Harlequin ichthyosis

Genetic testing is available for many genetic mutations that cause ichthyosis. Once a couple has had a child with ichthyosis, and they have had the genetic cause identified by DNA studies (performed from a small blood sample), prenatal testing for future pregnancies may be considered. Prenatal testing may not be possible if both mutations cannot be identified. Prenatal diagnosis is available via either chorionic villus sampling (CVS) or amniocentesis. CVS is a biopsy of the placenta performed in the first trimester of pregnancy under ultrasound guidance. Ultrasound is the use of sound waves to visualize the developing fetus. The genetic makeup of the placenta is identical to the fetus and therefore specific genes can be studied from this tissue. There is approximately a 1 in 100 risk of miscarriage with CVS. Amniocentesis is a procedure done under ultrasound guidance in which a long, thin needle is inserted through the mother’s abdomen into the uterus, to withdraw a couple of tablespoons of amniotic fluid (fluid surrounding the developing baby) to study. Genetic material can be studied using cells from the amniotic fluid. Other genetic tests, such as a chromosome analysis, may also be performed through either CVS or amniocentesis.

Some congenital ichthyosis syndromes may also be detected by prenatal ultrasound. Specific fetal measurements and features such as foot length, persistently open mouth, dense amniotic fluid, and fixed flexion of the extremities may be early symptoms of ichthyosis like harlequin ichthyosis.

Treatment and management

Most treatments for ichthyosis are topical, which means they are applied directly to the skin, not taken internally. Some forms of ichthyosis require two forms of treatment—a reduction in the amount of scale buildup and moisturizing of the underlying skin. Several agents are available for each purpose. Reduction in the amount

of scales is achieved by keratolytics. Among this class of drugs are urea, lactic acid, and salicylic acid. Petrolatum, 60% propylene glycol, and glycerin are successful moisturizing agents, as are many commercially available products. Increased humidity of the ambient air is also helpful in preventing skin dryness.

Because the skin acts as a barrier to the outside environment, medicines have a hard time penetrating, especially through the thick skin of the palms of the hands and the soles of the feet. This resistance is diminished greatly by maceration (softening the skin). Soaking hands in water macerates skin so that it looks like prune skin. Occlusion (covering) with rubber gloves or plastic wrap will also macerate skin. Applying medicines and then covering the skin with an occlusive dressing will facilitate entrance of the medicine and greatly magnify its effect.

Secondary treatments are necessary to control pruritus (itching) and infection. Commercial products containing camphor, menthol, eucalyptus oil, aloe, and similar substances are very effective as antipruritics. If the skin cracks deeply enough, a pathway for infection is created. Topical antibiotics like bacitracin are effective in prevention and in the early stages of these skin infections. Cleansing with hydrogen peroxide inhibits infection as well.

Finally, there are topical and internal derivatives of vitamin A called retinoids that improve skin growth and are used for severe cases of acne, ichthyosis, and other skin conditions.

This condition requires continuous care throughout a lifetime. Properly treated, in most cases it is a cosmetic problem. There are a small number of lethal forms, such as harlequin fetus.

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ORGANIZATIONS

- Foundation for Ichthyosis and Related Skin Types, 2616 N. Broad St., Colmar, PA 18915, (215) 997-9400, <http://www.firstskinfoundation.org>
- National Organization for Rare Disorders, 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0010, (203) 789-2291, <http://www.rarediseases>
- National Registry for Ichthyosis and Related Disorders. University of Washington Dermatology Department, Box 356524, 1959 NE Pacific, Rm. BB1353, Seattle, WA 98195, (206) 616-3179 or (800) 595-1265, <http://www.skinregistry.org>

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Ichthyosis bullosa of siemens see **Ichthyosis**

Ichthyosis congenita see **Ichthyosis**

Imprinting

Definition

Genetic imprinting is the differential expression of a gene depending on whether it was maternally or paternally inherited. It is a method for silencing gene expression, making the gene nonfunctional. Imprinting is believed to play a critical role in fetal growth and development, but its exact role is unclear. Imprinting can sometimes lead to genetic disorders.

Description

Normal genetic imprinting process

A gene is made up of long sequences of DNA. The DNA is transcribed into messenger RNA (mRNA), and the mRNA is translated into protein. Some genes are constitutively (continually) transcribed. Others are transcribed only when their protein products are required.

Genetic imprinting is a natural phenomenon that does not follow the pattern of traditional Mendelian genetics. According to Mendelian genetics, an individual inherits two functional copies (alleles) of every non-sex-linked gene. One copy is paternally inherited, and the other is maternally inherited. When genes follow the Mendelian inheritance pattern, both the paternal and maternal copies are functionally expressed, regardless of which parent the copy came from. Imprinting, however, results in the preferential expression of some alleles

depending on their parental origin. For this reason, genetic imprinting is sometimes called the parent-of-origin effect. A gene is imprinted when its expression depends on the sex of the parent that transmitted the copy of the gene. Usually, one allele is partially or completely silenced, either temporarily or permanently, so that only one parental copy is active. Genes that are silenced are not transcribed and translated and so exert no effect on the biological system. Genes may be imprinted in some cells and tissues and not in others, because imprinting can change when cells differentiate and become specialized. For example, some genes are imprinted or silenced only in certain regions of the brain.

Imprinting of genes occurs during the formation of the parental egg or sperm. Imprinting occurs in each generation when new egg and sperm cells are produced. A female that inherits a paternally imprinted gene will maintain the paternal imprint. However, when she eventually forms her own new egg cells (gametes), the original paternal imprint may be erased and replaced with her own imprinted patterns. The same is true for males who inherit maternally imprinted genes. Thus, imprinting is not permanent, since it may be erased when gametes (eggs or sperm) are formed. This germline conversion process is regulated by the imprinting center, a piece of DNA located within the imprinted chromosome. Relatively few human genes are imprinted, and they tend to cluster together in the same genomic regions. Imprinted genes have signals that are recognized by the cellular machinery as “active” or “silenced.” The signal is often a methyl group (CH_3) that is added to a base of DNA in a process called methylation, which causes it to be silenced. These signals are referred to as “epigenetic,” because the alterations do not involve changes in the DNA sequence.

Genetic imprinting is thought to play a role in the transmission of nutrients from the mother to the fetus and to the newborn. Imprinted genes also impact fetal growth and the behavior of the newborn infant. It has been suggested that imprinting ensures that one allele of a gene is preferentially active at a given stage of development, so that the other allele is preserved for epigenetically distinct regulation at a later stage in development.

Imprinting also plays an important part in the development of many diseases. However, current knowledge of the genes that carry out the imprinting, their chromosomal locations, and their interactions with other genes is limited.

Complications in the genetic imprinting process

Multiple complications can arise involving imprinted genes. Typically, if a mutation in one allele of a gene

KEY TERMS

Allele—Any of the alternative versions of a gene that are present in the population.

Angelman syndrome (AS)—A disorder caused by the deletion or absence of active imprinted genes.

Embryogenesis—The formation and growth of the embryo.

Epigenetic—A modification to DNA, such as the addition of a methyl group, that does not change the DNA sequence.

Gamete—A reproductive cell; an ovum or sperm.

Germline—The cell line from which gametes arise.

Mendelian genetics—A set of parameters describing the traditional method of the transmission of genes from one generation to the next.

Methyl group (CH_3)—A molecule of one carbon and three hydrogen atoms that can be attached to DNA bases as a signal for regulating gene expression.

Prader-Willi syndrome (PWS)—A disorder caused by the deletion or absence of active imprinted genes.

Spasticity—Increased muscular tone or contractions that cause stiff or awkward movements.

Uniparental disomy—The inheritance of both copies of a chromosome from one parent.

eliminates its function, the other allele can continue to function and produce the gene product. However, with an imprinted gene, if the functional allele is deleted or mutated, there is no functional backup allele; thus, mutation of the active copy of an imprinted gene may result in disease. Another complication occurs if, as a result of an error, cells receive all or part of a pair of chromosomes from a single parent. This is known as uniparental disomy. If uniparental disomy occurs with imprinted genes, the cell receives either two silenced copies or two active copies. If both copies are silenced, there is no functional copy of that gene.

Loss of gene activity and gain of inappropriate activity can both be harmful. A mutation in a silenced gene may activate that gene, resulting in two active copies when one copy should be silenced. This can result in overexpression of the gene product, which is involved in some diseases. For example, some types of cancer are associated with a failure to imprint or silence genes that encode for growth factors. Overexpression of these growth factors contributes to uncontrolled cell growth

QUESTIONS TO ASK YOUR DOCTOR

- Can you explain what is meant by imprinting?
- Could my child's disorder be caused by an imprinting error?
- What are the chances that we could have another child with an imprinting disorder?
- Can imprinting disorders be detected by genetic testing?

and the development of cancer. Environmental factors, such as exposure to toxins, can sometimes cause changes in DNA that alter imprinted gene expression, resulting in diseases such as cancer or behavioral disorders.

Two of the best-studied diseases caused by genomic imprinting are Prader-Willi syndrome (PWS) and Angelman syndrome (AS). Both syndromes are caused by alterations in chromosome 15, which contains a number of imprinted genes. PWS is a neurobehavioral disorder characterized by excessive eating, obesity, short stature, intellectual disability, and small hands and feet. Approximately 70% of PWS cases are caused by a deletion in a specific region of the paternally active chromosome 15. Since the corresponding genes on the maternal chromosome 15 are inactive, they cannot compensate for the gene deletion. These deleted genes are associated with feelings of hunger and fullness. Approximately 29% of PWS cases are caused by inheriting two maternal copies of chromosome 15, in which the genes are imprinted as inactive. About 1% of PWS cases involve a mutation in the imprinting center itself. AS is characterized by hyperactivity, an unusual facial appearance, short stature, intellectual disability, spasticity, inappropriate laughter, and seizures. Approximately 70% of AS cases are caused by a deletion of the maternal *UBE3A* gene on chromosome 15. Both copies of this gene are active in many tissues; however, in the brain only the maternal copy is active, and its deletion leads to the symptoms of AS. Other cases of AS are caused by inheriting two copies of the paternal chromosome 15 with *UBE3A* genes that have been imprinted as inactive. Beckwith Wiedemann syndrome (BWS) is a disorder associated with overgrowth and malformations due to an imprinting defect in a specific region of chromosome 11.

Imprinting and epigenetics are very active areas of research. Epigenomic maps are being developed for various cell types, tissues, and organs. Researchers hope this will lead to better prevention, diagnosis, and treatment

of disease. Researchers are also studying whether assisted reproduction techniques such as in vitro fertilization (IVF) may interfere with the imprinting process during early embryogenesis.

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Eunice Kennedy Shriver National Institute of Child Health and Human Development, NICHD Information Resource Center, PO Box 3006, Rockville, MD 20847, (800) 370-2943, (866) 760-5947, NICHDInformationResourceCenter@mail.nih.gov, <https://www.nichd.nih.gov>

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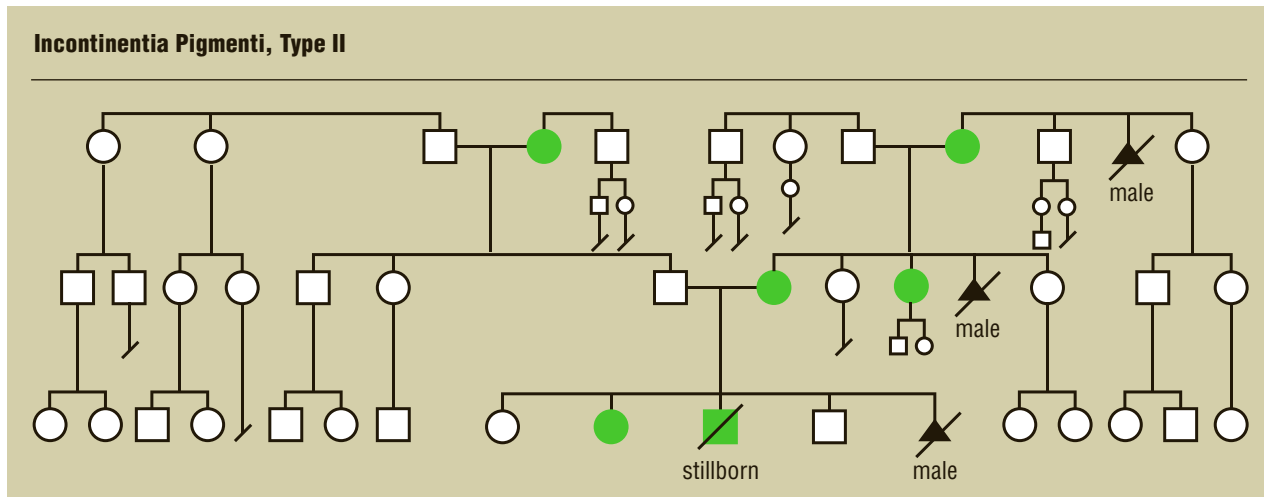
Incontinentia pigmenti

Definition

Incontinentia pigmenti (IP) is an X-linked dominant disorder affecting primarily the skin, hair, teeth, and nails (all components of the epidermis). This disease may have been initially described by Garrod in 1906. It was completely characterized by Bloch and Sulzberger in 1928. For this reason, incontinentia pigmenti has also been referred to as Bloch-Sulzberger syndrome.

Description

Incontinentia pigmenti has been traditionally classified into two types: type I and type II. Much debate has occurred over whether or not type I, or sporadic, incontinentia pigmenti is actually the same disease as type II, or familial, male-lethal type incontinentia pigmenti. The growing consensus is that sporadic (type I) incontinentia



Incontinentia pigmenti: pedigree analysis chart (Gale)

pigmenti is not, in fact, the same disease as familial, male-lethal (type II) incontinentia pigmenti. Type II (familial, male-lethal) incontinentia pigmenti is considered to be the “classic” case of incontinentia pigmenti that matches the disease characterized by Bloch and Sulzberger in 1928.

Genetic profile

The locus of the gene mutation responsible for incontinentia pigmenti type II has been mapped to the long end of the X chromosome at gene location Xq28. The affected gene is known as the *NEMO* gene.

A chromosome is a long chain of deoxyribonucleic acid (DNA), a double-stranded molecule composed of individual units called nucleotides. The two strands that make up a single DNA molecule are held together by a matching (base pairing) of the nucleotides on one strand with the nucleotides on the other strand. Each set of a nucleotide on one strand paired with its nucleotide on the other strand is called a base pair.

A gene is a particular segment of a particular chromosome. Within the segment containing a particular gene there are two types of areas: introns and exons. Introns are sections of the particular chromosomal segment that do not actively participate in the functioning of the gene. Exons are those sections that do actively participate in gene function. A typical gene consists of several areas of exons divided by several areas of introns.

The *NEMO* gene was completely sequenced by the International Incontinentia Pigmenti Consortium in 2000. The *NEMO* gene consists of approximately 23,000 base pairs that compose ten exons. The first exon of this gene, which is the exon that tells this gene to “turn

on,” has been found to have three variants; these are designated: 1a, 1b, and 1c.

The *NEMO* gene is known to partially overlap with the gene responsible for the production of glucose-6-phosphate dehydrogenase (*G6PD*). Mutations in the *G6PD* gene cause an underproduction of red blood cells (anemia) that results in an insufficient amount of oxygen being delivered to the tissues and organs. Anemia resulting from mutations in the *G6PD* gene is observed with higher frequencies in Africans, Mediterraneans, and Asians.

The locus of the gene mutation responsible for type I incontinentia pigmenti has been mapped to band Xp11, on the short arm of the X chromosome. Individuals affected with this disorder show many of the signs of incontinentia pigmenti type II, but it is not an inherited condition. Type I incontinentia pigmenti is only exhibited as a sporadic and *de novo* trait. This means that when an affected individual has the symptoms of type I IP, that individual did not inherit this condition from his or her parents; rather, the condition was caused by a mutation that occurred after conception.

Demographics

Incontinentia pigmenti is observed with higher frequencies in Africans, Mediterraneans, and Asians than in other portions of the population. This was originally thought to be due to the greater ability to observe the skin-related symptoms in these individuals. But, with the additional evidence that the *NEMO* gene and the *G6PD* gene overlap and that anemia resulting from mutations in the *G6PD* gene also disproportionately affects these populations, this anecdotal explanation has to be discarded.

KEY TERMS

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

De novo mutation—Genetic mutations that are seen for the first time in the affected person, not inherited from the parents.

Exon—The expressed portion of a gene. The exons of genes are those portions that actually chemically code for the protein or polypeptide that the gene is responsible for producing.

Hyperpigmentation—An abnormal condition characterized by an excess of melanin in localized areas of the skin, which produces areas that are much darker than the surrounding unaffected skin.

Intron—A portion of the DNA sequence of a gene that is not directly involved in the formation of the chemical that the gene codes for.

Pustule—A pus-filled lesion of the skin that resembles the “pimples” of adolescent acne.

Type I incontinentia pigmenti—Sporadic IP. This disorder is caused by mutations in the gene at Xp11. These mutations are not inherited from the parents, they are *de novo* mutations. This type of IP probably represents a different disease than type II IP.

Type II incontinentia pigmenti—Familial, male-lethal type IP. This type of IP is the “classic” case of IP. It is caused by mutations in the *NEMO* gene located at Xq28. Inheritance is sex-linked recessive.

More than 95% of all patients diagnosed with IP are female. The occurrence in males is probably due to a spontaneous (*de novo*) mutation in the *NEMO* gene that is not as severe as the typical mutation leading to IP or the misdiagnosis of type I IP. Approximately 70% of all IP affected individuals have been found to have the same mutation in the *NEMO* gene. In these families, 100% lethality prior to birth is observed in males.

Signs and symptoms

Familial, male-lethal (type II) IP is characterized by progressive rashes of the skin. These have been classified into four stages: the red (erythematic) and blister-like (vesicular) stage; the wart-like (verrucous) stage; the

darkened skin (hyperpigmented) stage; and the scarred (atrophic) stage.

The first, or erythematic vesicular, stage consists of patches of red skin containing blisters and/or boils. This condition usually appears in affected individuals at or near birth and is generally localized to the scalp, the arms, and the legs. This stage generally lasts from a few weeks to a few months and may recur within the first few months of life. It rarely recurs after the age of six months. This condition is often misdiagnosed as chicken pox, herpes, impetigo, or scabies. Each of these alternative diseases is potentially life-threatening in an infant, so most IP-affected infants are treated for one of these diseases before the appropriate diagnosis of incontinentia pigmenti can be made.

The second, or verrucous, stage of IP is characterized by skin lesions that look like adolescent acne (pustules). Upon healing, these pustules generally leave darkened skin. This stage almost exclusively affects the arms and legs, but it may be observed elsewhere. The verrucous stage may occur at birth, which may indicate that the erythematic vesicular stage occurred prior to birth. But, more generally, the second stage of IP skin disorder is observed after the first stage has completed. The verrucous stage tends to persist for months. Rarely, it may last for an entire year.

The third, or hyperpigmented, stage is characterized by “marbled skin,” in which darkened areas of skin seem to make swirling patterns across the normal and less pigmented skin. This third stage generally occurs between 6 and 12 months of life. In 5%–10% of affected individuals, this third stage is present at birth. These areas of hyperpigmentation tend to fade with age such that they are barely visible in adults affected with type II IP.

Areas of scarred skin caused by the first two stages characterize the fourth, or atrophic, stage. These scars are often noticeable before the third stage has begun to fade. Adolescents and adults affected with type II IP will generally have pale, hairless patches or streaks, most visibly on the scalp or calves, that are associated with this fourth stage. In many adults affected with IP, the skin abnormalities may have faded to such a significant degree that they are no longer noticeable to the casual observer. Many type II IP affected individuals have a loss or lack of hair on the crown of the head (alopecia). This is suspected to be caused by the underlying skin atrophies of IP.

More than 80% of individuals affected with type II IP have abnormalities of the teeth including missing teeth, late eruption of both the baby teeth and the adult teeth, unusually pegged or cone-shaped teeth, and deficiencies in the enamel. A smaller percentage

(approximately 40%) of affected individuals have irregular formations of the finger and toe nails including missing nails, thickened nails, and ridged or pitted nails. In a small number of cases, the skin lesions associated with the first two stages of skin abnormalities may be present underneath a nail. In these cases, it is possible for this lesion to develop into a benign tumor that may cause abnormal bone development in the affected finger or toe.

Approximately 30% of all individuals affected with IP experience visual problems. Less than 10% of type II IP-affected individuals have vision problems related to an abnormal growth of blood vessels in the retina, which may, if untreated, lead to a detachment of the retina, possibly resulting in blindness. These symptoms generally are seen before the affected individual reaches the age of five. Other vision problems that have been observed in type II IP-affected individuals include crossed eyes or “wall eyes” resulting from an improper alignment of the eyes (strabismus); partial or complete opaqueness in one or both lens (cataract); and, occasionally abnormally small eyes (microphthalmia). Because of these vision problems, some individuals affected with IP are blind at birth or will go blind if corrective treatment is not sought.

The incidence of breast development anomalies in type II-IP affected girls is quite common. It is estimated to be more than ten times that of the general population. These anomalies range from the presence of an extra nipple to the complete absence of breasts.

Approximately 25% of all IP-affected individuals have disorders of the central nervous system. These include mental retardation, slow motor development, epilepsy, an abnormally small brain (microcephaly), and increased muscle tone in both legs (spastic diplegia) or in all four limbs (spastic tetraplegia) similar to that seen in the classic case of cerebral palsy.

Diagnosis

The genetic mutation responsible for type I incontinentia pigmenti has been fully mapped and sequenced; therefore, it is possible to perform a genetic test for the existence of this disease. However, most cases are still diagnosed on a clinical basis.

Clinical diagnosis of type I IP is based primarily on the skin abnormalities seen at birth. These skin problems may still be misdiagnosed as chicken pox or herpes. This misdiagnosis is easily corrected when the affected individual begins to develop the later stages of the skin anomalies. All suspected male infants should have a chromosome test performed to confirm diagnosis.

In older patients with scarred skin, a skin biopsy that shows “loose” melanin (the pigment that produces color in the skin) confirms a diagnosis of IP.

When the skin appears normal, a diagnosis of IP is indicated when an individual shows one or more of the physical symptoms characteristic of IP: teeth abnormalities, missing patches of hair (alopecia), and/or overgrowth and scarring of the retinal blood vessels; and, that individual is female, has two or more IP-affected daughters, is the daughter or sister of an affected woman, or has experienced the miscarriage of two or more male fetuses.

The presence of seizures within the first weeks of life indicate central nervous system involvement in the IP-affected individual and indicate an extremely high likelihood of subsequent developmental delay.

Treatment and management

Usually no treatment for the skin conditions associated with IP is necessary other than the control of secondary infection that may occur.

In a female newborn where IP is suspected, an eye exam to look for retinal abnormalities, or any of the other possible eye disorders associated with IP, should be conducted within the first few days after birth. Older affected individuals should have regular eye exams to ensure that retinal abnormalities do not develop. Laser treatments and freezing treatments (cryopexie) are often required to prevent retinal detachment.

Dental treatment is often necessary to repair damaged enamel or for cosmetic reasons in the cases of missing teeth or abnormally shaped teeth.

In cases where there is involvement of the central nervous system, the necessary treatments are on a symptomatic basis. These may include early and continuing intervention programs for developmental delays, anticonvulsants to control seizures, muscle relaxants to control spasticity, and/or surgery to release the permanent muscle, tendon, and ligament tightening (contracture) at the joints that is characteristic of longer term spasticity.

Prognosis

Incontinentia pigmenti is generally fatal in males prior to birth. Females, and the few surviving males, who are affected with IP can expect a normal lifespan if treatment is undertaken to repair or manage any of the associated symptoms.

Resources

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- Klug, William S., et al., eds. *Concepts of Genetics*. 12th ed. London: Pearson, 2019.

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WEBSITES

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ORGANIZATIONS

Incontinencia Pigmenti International Foundation (IPIF), 78 Saint Moritz Dr., Erial, NJ 08081, (212) 452-1231, (212) 452-1231, ipif@ipif.org, <http://www.ipif.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Paul A. Johnson, PHD

Infertility

Definitions

Infertility is defined as the failure of a couple to conceive (or become pregnant), regardless of cause, after of year of unprotected intercourse. Some physicians consider infertility to be likely if the female partner is over 35 and has failed to conceive after six months of unprotected intercourse. Recurrent pregnancy loss (miscarriages or stillbirths) is included in the definition of infertility in the United States.

Primary infertility is defined as inability to become pregnant at all, while secondary infertility is defined as inability to become pregnant after a previously successful pregnancy.

Sterility is defined as complete inability in either a man or a woman to produce offspring. It may result from disease, physical injury, a genetic disorder, a surgical procedure to prevent conception (vasectomy in men, tubal ligation or hysterectomy in women), or exposure to radiation.

Demographics

Infertility is fairly common worldwide. In the United States, infertility affects between 10% and 15% of couples of reproductive age. Worldwide estimates range between 12% and 28% of couples, with the World Health Organization (WHO) stating that about 48 million

couples and 186 million individuals around the world are infertile.

Infertility of the male partner is responsible for 20% to 30% of infertility cases, while 20% to 35% are due to infertility in the female; and 25% to 40% of cases are due either to medical issues in both partners or to unknown causes.

General causes of infertility

In men

Causes of infertility in men may include:

- Antisperm antibodies (ASAs). These are proteins produced by the immune system, in either men or women, that mistake sperm for foreign invaders and inactivate or kill sperm. ASAs can be detected in male ejaculate or female vaginal fluids.
- Aging. Although aging plays a more important role in female infertility than in male infertility, men over age 40 are more likely to have difficulty fathering a child. It is thought that the lowered quality of sperm in older men is due to DNA damage.
- Physical trauma to the testicles.
- Structural abnormalities of the male genitalia. These may include blockages of the vasa deferentia, the ducts that carry sperm toward the ejaculatory ducts in preparation for ejaculation; obstruction of the



Color-enhanced micrograph of a karyotype of an infertile male. There are 22 pairs of chromosomes and also the gender determining pair (lower right corner). In men, this comprises one X and one Y chromosome. In women, it is made up of two X chromosomes. The Y chromosome carries genetic information responsible for the development of male characteristics. Karyotypes are an arrangement of chromosomes based on their appearance under a light microscope. (Leonard Lessin/Science Source)

ejaculatory ducts; missing or absent testis (monorchism); varicocele, an abnormal enlargement of the veins in the scrotum; hypospadias, a birth defect in which the opening of the urethra is located on the lower surface of the penis; and chordee, an abnormal downward curve to the erect penis.

- Medical conditions. These include celiac disease (CD), diabetes, cystic fibrosis, some autoimmune disorders, inflammation of the prostate gland, and infectious diseases like mumps, malaria, hepatitis B, and sexually transmitted infections (STIs) like chlamydia and gonorrhea. STIs not only can affect the quality of sperm but can also cause inflammation of the epididymis, the tube behind the testes that stores and transports sperm.
- Disorders of the hypothalamus, pituitary, and adrenal glands, including tumors of the pituitary gland, whether benign or cancerous; Cushing's syndrome, which results from heavy use of corticosteroid drugs or a tumor of the adrenal glands causing excessive cortisol production; and congenital adrenal hyperplasia (CAH), a group of disorders that affects the adrenal glands' ability to make certain specific hormones, resulting in abnormal external genitalia and early, delayed, or absent puberty.
- Medications. Drugs that are known to affect sperm production include flutamide, cyproterone, and bicalutamide (drugs used to treat prostate cancer); spironolactone (used to treat fluid retention); ketoconazole (an antifungal drug); and cimetidine (a drug given to reduce stomach acid production).
- Testicular cancer.
- Radiation or chemotherapy used to treat any form of cancer.
- Occupational exposure to radiation, pesticides, lead, cadmium, or mercury.

Lifestyle factors that can lower sperm production include obesity; heavy use of alcohol and drugs of abuse, particularly marijuana; abuse of testosterone or anabolic steroids to build muscle; smoking; strenuous bicycle or horseback riding; and frequent use of saunas and hot tubs.

In women

Causes of infertility in women may include:

- Presence of antisperm antibodies (ASAs) in vaginal fluid.
- Aging. Women's fertility peaks in the mid-20s, after which it starts to decline.
- Structural abnormalities of the female reproductive tract. These may include endometriosis, a condition in which the tissue that normally lines the uterus is found elsewhere outside the uterus, often covering the ovaries and fallopian tubes; blocked fallopian tubes (a common

result of pelvic inflammatory disease); an abnormally shaped or half-formed uterus; the presence of fibroids or polyps in the uterus; scar tissue in the uterus resulting from infections or surgery; history of ruptured appendicitis; ambiguous external genitalia as a result of CAH; lack of connection between the uterus and the cervix; vagina missing or partially blocked between the hymen and the cervix; presence of an extra ovary or tissue attached to the ovaries. Many of these abnormalities in women and girls are caused by disturbances in the development of structures called the Müllerian ducts in female embryos.

- Sexually transmitted infections (STIs). Infections like gonorrhea and chlamydia are a common cause of infertility in women in that they can lead to blockage of the fallopian tubes. Syphilis increases a woman's risk of stillbirth. Human papillomavirus (HPV) infections can affect a woman's fertility in that the removal of abnormal cells from the woman's cervix to treat HPV can affect the production of cervical mucus.
- Hormonal disorders. Polycystic ovary syndrome (PCOS) is a hormonal disorder characterized by underproduction of follicle-stimulating hormones and overproduction of androgens. Overproduction of the hormone prolactin by the pituitary gland may lead to failure to ovulate. Tumors of the pituitary, thyroid, and adrenal glands can also lead to a failure to ovulate.
- Autoimmune disorders. Such disorders as lupus, Hashimoto's thyroiditis, and rheumatoid arthritis can reduce a woman's fertility.
- Anovulation. Failure to ovulate (produce an egg during a normal menstrual cycle) can result from any of a number of factors; hormonal disorders have already been mentioned. Many teenagers do not ovulate for a year or even longer after their first menstrual period (menarche). Emotional stress can lead to a condition called functional hypothalamic amenorrhea or FHA. Inadequate nutrition, including eating disorders, is another common cause of anovulation. Premature ovarian insufficiency (POI) is a term used to describe the failure of a woman's ovaries before 40 years of age. Last, women cease to ovulate when they reach menopause, which occurs around age 50 in most women.
- Scar tissue inside the abdomen, resulting from surgery to repair traumatic injuries or remove diseased tissue.
- Radiation or chemotherapy used to treat any form of cancer.

Lifestyle factors that affect fertility in women include obesity, eating disorders, being underweight, under- or over-exercising, smoking, heavy drinking, using drugs of abuse, and high levels of emotional stress.

KEY TERMS

Amenorrhea—Absence of menstruation, usually defined as missing one or more menstrual periods.

Androgen insensitivity syndrome—An intersex condition found in people who are chromosomally male (karyotype XY) but have a mutation in the *AR* gene that makes them unable to respond to male sex hormones. As a result, they may have some or all of the physical traits of a female.

Aneuploidy—An abnormal number of chromosomes in a cell, whether extra or missing chromosomes.

Assisted reproductive technologies (ART)—A collective term for a group of procedures done to address problems with fertility. ART includes such techniques as in vitro fertilization, cryopreservation of donated gametes or embryos, and preimplantation genetic diagnosis.

Autosome—Any chromosome that is not a sex chromosome. The human genome has 22 pairs of autosomes.

Azoospermia—The absence of live sperm in male semen.

Fragile X syndrome—A genetic condition caused by a mutation in the *FMR1* gene on the X chromosome and characterized by intellectual disability.

Galactosemia—A rare genetic disorder in which the person cannot metabolize galactose, a simple sugar found in dairy products.

In vitro fertilization (IVF)—A form of assisted reproduction technology in which a human ovum (egg) is combined with sperm outside the body in a laboratory container (“in vitro” means “in a glass”).

Informed consent—The process of obtaining permission from a person before conducting a health care procedure on a person, enrolling a person in a clinical trial, or disclosing that person’s private information.

Karyotype—The complete set of chromosomes in a species or individual organism. The term can also refer to the laboratory technique used to produce an image of an individual’s chromosomes.

Klinefelter syndrome—A genetic disorder characterized by one or more extra X chromosomes in a male, with a 47,XXY, 48,XXX, or 49,XXXXY karyotype. Most men with this syndrome are infertile or have reduced fertility. The syndrome is named for Harry Klinefelter (1912–1990), an American endocrinologist who first described it in 1942.

Leiomyomas—Benign tumors in the smooth muscle tissue of the uterus. They are also known as fibroids.

Menarche—The medical term for the first menstrual period in girls, usually around age 12.

Microdeletion—A chromosome deletion that is too small to be detected by standard karyotyping methods. Microdeletions are typically one to three mega bases in

Genetic causes of infertility

Genetic disorders can cause infertility in both men and women.

In men

Genetic disorders causing infertility in men fall into several different categories:

- Defects in the number of chromosomes (aneuploidy). Infertile men may have extra sex chromosomes, as in Klinefelter syndrome (karyotype 47,XXY), which is found in up to 14% of men with azoospermia (total absence of sperm in semen); and 47,XYY syndrome, which is often characterized by oligospermia (abnormally small number of sperm).
- Abnormalities in chromosome structure. These include microdeletions on the Y chromosome, which affect sperm production; Robertsonian translocations (in which the long arms of two acrocentric chromosomes fuse), which increase the risk of trisomy 21 (Down

syndrome) in the next generation; and XX male syndrome, which is also known as de la Chapelle syndrome and 46,XX testicular difference of sex development (46,XX DSD). This syndrome is very rare; it develops when the *SRY* gene on the Y chromosome, which is essential to normal male reproductive development, crosses over to the father’s X chromosome during germ cell development. When the X with an *SRY* gene combines with a normal X chromosome from the mother, an XX male will result. Men with a 46,XX karyotype typically have abnormally small testicles and do not produce sperm.

- Single-gene disorders. These include congenital bilateral aplasia of the vas deferens (CBAVD), a condition in which the tubes that convey sperm from the testicles to the penis are missing from birth. CBAVD is associated with mutations in the *CFTR* gene. Other single-gene mutations associated with androgen insensitivity syndrome, the production of abnormally shaped sperm, or absence of sperm production have been identified in

length (one to three million base pairs), whereas standard deletions are five mega bases or longer.

Müllerian ducts—Structures found in the human embryo that develop into the fallopian tubes, the uterus, the cervix, and part of the vagina in females. They are named for Johannes Müller, a nineteenth-century German physician and anatomist.

Multifactorial disorders—A general term for polygenic disorders complicated by the effects of environmental factors. Multifactorial disorders do not have clear patterns of inheritance. They are sometimes called complex diseases or disorders. PCOS in women is a multifactorial disorder.

Oligospermia—A low concentration of sperm in a semen sample, usually defined as fewer than 15 million sperm per milliliter.

Polycystic ovary syndrome (PCOS)—A multifactorial disorder in women characterized by absent or infrequent ovulation, hirsutism (excessive body hair), infertility, acne, and increased susceptibility to obesity and type 2 diabetes.

Reproductive endocrinologist—A doctor (usually a gynecologist) with subspecialty training in hormonal functioning as it pertains to infertility.

Robertsonian translocation—A chromosomal abnormality in which the long (q) arms of two acrocentric chromosomes (chromosomes in which

the p arm is much shorter than the q arm; in humans, these are chromosomes 13, 14, 15, 21, and 22, and the Y chromosome) fuse together. The anomaly is named for William R.B. Robertson (1881–1941), who first identified it in grasshoppers in 1916.

Sterility—The inability of either a male or a female to produce offspring. Sterility may result from physical injury, disease, genetic disorders, or exposure to radiation.

Trisomy—A type of aneuploidy in which there are three copies of a specific chromosome in cells instead of the normal two. Some trisomies result in infertility.

Turner syndrome—A chromosomal disorder with a 45,X or 45,X0 karyotype that affects only females, in which one of the X chromosomes is either partially or completely missing. Most women with Turner syndrome are infertile because of a lack of ovarian function.

Varicocele—Enlargement of the veins within the male scrotum. Sometimes described as resembling a bag of worms, varicoceles are a common cause of low sperm production and reduced sperm quality.

Y chromosome—The sex chromosome (allosome) that is found together with an X chromosome in normal human males. Microdeletions in the Y chromosome can affect a man's fertility in adult life.

connection with the *AR*, *AURKC*, *HSF2*, *KLHL10*, *NR5A1*, *PRM1*, *SLC26A8*, *SOHLH1*, *SPATA16*, and *ZBPB1* genes.

In women

As in men, genetic disorders in women fall into several different categories:

- Defects in the number of chromosomes. Turner syndrome (45,X0, also known as monosomy X) is a condition in which a woman has only one X chromosome and can have children only by assisted reproductive technology (ART). 47,XXX syndrome, also known as trisomy X, is associated with premature ovarian insufficiency (POI) or abnormalities of the kidneys and urinary tract, while some women with this karyotype have normal fertility.
- Single-gene disorders. These include fragile X syndrome, caused by a mutation in the *FMR1* gene; galactosemia, a metabolic disorder, caused by a mutation

in the *GALT* gene; POI, associated with the X-linked genes *FMR1* and *BMP15* as well as with the *AR*, *CDKN1B*, *CYP19A1*, *GDF9*, *FIGLA*, *FOXL2*, *FOXO1a*, *FOXO3a*, *INHA*, *LHX8*, *NOBOX*, *NANOS3*, *FSHR*, and *SALL4* genes on autosomal chromosomes; and leiomyomas (fibroids), associated with mutations in the *MED12* gene.

- Polygenic/multifactorial disorders. Polygenic disorders are complex genetic disorders involving more than one gene; multifactorial disorders include the effects of environmental as well as genetic factors. Disorders affecting female fertility that are thought to have complex genetic linkages include endometriosis, which is known to run in families; and PCOS, a multifactorial disorder.

Diagnosis

Couples are advised to have a diagnostic workup after a year of unprotected intercourse without signs of

pregnancy if the woman is younger than 35, and after six months if she is 35 or older.

Men

A diagnostic workup for causes of infertility in men is usually done by a urologist, a physician who specializes in disorders of the urinary tract and the male reproductive system. The workup includes the following:

- Detailed personal and medical history. The doctor will ask about the patient's sexual history, including any STIs; mumps after puberty; hernia repairs or athletic injuries to the groin; use of alcohol, marijuana, and other recreational drugs; present prescription medications; urinary tract infections; impotence or premature ejaculation; other surgeries, including appendectomy; and work environment.
- Physical examination. The doctor will examine the patient's penis, testicles, and prostate gland for any signs of enlargement, abnormal texture, abnormal shape, or the presence of a varicocele in the scrotum. The doctor will also order blood tests to measure the patient's levels of testosterone and follicle-stimulating hormone (FSH). FSH is a hormone that is essential to the production of normal sperm.
- Semen analysis. The patient will be asked to provide a semen sample, which will be examined in the laboratory for the number of sperm, their ability to move (motility), their velocity, their morphology (size and shape), and the ability of the semen to liquefy after ejaculation.
- Other types of semen and sperm tests. These may be done if needed. They measure the ability of the patient's sperm to break through the outer membrane of an egg to fertilize it and to move through cervical mucus. Semen may also be tested for the presence of antisperm antibodies.

Women

A diagnostic workup for causes of infertility in women is usually done by a gynecologist and includes the following:

- Detailed personal and medical history. The doctor will ask about the patient's sexual history, including any STIs; age at menarche (first period) and characteristic menstrual patterns; previous pregnancies, if any; use of alcohol, marijuana, and other recreational drugs; present prescription medications; urinary tract infections; other surgeries, including appendectomy; eating and exercise patterns; and work environment.
- Physical examination. The doctor will examine the thyroid gland in the throat for any abnormalities as well as measuring the patient's height, weight, and hair

distribution (for evidence of PCOS or other masculinizing disorders); examine the patient's breasts; perform a pelvic examination (to check the cervix for signs of infection or unusual growths); and perform a Pap smear (to examine the cervical mucus and rule out cervical cancer).

- Blood tests and ultrasound examination. The doctor may order blood tests to measure ovarian function. These tests measure the levels of estradiol, an estrogen; FSH; and inhibin B. The ultrasound test is given to see whether ovulation has occurred. Ultrasound can also be used to look for the presence of fibroids or ovarian cysts. In some cases, the patient may be referred to a reproductive endocrinologist for further testing.
- Invasive testing. Because the female reproductive system is contained within the abdomen, special procedures may be necessary to look for structural abnormalities in the uterus, fallopian tubes, or ovaries. These procedures include hysterosalpingography (HSG), in which a contrast dye is injected into the uterus through the vagina and cervix and tracked on x-ray; and hysteroscopy, in which an endoscope is inserted through the vagina to inspect the uterine cavity.
- Laparoscopic surgery. This type of diagnostic surgery is performed under general anesthesia before or around the time of ovulation to obtain a clear view of the exterior of the ovaries, uterus, and fallopian tubes. If endometriosis is found during this surgery, it can be treated with a laser.

If the doctor suspects a genetic disorder in the patient, he or she may recommend genetic testing to look for the presence of chromosome abnormalities or single-gene mutations. The test can be ordered by the patient's urologist or gynecologist, or by a genetic counselor; it requires the patient's informed consent. This type of testing requires only a blood draw or a buccal swab, in which a few skin cells from the lining of the cheek are collected on a small brush or cotton swab.

Treatment and management

Treatment of infertility depends on its cause(s) and whether the male, the female, or both partners are affected. In some cases, treatment is relatively simple and may involve little more than discontinuing a medication that interferes with sperm production or taking a medication (usually clomiphene citrate, letrozole, FSH, or bromocriptine) to stimulate egg production. In other cases, the doctor can inject specially prepared sperm from the male partner directly into the woman's uterus through a catheter; this is known as intrauterine insemination or IUI. On the other hand, genetic disorders involving chromosome number or structure are usually not treatable.

QUESTIONS TO ASK YOUR DOCTOR

- Have any of your parents consulted you about infertility?
- If so, what advice did you give them?
- Have you ever referred a patient to a reproductive endocrinologist?
- Have you ever recommended psychological counseling for a patient who was distressed about infertility?
- In your opinion, are men or women more likely to be disturbed by infertility?

Psychological counseling

In addition to medical testing and counseling, infertile couples often benefit from psychological counseling. Infertility is a blow to the self-image of many people, as infertile people within many cultures around the world experience stigma. In addition to individual stress, infertility may lead to conflict or the breakdown of the relationship between the partners, especially when the cause is traced to one partner rather than to both or remains unknown. The website of RESOLVE: The National Infertility Association, listed under Resources below, contains links to support groups and other useful information about managing infertility stress.

Assisted reproductive technologies (ART)

If there is no effective treatment for the cause of a couple's infertility, the doctor may recommend assisted reproductive technologies or ART. ART techniques include in vitro fertilization (IVF); intracytoplasmic sperm injection (ICSI), in which a single sperm from the male partner is injected into a mature egg from the female; or the use of donated sperm and eggs to produce viable embryos via IVF.

Resources

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- Puscheck, Elizabeth E. "Infertility." Medscape Reference. Updated January 30, 2020. <https://emedicine.medscape.com/article/274143-overview> (accessed May 29, 2021).

ORGANIZATIONS

American College of Obstetricians and Gynecologists (ACOG), 409 12th Street, SW, Washington, D.C. 20024-2188, (800) 673-8444, (202) 638-5577, <https://www.acog.org/>

American Society of Human Genetics (ASHG), 6120 Executive Boulevard, Suite 500, Rockville, MD 20852, (301) 634-7300, society@ashg.org, <https://www.ashg.org/>

American Society for Reproductive Medicine (ASRM), J. Benjamin Younger Office of Public Affairs, 726 7th Street, SE, Washington, D.C. 20003, (202) 863-4985, asrm@asrm.org, <https://www.asrm.org/>

American Urological Association (AUA), 1000 Corporate Boulevard, Linthicum, MD 21090, (866) 746-4282, (410) 689-3700, (410) 689-3800, aue@AUAnet.org, <https://www.auanet.org/>

National Society of Genetic Counselors (NSGC), 330 North Wabash Avenue, Suite 2000, Chicago, IL 60611, (312) 321-6834, nsgc@nsgc.org, <https://www.nsgc.org>

RESOLVE: The National Infertility Association, 7918 Jones Branch Drive, Suite 300, McLean, VA 22102, (703) 556-7172, (703) 506-3266, info@resolve.org, <https://resolve.org>

Society for Assisted Reproductive Technology (SART), 1209 Montgomery Highway, Birmingham, AL 35216-2809, (205) 978-5000, (205) 978-5018, sart@asrm.org, <https://www.sart.org/>

U.S. Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, Atlanta, GA 30333, (800) CDC-INFO (232-4636), <http://www.cdc.gov/cdc-info/requestform.html>, <http://www.cdc.gov>

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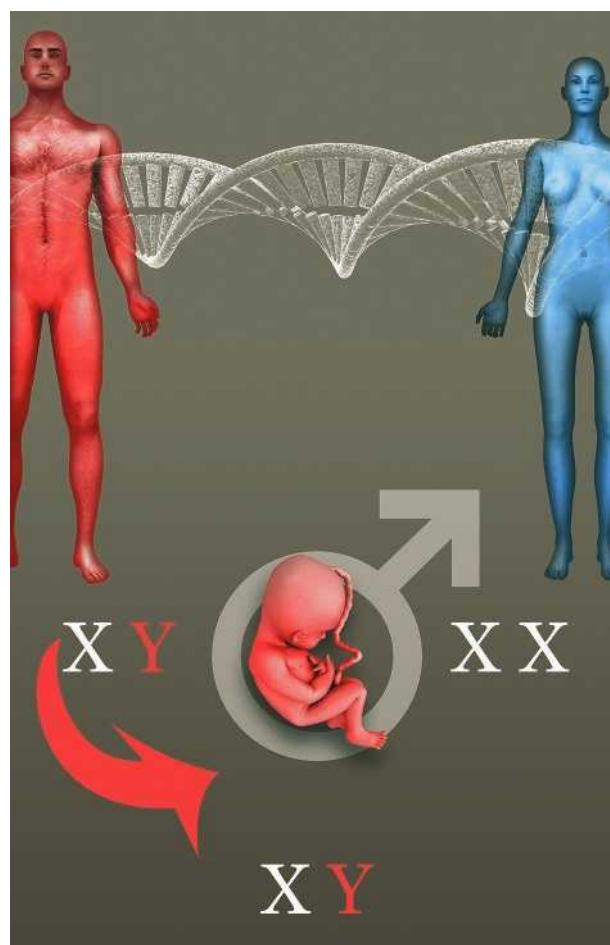
Inheritance

Definition

Inheritance (generally) and heredity (scientifically) both refer to the transmission of genes from parent to offspring, along with the physical, behavioral, and biochemical traits/characteristics they produce.

Description

Throughout history, people have puzzled over heredity. While it is obvious that physical traits and behavioral traits are passed from parent to offspring, both in plants and animals, the puzzling aspects of heredity are the exceptions and quirks in what should be a very basic process. For instance, apparently hereditary characteristics sometimes skip a generation or two, disappear altogether, or appear in an individual or generation for the first time, seemingly from nowhere. A further mystery, the finer points of which are still being unraveled, lay in the mechanism of exactly how traits get from parent to offspring. Even more perplexing to those in the past was the occurrence/recurrence of congenital anomalies and disorders, resulting in physical and/or behavioral disability.



An illustration depicting how DNA passes along genetic disorders based on gender. (3D4Medical/Science Source)

Answers to many of the questions about heredity were deduced in the mid-nineteenth century by a scientist, Gregor Mendel, at a monastery in what is now the Czech Republic. The deductions he made from the results of his experiments came to be known as Mendel's laws of heredity, since shortened to just Mendelian inheritance. These are the patterns of inheritance, dominant and recessive, with which most people are familiar. However, geneticists have learned in recent years that even Mendel's laws are not immutable and that other non-Mendelian types of inheritance also exist.

A common misconception is that genetic is synonymous with hereditary and that the terms can be used interchangeably. In fact, while something that is hereditary is always genetic, something that is genetic is not necessarily hereditary. For example, all cancer at the most basic level is genetic, caused by errors in the genetic control of cell division and proliferation. However, only a small proportion of individuals with cancer inherited the causative gene mutation from a parent. In most cases, an

external agent (carcinogen) induces a genetic mutation in a cell somewhere in the body (e.g., tobacco smoke in a lung cell, or ultraviolet radiation in a skin cell), an error in DNA replication results in a mutation, or both. Gene mutations that occur anywhere in the body other than sperms, eggs, or their precursor cells (germline) are called somatic mutations and are not hereditary. As noted, a small percentage of cases of any particular type of cancer (usually about 5%–10% for the most common types) exhibit a hereditary pattern. Most often, it is a predisposition to developing cancer that is inherited, placing someone at increased risk for cancer. In fact, most common diseases, such as diabetes, hypertension, heart disease, and so on, are thought to follow the same general pattern as cancer, with a small percentage of cases due to heredity, most due to environmental effects acting on normal, but susceptible, variants of genes, and the remaining proportion caused by purely environmental or purely somatic genetic events.

Classifying the different types of heredity can be done in various ways. However, most people are only familiar with traditional types of Mendelian inheritance and know little or nothing about other types of heredity. Accordingly, inheritance can be classified as either Mendelian or non-Mendelian, and then further divided and subdivided on that basis.

Mendelian inheritance

All somatic cells in humans (except mature red blood cells) normally contain 46 chromosomes, in 23 pairs. Sperms and eggs carry 23 chromosomes, one of each pair. The process of sperm development is spermatogenesis, egg development is oogenesis, and the general term for both is gametogenesis. The process that is the basis for Mendelian inheritance is meiosis, which takes place only during gametogenesis (chromosome duplication and cell division in somatic cells is mitosis). During meiosis, the 46 chromosomes in precursor cells in testes and ovaries duplicate to produce a total of 92. Two cell divisions then take place, reducing the number of chromosomes per cell to 23. During spermatogenesis, the process results in four sperm, but oogenesis produces only one egg (along with two nonfunctional polar bodies with 46 and 23 chromosomes each). All eggs normally carry a single X chromosome, whereas half of all sperm carry an X, and the other half carry a Y chromosome.

Humans have 24 different chromosomes, the first 22 numbered sequentially, with the twenty-third and twenty-fourth designated as X and Y. Chromosomes 1 through 22 are called autosomes. The X and Y are the sex chromosomes, although only the Y chromosome has any effect in determining sex (gender). Although it is commonly believed that female gender is determined by an

XX chromosome constitution, and likewise males are XY, this is misleading. Male and female genders are determined by specific genes and hormonal influences. Certain genetic conditions result in males that are 46, XX, and others in females that are 46,XY. Therefore, it is appropriate and technically more accurate to state that females and males typically or usually have 46,XX and 46,XY chromosome constitutions, respectively.

Mendelian inheritance is either autosomal or sex linked and dominant or recessive. Given the small number of genes on the Y chromosome and their relative unimportance in producing genetic disease, for all practical purposes, sex-linked inheritance is equivalent to X-linked inheritance. Sex-linked inheritance should also not be confused with sex-influenced inheritance, which involves autosomal inheritance with different phenotypic results in males and females due to hormonal differences. For the purposes of the criteria and terminology that follow, genetic disorders will be assumed, rather than normal characteristics (e.g., blue eyes, brown eyes, etc.) that might follow dominant or recessive inheritance patterns.

Genetic conditions that display Mendelian inheritance are often referred to as single-gene disorders. However, this is somewhat of a misnomer, since these conditions nearly always involve two genes, one on each chromosome of a particular pair. To clarify, the word *gene* is typically used in a broad context and includes all the variations of that gene, known as alleles. For instance, there may be a single gene for eye color, with different alleles for brown, blue, green, and so on. Some changes in genes result in alleles with no functional difference, or in neutral variations, such as the eye color example. Other genetic changes (mutations) result in alleles associated with disease. If an individual has two identical alleles of a gene, they are considered homozygous; if the alleles are different, that person is said to be heterozygous. Hemizygous refers to the presence of only one allele of a gene, instead of the expected two. Males are normally hemizygous for all the genes on the X and Y chromosomes, since they have only one copy of each. Hemizygosity for an autosomal gene may cause disease, and the symptoms may be different based on whether it is the maternal or paternal allele (gene) that is missing.

Autosomal dominant

The hallmarks of autosomal dominant inheritance include:

- A disorder that is caused by an anomaly in an autosomal gene, requiring only one disease-causing allele to produce symptoms (i.e., heterozygotes affected).

- The condition affects and can be transmitted by both sexes equally.
- A carrier of the gene, whether affected or not, has a 50% chance of transmitting it to each child.
- A later age of onset, with milder symptoms and greater variability, as compared to recessive disorders (on average).
- Sporadic (isolated) cases are not uncommon and are usually the result of new mutations (no previous family history).

Some conditions (e.g., Huntington disease) display what has been referred to as true dominance, which means that individuals with one-disease allele (heterozygotes) exhibit the same signs and symptoms as individuals with two-disease alleles (homozygotes). In other conditions, the effects of the gene are additive. For example, it is not unusual for two heterozygous individuals with achondroplasia (a common dwarfing condition) to meet and have children. With each conception, there is a 25% chance the child will receive a normal gene from each parent (homozygous unaffected), a 50% chance of receiving one normal gene and one achondroplasia gene (heterozygous, affected-like parents), and a 25% chance of receiving the achondroplasia gene from each parent, which results in severe limb shortening and other skeletal problems that result in death before or shortly after birth. It could be argued that this type of situation more closely resembles autosomal recessive inheritance, with heterozygotes simply showing more pronounced symptoms than most other recessive disorders.

Other important issues complicating autosomal dominant inheritance include reduced penetrance, variable expression, and possible gonadal mosaicism in the parent of an isolated case. If each person who carries the gene for a particular disorder exhibits symptoms, the gene is said to have 100% penetrance. Therefore, reduced penetrance means that some proportion less than 100% of heterozygotes will develop detectable signs of the condition. For some disorders that have been well studied, penetrance figures at specific ages have been calculated (e.g., a disorder is 50% penetrant at age 30, 70% penetrant at age 50, and so on). Variable expression simply means that two individuals with the same disease allele, even within the same family, may show markedly different ages of onset and/or severity of symptoms.

Autosomal recessive

The hallmarks of autosomal recessive inheritance include:

- The genetic disorder is fully expressed only in individuals homozygous for the disease-causing gene.

- The disorder is usually found only in siblings, with males and females at equal risk.
- When both parents are carriers (unaffected heterozygotes), the risk in each pregnancy of having an affected child is 25%.
- An unaffected sibling of an affected individual has a 66% (two-thirds) chance of being a carrier.
- The incidence of consanguinity in general is increased in autosomal recessive disorders, with a higher likelihood the more rare the condition. Conversely, consanguinity noted in the parents of a child with an unidentified disorder suggests autosomal recessive inheritance as a possible cause.

Many sporadic cases of recessive disorders are noted, because modern families tend to be small and geographically dispersed. Unfortunately, in some cases, the only way that autosomal recessive inheritance is proved is when a second or third affected child is born.

If an affected person has children with a carrier of the same disorder, each child has a 50% risk of being affected, and a 50% risk of being a carrier. If two individuals are affected by the same genetic disorder and have children (rare, but more likely for recessive disorders involving deafness, blindness, or other symptoms that tend to bring people together), all of their children will be affected.

X-linked recessive

The hallmarks of X-linked recessive inheritance include:

- The genetic disorder in which females are carriers, and usually only males are affected.
- There is no male-to-male transmission, since males transmit an X chromosome only to daughters.
- All sons of an affected male will be unaffected, but all daughters will be carriers.
- Typically, carrier females have a 25% chance in each pregnancy of having an affected child (50% chance of transmitting the X chromosome with the disease gene, but only half of those will be passed to boys).

Unlike carriers of autosomal recessive disorders, who, at most, usually show only clinically insignificant biochemical or physical changes, female carriers of X-linked recessive disorders often show mild to moderate effects of the disorder. In rare cases, they may even be as severely affected as their affected male relatives. While it is true that females normally have two X chromosomes and males have only one, it is also true that most of one of the X chromosomes in each cell are randomly inactivated in females shortly after conception. If, by chance, most cells in the body have an active X chromosome that

carries the disease gene, a female carrier can show marked symptoms of the disorder. If the reverse is true, she will likely appear completely unaffected.

Women are considered obligate carriers if they have more than one affected son, or an affected male relative and a proven carrier daughter, or an affected son and an affected brother or maternal uncle. Women are at risk for being carriers if they have one affected son, or one affected brother, or one affected maternal uncle, or a sister with an affected son (since any of them may have a new mutation).

An isolated case of a diagnosed X-linked disorder may be the result of a new mutation in the affected individual or in the mother, or may be the result of carrier status transmitted to the mother by her mother. Clarification of this point can make the difference between 50% (mother is a carrier) and negligible (new mutation) in the recurrence risk for the next male pregnancy and in the risk for daughters or sisters to be carriers. Unfortunately, carrier status of the mother may be very difficult to determine unless reliable carrier testing is available. Molecular genetic testing is making this possible for an increasing number of diseases (e.g., Duchenne muscular dystrophy and fragile X syndrome). An isolated case of an X-linked disorder may also be the result of germline mosaicism in the mother in which some of her eggs carry the mutation and others do not.

X-linked dominant

X-linked dominant disorders are rare. Females are usually affected more mildly than males. However, since both males and females can show symptoms, the inheritance pattern may resemble autosomal dominant inheritance, with the critical difference being no male-to-male transmission in X-linked inheritance. A few X-linked dominant disorders are lethal in males (e.g., incontinentia pigmenti).

Non-Mendelian inheritance

Chromosomal heredity

For purposes of broad classification, chromosome anomaly syndromes are considered either numerical or structural. As the term implies, numerical chromosome anomalies involve a change in the total number of chromosomes in each cell, most often presenting as a trisomy, such as the most common type of Down syndrome (trisomy 21). Numerical chromosomal syndromes are not considered to be hereditary. Structural chromosome anomalies can take various forms, but most often involve a translocation of some type, either an exchange of chromosomal material between two chromosomes (reciprocal translocation), or two chromosomes attached to each other to form a single chromosome (Robertsonian translocation). Either type of translocation

KEY TERMS

Allele—One of two or more alternative forms of a gene.

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes; human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Hemizygous—Having only one copy of a gene or chromosome.

Heterozygous—Having two different versions of the same gene.

Homozygous—Having two identical copies of a gene or chromosome.

Mitochondrial inheritance—Inheritance associated with the mitochondrial genome, which is inherited almost exclusively from the mother.

Penetrance—The proportion of individuals with a dominant gene mutation, expressed as a percentage, who actually exhibit recognizable signs or symptoms of the disorder.

Phenotype—The physical expression of an individual's genes.

Sex-linked—A gene located on, and thus a trait linked to, the X or Y chromosomes.

Uniparental disomy (UPD)—An unusual genetic status in an individual in which one parent is the source of both chromosomes of a pair.

can be balanced (no extra or missing chromosomal material, just rearranged) or unbalanced (missing and/or extra chromosomal material). Individuals who carry a balanced translocation have no ill health effects from it, but when they produce sperms or eggs, the translocation can be passed on in an unbalanced form, which can produce a syndrome of some type in a child or very often results in repeated pregnancy loss. There is also an equally likely chance that a sperm or egg will receive the translocation in the balanced state as the parent carries it, or receive a normal chromosome complement. Other types of structural chromosome anomalies include ring chromosomes and different types of inversions of material within a single chromosome, each of which can be hereditary and present reproductive risks.

Mitochondrial inheritance

Mitochondria are tiny structures (organelles) in the cytoplasm of cells that are the primary site of energy production. They are also the only location outside of the

nucleus that contains DNA. The DNA exists in a ring structure, with about two to ten rings per mitochondrion. Additionally, depending on cell type, there may be anywhere from several dozen to more than a hundred mitochondria per cell. Approximately 70 mitochondrial genes have been identified, many of which are associated with specific genetic disorders.

Mitochondrial inheritance is unusual in that, with rare exceptions, a person inherits all their mitochondria through the egg from their mother. Again, with few exceptions, a typical mitochondrial inheritance pattern involves an affected female who transmits the condition to all of her children, but none of her affected sons will pass on the disorder. However, this straightforward pattern is usually complicated by the fact that each mitochondrion may be mosaic for the gene mutation (e.g., five rings with the mutation and five rings with normal DNA), any particular cell is likely to be mosaic for mitochondria that are themselves mosaic, and this complicated mosaic pattern can apply to any egg that results in conception. All of which makes it nearly impossible to predict specific recurrence risks or the degree of severity if a child is affected.

Uniparental disomy

Uniparental disomy (UPD) refers to an unusual genetic status in an individual in which one parent is the source of both chromosomes of a pair. Again, before it was possible to analyze chromosomes at the microscopic (DNA) level, the logical assumption was that one chromosome of each pair is always maternal in origin and the other one paternal in origin. Through various means, this supposed rule of heredity was found to have exceptions.

There are two possible mechanisms for the occurrence of UPD. The first involves a conception in which the embryo is trisomic for a particular chromosome, and at some early stage one of the extra chromosomes is “lost” during mitotic cell division. The result is a normal, diploid cell, and every cell produced from it from that point on will also be diploid. The remaining trisomic cell(s) may produce only a small percentage of the total cells in the body (mosaicism), or they may die off completely. In any case, if the disomic (diploid) cells contain the two chromosomes contributed by either the sperm or the egg, the result is UPD. This process is sometimes referred to as trisomy rescue. The other, less likely possibility is that one gamete at conception carries an extra chromosome (24 total, which is common), but the other gamete is coincidentally missing that same chromosome. If UPD involves two identical chromosomes (the first stage of meiosis produces two pairs of identical chromosomes at each position/number), the situation is further distinguished as uniparental isodisomy. On the

other hand, if the chromosome constitution at that position is the same as the parent’s, it is termed uniparental heterodisomy. Uniparental isodisomy presents a much greater risk of transmitting an autosomal recessive disorder than does the alternative.

Gonadal mosaicism

Just as individuals may be mosaic for chromosome anomalies, such as mosaic Down syndrome, so also can mosaicism for single-gene anomalies exist. Mosaicism can have both medical (the individual’s health) and reproductive (the individual’s children’s health) implications. Medical significance is determined by the degree of somatic mosaicism, while reproductive risks depend on the presence or absence of gonadal (germline) mosaicism. A person may have either type of mosaicism, but most cases probably involve both. While the presence of mosaicism in a particular tissue can be proved, the actual level (percentage of abnormal cells) can never be determined, since doing so would require genetic testing of every cell. Likewise, without testing every cell, the absence of mosaicism cannot be confirmed.

Epigenetic effects (imprinting)

Epigenetics is the study of heritable changes in gene expression that occur without a change in DNA sequence. Imprinting, the selective deactivation of certain genes in sperm and others in eggs, is the best-known and most dramatic epigenetic effect. There is also mounting evidence that certain maternal biochemical or physical influences on the embryo/fetus may alter the function of some genes. As a general rule, imprinting is removed and then reapplied during gametogenesis. It remains to be seen whether other types of epigenetic effects are similarly reversible. However, the discovery of new exceptions to old rules continues, with no evidence of slowing down.

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Genetic Alliance, 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008, (202) 966-5557, info@geneticalliance.org, <http://www.geneticalliance.org>
 March of Dimes Foundation, 1275 Mamaroneck Ave., White Plains, NY 10605, (914) 997-4488, <http://www.marchofdimes.com>
 National Society of Genetic Counselors, 330 N. Wabash Ave., Suite 2000, Chicago, IL 60611, (312) 321-6834, nsgc@nsgc.org, <http://www.nsgc.org>

Scott J. Polzin, MS

Inherited arrhythmia

Definition

Inherited arrhythmia, also known as cardiac channelopathy, is an inherited disorder affecting the ion channels of the heart and leading to an irregular heartbeat. Symptoms of the disorder range from no symptoms at all to sudden cardiac death, particularly when undiagnosed and untreated. Types of inherited arrhythmias include congenital long QT syndrome (LQTS), short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT).

Description

The cardiac cycle is a complex cycle involving many channels, valves, chambers, and neurological events with the end goal of circulating blood throughout the body for tissue oxygenation. The cardiac cycle is generated by cardiac action potentials, which are neurological events that communicate from the brain to the nerve to the desired cell in order for the cell to do its specific job. These action potentials occur in the myocytes for the ultimate goal of causing them to contract. Within myocytes, cardiac action potentials are propagated through the correct amount and flow of ions, particularly sodium, calcium, and potassium. Potassium ions leave the cell via channels, causing the cell to become more negative. This allows for sodium and calcium ions to come in through their own channels. When the correct number of ions inside and outside of the cell is reached, an action potential is propagated, and the cell contracts. This event occurs in a pattern throughout the heart for the proper function of the atria, ventricles, and valves, all of which work together to oxygenate blood and pump it to the rest

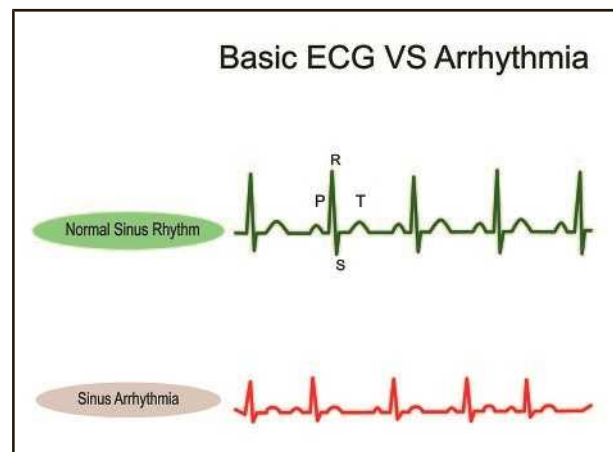
of the body. An arrhythmia is any disruption to this pumping of the blood, due to either an issue with the cardiac action potential or a step in the cardiac cycle itself.

Cardiac arrhythmia is the broad term for an alteration in the beat or rhythm of the heart. There are two main types of arrhythmias: bradycardia (slower heartbeat than normal) and tachycardia (faster heartbeat than normal), where normal heart rate is considered as 60 to 100 beats per minute. An arrhythmia may occur congenitally due to birth defects in the heart or a mutation in a gene such as *DPP6*. An arrhythmia may also develop in life insidiously, due to drugs or smoking or after a cardiac event such as a heart attack.

The most common types of inherited arrhythmias include long QT syndrome, short QT syndrome, Brugada syndrome (a ventricular arrhythmia), early repolarization syndrome, and catecholaminergic polymorphic ventricular tachycardia. All of these syndromes are related to a defect in one or more genes, causing a channelopathy.

Genetic profile

Inherited arrhythmia is an autosomal dominant hereditary disorder, though it has been seen to be inherited as an autosomal recessive or *de novo* mutation. Sequencing studies have shown a link between inherited arrhythmia and the *DPP6* gene located on the long arm of chromosome 7. The *DPP6* gene codes for dipeptidyl aminopeptidase-like protein-6, which is a protein that helps regulate potassium channels in the heart, specifically in the repolarizing event of the cardiac action potential. When this gene is not coded correctly, these channels do not allow the correct amount of potassium to leave the cell, keeping the cell less negative than it should be and leading to an action potential that is not properly propagated. Long QT syndrome, one type of inherited



How normal and irregular heartbeats appear on a heart monitor. (Shutterstock/Simple Deigns)

KEY TERMS

Arrhythmia—Abnormal heart rhythm; examples are a slow, fast, or irregular heart rate.

Bradycardia—An irregularly slow heartbeat.

Channelopathy—A disease caused by disturbed function of ion channel subunits or the proteins that regulate them.

Tachycardia—An excessively rapid heartbeat; a heart rate above 100 beats per minute.

arrhythmia, is related to 13 gene mutations, most of which encode for cardiac ion channels. Three out of these 13 genes—*LQT1*, *LQT2*, and *LQT3*—account for approximately 75% of the cases of LQTS. Brugada syndrome is associated with 12 gene alterations with 30% of the cases due to a mutation in the *SCN5A* gene, which is located on the short arm of chromosome 3 and makes sodium channels. Short QT syndrome is associated with mutations in the *KCH2*, *KCNJ2*, and *KCNQ1* genes, all of which make ion channels. Early repolarization syndrome (ERS) is associated with six different genes (most notably *KCNJ8*, which codes for inward potassium protein channels), and catecholaminergic polymorphic ventricular tachycardia (CPVT) has a 60% association with *RYR2*, which helps form calcium channels.

The potassium channel *KCNQ1* plays a critical role in the cardiac action potential. Inherited mutations resulting in loss of channel function or gain of function (GOF) cause heart rhythm abnormalities. A study that surveyed known disease-linked GOF mutations in *KCNQ1* found that seven of 15 increased the amount of *KCNQ1* that reached the cell surface, an effect called supertrafficking. A particular supertrafficking mutant channel, R231C, had plasma membrane levels five times the wild-type channel. Whole-cell electrophysiology noted that the R231C channel is incorrectly always open, but that its open-state current is only 20% that of the wild-type channel. The GOF of R231C reflects the combined effects of supertrafficking, constitutive channel activation, and reduced ion flux.

Researchers have used the zebrafish (*Danio rerio*) to identify the role of a gene involved in cardiac rhythm, which may help explain the fundamentals of what it takes to make a human heartbeat. A study from the University of Melbourne found that mutation of the gene *Tmem161b* causes potentially fatal cardiac arrhythmia. *Tmem161b* appears to play a central function and may be important in more than just controlling heart rhythm. If it is found to be significant in humans, it could also provide a new

candidate for genetic screening of patients with cardiac arrhythmias.

Demographics

The prevalence of inherited arrhythmias is relatively low, ranging from one in 500 to one in 2,500. Brugada syndrome, for example, is estimated to affect five in 10,000 people worldwide, with a high incidence in Asians. It is found far more often in men than in women, which could be indicative of hormonal involvement.

Signs and symptoms

The first signs and symptoms of an arrhythmia include palpitations, syncope (fainting, loss of consciousness) with spontaneous recovery, seizures, chest pain, and altered breathing. These may occur spontaneously or during physical triggers such as exercise or strenuous activity, fever, or emotional triggers such as stress or alarm from loud, unexpected noises. Arrhythmias may even occur during sleep.

Diagnosis

The diagnosis of inherited arrhythmia is made via diagnostic tools such as an echocardiogram (ECG), which detects any change in the rhythm of the heart, either at rest, in transition from lying to standing, or during exercise with or without an infusion of anti-arrhythmic drugs such as ajmaline.

Once a diagnosis is made via physical examination and diagnostic testing, genetic testing is done to further diagnose the patient and is considered the current gold standard for testing of inherited arrhythmia.

Treatment and management

Treatment and management of inherited arrhythmias include lifestyle modification, pharmaceuticals, devices such as an implantable cardioverter defibrillator (ICD), and, in some cases, surgical procedures. The most utilized pharmaceutical agents include beta blockers and sodium channel blockers. Beta blockers are used for decreasing blood pressure, thus decreasing the amount of stress placed on the heart. Recent studies correlating inherited arrhythmia with a disturbance to the *DPP6* gene and the potassium channels essential to the repolarizing event of the cardiac action potential have determined that drugs that directly inhibited said channels have a therapeutic effect on heart rate, increasing the heart rate and correcting the pumping of blood, thus correcting the arrhythmia. These drugs include dalfampridine and cilostazol, especially when coupled with secondary therapies such as quinidine, enoxaparin, warfarin, and potassium.

QUESTIONS TO ASK YOUR DOCTOR

- Should all of my immediate family members be screened for this disorder?
- What lifestyle modifications do I need to maintain?
- How often should I be assessed by my doctor?
- Which type of arrhythmia do I have, and what treatment options are best for me?

Depending on the high risk of the individual as seen in the signs and symptoms of the case, particularly with a high number of syncope episodes, frequent monitoring will be necessary. An implantable cardioverter defibrillator may also be utilized, which gets the heart back to the correct rhythm before a major cardiac event occurs. Monitoring is also important because arrhythmias due to physical or emotional triggers can be fatal. Triggers, even when the arrhythmia is latent, include stress, drugs, electrolyte imbalances, exercise, and fevers.

Lifestyle changes are particularly important in the management of arrhythmia. They include dietary changes to keep a normal weight, limiting intake of caffeine and alcohol, and limiting foods associated with high blood pressure, high cholesterol, and heart disease. Proper physical exercise and decreasing stress levels are also important factors and are necessary lifestyle modifications for the management of arrhythmias and the prevention of further cardiac damage.

Prognosis

The prognosis of inherited arrhythmia is good to very good when there is an early diagnosis. In some cases, inherited arrhythmia in infancy may cause death due to the lack of symptoms and/or absence of diagnosis. Recent studies have determined that the incidence of sudden cardiac death in persons under age 40 is approximately three in 100,000, many of which are due to hereditary factors. This information highlights the importance of familial genetic testing when there is known inherited arrhythmia in the immediate family.

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American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231, (800) 242-8721 and (800) AHA-USA-1, <http://www.heart.org>

Sudden Arrhythmia Death Syndromes Foundation, 4527 South 2300 East, Suite 104, Salt Lake City, UT 84117, (801) 948-0654 and (801) 272-3023, <http://www.sads.org>

Bharati K. Hegde, BE, MS, PhD
and Taryn Terry, DC, MSACN, BA

Isolated X-linked sensorineural deafness see **PRPS1 gene mutation—progressive hearing loss**

Ivemark syndrome see **Asplenia**



Jackson-Weiss syndrome

Definition

Jackson-Weiss syndrome (JWS) is a hereditary disease of varying severity characterized by face and foot abnormalities and the premature fusion of skull bones (craniosynostosis). JWS is one of eight conditions of the FGFR-related craniosynostosis disorders.

Description

Jackson-Weiss syndrome is characterized by a small midface, unusual skull shape, and foot abnormalities. The feet display very wide big toes and webbing of the skin between the second and third toes. Additionally, the toes are angled inward. Bony foot defects apparent on x-ray include short, wide foot bones and fusion of some of the foot and ankle bones.

The hallmark skull differences associated with JWS are caused by the premature closure of skull sutures, or skull plates. Other features include a small jaw, flattening of the nasal bridge and the middle third of the face, and a beaked nose. The eyes may be crossed and are widely set and slanting downward with droopy eyelids. High arching of the roof of the mouth or cleft palate, an incomplete closure of the roof of the mouth, may also be present. Intellectual disability has been reported in some individuals with JWS.

Genetic profile

JWS is inherited in an autosomal dominant manner. This means that possession of only one copy of the defective gene is enough to cause disease. When a parent has JWS, each of his or her children has a 50% chance to inherit the disease-causing mutation. JWS is believed to have a high rate of penetrance. This means that almost all people who inherit the altered gene will manifest symptoms. JWS has also occurred spontaneously in

babies with no family history of it or any similar disorder. This is known as a sporadic occurrence.

JWS has been associated with mutations in the *FGFR2* (fibroblast growth factor receptor 2) gene that provides instructions for making a protein also called fibroblast growth factor receptor 2. This protein is involved in important processes such as cell division, regulation of cell growth and maturation, formation of blood vessels, wound healing, and embryonic development.

JWS is caused by one of several mutations that change single amino acids in the FGFR2 protein. Each of these mutations occurs in a region of the FGFR2 protein known as the IgIII domain, which is required for receiving signals and interacting with growth factors. It is believed that the mutations appear to overstimulate signaling by the FGFR2 protein, which promotes premature fusion of skull bones and affects the development of bones in the feet.

Demographics

JWS has been described in different races and geographic regions. The original Jackson-Weiss family was a large Amish family with at least 138 affected members. JWS affects both sexes equally. The strongest risk factor for JWS is a family history of the disorder. As of 2015, the incidence of JWS was still unknown. The overall incidence for all forms of craniosynostosis is estimated at 1 in 2,000 to 1 in 2,500 live births.

Signs and symptoms

Jackson-Weiss syndrome's hallmarks are variable skull differences, flattened midface, and wide big toes that angle inward toward each other. The hands are usually not involved. Rarely, deafness or intellectual disability can be seen in people with JWS.

Skull abnormalities vary between individuals. Abnormalities in skull shape happen when the sutures, or open seams between the bony plates that form the skull, fuse before they normally would (craniosynostosis). Growth of

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted through the either mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

FGFR-related craniosynostosis—A group of eight disorders, including Pfeiffer syndrome, Apert syndrome, Crouzon syndrome, Beare-Stevenson syndrome, *FGFR2*-related isolated coronal synostosis, Jackson-Weiss syndrome, Crouzon syndrome with acanthosis nigricans (AN), and Muenke syndrome (isolated coronal synostosis), all caused by a mutation of an *FGFR* gene.

Sporadic—Isolated or appearing occasionally with no apparent pattern

the brain pushes outward on skull plates that have not yet fused. In JWS different sutures may be involved, leading to different head shapes. The face may be lopsided due to skull deformity.

Facial differences also vary between individuals with Jackson-Weiss syndrome. Some individuals have no obvious facial differences. The hallmark face of Jackson-Weiss syndrome has very prominent, bulging, down-slanting, sometimes crossed eyes that are slightly farther apart than normal with droopy eyelids. The middle third of the face is underdeveloped and somewhat flattened with a beaked nose. The forehead is rounded prominently, and the hairline may be slightly lower on the forehead than usual. The chin may be small, and the lower jaw may come forward more than normal. Some people with JWS may have a cleft palate or a steeply arched palate (roof of the mouth). These changes may

cause unusually nasal sounding speech or more serious speech difficulties.

The feet display unusually wide big toes that curve inward toward each other. The large bones of the foot may be fused or abnormally shaped. Smaller bones of the feet and toes may be abnormally shaped or absent. These bony abnormalities may be obvious only on x-ray. The fingers and toes may be abnormally short with webbing of the skin between the second and third toes. Extra toes may be present at birth.

Diagnosis

Characteristic facial features and unusual toes may be obvious to an untrained eye, but a thorough physical exam by a physician is necessary to check for less obvious differences. Bony differences may not be obvious, appearing only on x-ray. Bony differences in the feet were found consistently, even in seemingly unaffected individuals, in the original Jackson-Weiss syndrome family. X-ray is considered to be a very important element in diagnosing JWS. X-rays are also important in determining what specific type of abnormal skull plate fusion is present.

DNA testing is available for Jackson-Weiss syndrome. This testing is performed on a blood sample in children and adults to confirm a diagnosis made on physical features. Prenatal genetic testing is also available. An unborn baby can be tested for JWS with DNA extracted from cells obtained via chorionic villus sampling or amniocentesis.

Treatment and management

There is no medication or cure for Jackson-Weiss syndrome. Treatment, if necessary, depends on an individual's symptoms. Surgery is always offered to correct the most severe physical complications, like cleft palate. Foot and facial abnormalities can also be treated with surgery if they are bothersome to an affected individual. Cosmetic surgery on the face can yield excellent results. In many cases facial differences are so mild that surgical intervention is not recommended. Counseling and support groups may be helpful to patients experiencing emotional difficulty due to physical differences.

Genetic counseling is offered to persons who have this inheritable disorder. Parents with this disease have a 50% chance of passing it to each of their children. Prenatal diagnosis for JWS is available. This prenatal genetic testing cannot, however, predict the severity or scope of an individual's symptoms. In the future, parents with genetic diseases like Jackson-Weiss syndrome may be able to opt for disease diagnosis from a cell of an embryo before the embryo is introduced to the mother's womb.

QUESTIONS TO ASK YOUR DOCTOR

- Will my child be intellectually disabled?
- How much surgery will my child need?
- Will my child be able to walk normally?

This testing is called preimplantation genetic diagnosis and is already available in some centers in the United States.

Prognosis

The lifespan of individuals with JWS is normal. Intelligence is often normal, although borderline intelligence and intellectual disability have been described in some patients with JWS.

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ORGANIZATIONS

- Children's Craniofacial Association, 13140 Coit Rd., Suite 517, Dallas, TX 75240, (214) 570-9099 or (800) 535-3643, (214) 570-8811, contactCCA@ccakids.com, <http://www.ccakids.com>
- March of Dimes Foundation, 1275 Mamaroneck Ave., White Plains, NY 10605, (914) 428-7100, <http://www.marchofdimes.com>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Jacobsen syndrome

Definition

Jacobsen syndrome is a rare chromosome disorder that affects multiple aspects of physical and mental development.

Description

Jacobsen syndrome is characterized by a distinctive facial appearance, some degree of mental impairment, and certain other types of birth defects, especially of the heart. Other common medical complications include failure to thrive, recurrent infections, decreased platelet counts, and slow growth. The syndrome derives its name from the Danish physician Petra Jacobsen, who first described an affected child in 1973. It is also known as 11q deletion syndrome, 11q terminal deletion disorder, or partial 11q monosomy syndrome. This is because the end of the long arm (q) of one copy of chromosome 11 is missing in the syndrome, so an affected person has only one copy of the genes in that region. It is the loss of these genes that leads to the multiple problems of Jacobsen syndrome.

Genetic profile

The loss of genetic material from a specific segment of chromosome 11q, which includes at least the critical region at band 11q24.1, leads to the manifestations of Jacobsen syndrome. There are several ways in which this portion of chromosome 11 can be deleted. In at least two-thirds of Jacobsen syndrome cases there is a partial chromosome 11q deletion (a terminal deletion) that begins at band q23 and extends through the end of the chromosome. The remainder of cases are attributed to the loss of this chromosome 11q genetic material due to a deletion within, but not including, the end of the chromosome (an interstitial deletion) or due to a chromosomal rearrangement, such as an unbalanced chromosome translocation or a ring chromosome.

Most deletions and chromosome rearrangements responsible for Jacobsen syndrome are not familial; they are the result of a new, or *de novo* genetic change that occurred in the gamete (the egg or sperm) contributed by the mother or father of the affected individual. Less often, the origin of the chromosome deletion or rearrangement is familial. In a minority of cases, a parent of an affected child has a folate-sensitive fragile site at chromosome band 11q23.3 that can cause chromosome breakage and subsequent deletion of chromosome 11q in a child. In a few cases, a child has inherited an unbalanced chromosome translocation from a parent who was a balanced translocation carrier.

KEY TERMS

Band—A specific region of a chromosome that is identified by its characteristic staining pattern and location within a chromosome, as seen in a karyotype. A band is either part of the short arm (p arm) or the long arm (q arm) of a chromosome and is further defined by a numeric location, such as chromosome band 11q24.1.

Chromosome—A microscopic thread-like structure found within each cell of the body and consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Coloboma—A birth defect in which part of the eye does not form completely.

Congenital—Refers to a disorder that is present at birth.

Cranial suture—Any one of the seven fibrous joints between the bones of the skull.

Craniosynostosis—Premature, delayed, or otherwise abnormal closure of the sutures of the skull.

Deletion—The absence of genetic material that is normally found in a chromosome. Often, the genetic material is missing due to an error in replication in an egg or sperm cell.

Echocardiogram—A noninvasive technique that uses ultrasonic waves to examine the various structures and function of the heart.

Failure to thrive—Significantly reduced or delayed physical growth.

Folate-sensitive fragile site—A chromosome location that, under folate-deficient conditions, appears as a gap in a chromosome and is susceptible to breakage.

Gastroesophageal reflux—The return of the contents of the stomach back up into the esophagus.

Gene—A building block of inheritance that contains the instructions for the production of a particular protein and is made up of a molecular sequence found on a section of DNA. Each gene is found at a precise location on a chromosome.

Inguinal hernia—A condition in which part of the intestines protrudes through a tear in the muscles of the abdomen.

Karyotype—A photographic representation of the full set of chromosomes numbered and arranged in pairs.

Microarray—A supporting material (usually glass or plastic) to which DNA fragments of known sequence are attached for the identification and sequencing of DNA samples.

Monosomy—Missing an entire copy of a chromosome or a piece of one copy of a chromosome.

Otitis media—Inflammation of the middle ear, often due to fluid accumulation secondary to an infection.

Pancytopenia—An abnormal reduction in the number of erythrocytes (red blood cells), leukocytes (a type of white or colorless blood cell), and blood platelets (a type of cell that aids in blood clotting) in the blood.

Pyloric stenosis—Narrowing of the stomach due to thickening of the pyloric muscle at the end of the stomach.

Ring chromosome—An abnormal chromosome in which the terminal ends of the short (p) and long (q) arms have been lost and the remaining p and q arms subsequently join to form a ring.

Strabismus—An improper muscle balance of the ocular muscles resulting in crossed or divergent eyes.

Thrombocytopenia—A persistent decrease in the number of blood platelets; usually associated with hemorrhaging.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosomal material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

Trigonocephaly—An abnormal development of the skull characterized by a triangular-shaped forehead.

Demographics

Although it is not known how many people have Jacobsen syndrome, estimates are that 1 person in every 100,000 is affected by the disorder. Females with Jacobsen syndrome outnumber males by 3 to 1.

Signs and symptoms

Symptoms of Jacobsen syndrome are variable, and the prognosis for an affected child depends on the presence of life-threatening birth defects or other medical problems. Individuals with Jacobsen syndrome have a

distinctive physical appearance. The face is characterized by wide-spaced eyes (hypertelorism), droopy eyelids (ptosis), redundant skin covering the inner eye (epicanthal folds), a broad or flat nasal bridge, a short nose with upturned nostrils, a small chin (micrognathia), low-set ears, and a thin upper lip. As many as 90%–95% of affected individuals have a malformation of the skull called trigonocephaly, a defect that results from premature closure of one of the cranial sutures. More than one-third of individuals have a small head (microcephaly). Overall, individuals with Jacobsen syndrome are smaller than their peers or siblings. Prenatal growth retardation occurs in about 75% of fetuses. A newborn with Jacobsen syndrome is usually small at birth and continues to have delayed growth and short stature. Feeding problems that can result in failure to thrive are also common.

Children with Jacobsen syndrome usually have some degree of developmental delay or intellectual disability, ranging from mild to severe. Nearly all affected individuals also have decreased muscle tone (hypotonia) or increased muscle tone (hypertonia), as well as fine and gross motor delays. Occasionally, brain abnormalities are present.

Multiple types of physical abnormalities are known to occur in individuals with Jacobsen syndrome. Congenital heart disease is present in about half of affected children and, if severe, can pose a significant health problem. Other common internal abnormalities include pyloric stenosis, undescended testes, inguinal hernia, kidney defects, and urinary tract abnormalities. Craniofacial abnormalities such as strabismus, ptosis, colobomas (eye fissures), a high-arched palate, and external ear anomalies are frequent. Orthopedic problems, primarily joint contractures and abnormalities of the digits (the fingers and toes), have been described in some cases.

In addition to congenital defects, there are a variety of other health problems found in individuals with Jacobsen syndrome. Illnesses including recurrent respiratory infections, sinusitis, and otitis media (middle ear inflammation) occur more frequently in children with Jacobsen syndrome. Gastrointestinal problems such as gastroesophageal reflux and chronic constipation may occur. Blood disorders such as thrombocytopenia and pancytopenia are often seen in childhood but may improve with time.

Diagnosis

Most individuals with Jacobsen syndrome are diagnosed after birth. The diagnosis is usually made by a blood test called karyotyping that analyzes the chromosomes of an infant or child with intellectual disability and an atypical facial appearance. The karyotype will

QUESTIONS TO ASK YOUR DOCTOR

- What does the term “11q deletion syndrome” mean?
- What are the most serious health risks faced by a child with Jacobsen syndrome?
- At what point in a child’s development can Jacobsen syndrome be diagnosed, and how is that diagnosis made?
- Are treatments available for Jacobsen syndrome and if so, what are they and at what stage of a child’s life should they be implemented?
- What are the risks of having a second child with Jacobsen syndrome?

show a deletion or rearrangement of the longer segment (q arm) of one copy of chromosome 11. Jacobsen syndrome can be diagnosed before birth through amniocentesis after an ultrasound has indicated one or more fetal abnormalities. Another technique, known as FISH (fluorescent in-situ hybridization), may be used to further define the chromosome 11q deletion breakpoints. A study published in 2012 found that microarray analysis of amniotic fluid detected Jacobsen syndrome and various other disorders that were missed by standard karyotyping, which cannot detect smaller chromosome abnormalities.

Treatment and management

There is no cure for Jacobsen syndrome, nor is there a therapy that can replace the missing genes from the deleted segment of chromosome 11. In addition to routine pediatric exams, there are management strategies and treatments that aim to prevent or minimize some of the serious health consequences associated with Jacobsen syndrome.

At the time of diagnosis, a series of evaluations should be undertaken to appropriately guide medical management. Pediatric specialists in genetics, cardiology, orthopedics, ophthalmology, and neurology should be consulted, especially since some problems can be treated if caught early. In addition to karyotyping, important tests may include an echocardiogram of the heart, a renal sonogram, platelet and other blood counts, brain imaging studies, hearing and vision screenings, and dental exams.

A neurodevelopmental evaluation should be initiated in infancy or at the time of diagnosis with implementation of age-appropriate early intervention services such as

speech therapy, occupational therapy, and physical therapy. An ear, nose, and throat specialist (ENT) may be needed to treat problems such as otitis media. Craniofacial and neurosurgery consults may be indicated if trigonocephaly or other forms of craniosynostosis are present.

Some children may require a gastroenterology specialist to evaluate problems such as failure to thrive, chronic constipation, and/or severe gastroesophageal reflux, which may require surgical intervention. About half of males with Jacobsen syndrome have undescended testes that often require surgery.

Prognosis

Approximately 25% of affected children die before two years of age, mainly from cardiac defects, a tendency to bleed, or infection. Other than respiratory infections, surviving children are generally healthy. However, little is known about the life expectancy for those who live beyond age two or the course of Jacobsen syndrome in adulthood.

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- Children's Craniofacial Association, 13140 Coit Rd., Suite 517, Dallas, TX 75240, (214) 570-9099 or (800) 535-3643, (214) 570-8811, contactCCA@ccakids.com, <http://www.ccakids.com>
- Chromosome Disorder Outreach, PO Box 724, Boca Raton, FL 33429-0724, (561) 395-4252, info@chromodisorder.org, <http://www.chromodisorder.org>
- Craniofacial Foundation of America, 975 E. Third St., Chattanooga, TN 37403, (423) 778-9176 or (800) 418-3223, (423) 778-8172, <http://www.craniofacialfoundation.org>
- Office of Rare Diseases Research, National Center for Advancing Translational Sciences. National Institutes of Health,

6701 Democracy Blvd., Suite 1001 MSC 4874, Bethesda, MD 29892, (301) 402-4336, (301) 480-4655, idr@nih.gov, <https://rarediseases.info.nih.gov>

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Jervell and Lange-Nielsen syndrome

Definition

Jervell and Lange-Nielsen syndrome (JLNS) is a rare inherited disorder characterized by congenital deafness and cardiac arrhythmias (irregularities in the electrical activity of the heart that can lead to cardiac arrest and sudden death).

Description

JLNS results from mutations, or changes, in either one of two genes that encode proteins that combine to form potassium ion channels. One of the potassium channels is important for proper heart function. It is also critical in the functioning of the cochlea of the inner ear. People with JLNS lack this channel and, thus, are born with profound deafness in both ears, as well as with cardiac abnormalities.

JLNS was first described in 1957 by A. Jervell and F. Lange-Nielsen. It is also known by the names cardio-auditory syndrome of Jervell and Lange-Nielsen; cardo-cardiac syndrome; surdocardiac syndrome; deafness-functional heart disease; and deafness, congenital, and functional heart disease. The cardiac (heart) symptoms of JLNS are very similar to those of long-QT syndrome (LQTS), including a longer-than-normal "QT interval" on an electrocardiogram (ECG or EKG) test. Thus, JLNS is sometimes called QT prolonged with congenital deafness.

Genetic profile

JLNS is caused by mutations in either the *KVLQT1* (*KCNQ1*) gene or the *KCNE1* (*MinK* or *IsK*) gene. It is an autosomal recessive disorder, which means it occurs only in people with two copies of the mutant gene, one from each parent. The mutations in the two copies do not have to be identical. Someone who inherits one copy of the mutant gene and one copy of the normal gene has LQTS types 1 or 5.

Demographics

Although it is the third most common type of autosomal recessive hearing loss, JLNS is a very rare disorder.

KEY TERMS

Action potential—The wave-like change in the electrical properties of a cell membrane, resulting from the difference in electrical charge between the inside and outside of the membrane.

Arrhythmia—Abnormal heart rhythm; examples are a slow, fast, or irregular heart rate.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Beta-adrenergic blocker—A drug that works by controlling the nerve impulses along specific nerve pathways.

Cochlea—A bony structure shaped like a snail shell located in the inner ear. It is responsible for changing sound waves from the environment into electrical messages that the brain can understand, so people can hear.

Congenital—Refers to a disorder which is present at birth.

Depolarization—The dissipation of an electrical charge through a membrane.

Electrocardiogram (ECG, EKG)—A test used to measure electrical impulses coming from the heart in order to gain information about its structure or function.

Endolymph—The fluid in the inner ear.

Fibrillation—A rapid, irregular heartbeat.

Heterozygous—Having two different versions of the same gene.

Homeostasis—A state of physiological balance.

Homozygous—Having two identical copies of a gene.

Ion channel—Cell membrane proteins which control the movement of ions into and out of a cell.

QT interval—The section on an electrocardiogram between the start of the QRS complex and the end of the T wave, representing the firing or depolarization of the ventricles and the period of recovery prior to repolarization or recharging for the next contraction.

Repolarization—Period when the heart cells are at rest, preparing for the next wave of electrical current (depolarization).

Syncope—A brief loss of consciousness caused by insufficient blood flow to the brain.

Tachycardia—An excessively rapid heartbeat; a heart rate above 100 beats per minute.

Torsade de pointes—A type of tachycardia of the ventricles characteristic of Jervell and Lange-Nielsen syndrome.

Worldwide, there are an estimated 1.6 to 6 cases per one million people. Denmark, however, has a much higher incidence of JLNS, estimated at 1 in 200,000.

Because JLNS requires two copies of the abnormal gene, one from each parent, it most often is found in the offspring of related parents, such as cousins (termed a “consanguineous” marriage). Individuals who carry one copy of the abnormal gene and one normal gene copy will have LQTS, but will have normal hearing or only partial hearing loss. However, a child of two such individuals has a 25% chance of having JLNS. Thus, although JLNS occurs across racial and ethnic groups, it is more common in small isolated groups where marriage between relatives is frequent.

Signs and symptoms

The deafness associated with JLNS usually is apparent in infancy or early childhood. Although the severity of JLNS varies, children with acute JLNS are profoundly deaf in both ears.

Depending on the severity of the disorder, the cardiac symptoms of JLNS may be overlooked. Thus, people with JLNS can be at serious risk for sudden death. In addition to a prolonged QT interval on an ECG/EKG, cardiac arrhythmias, dizziness, periods of unconsciousness (syncope episodes), and seizures are common symptoms of JLNS. These symptoms most often occur upon awakening, during strenuous physical activity, or during moments of excitement or stress.

Diagnosis

Deaf children, particularly those with a family history of sudden death, syncope episodes, or LQTS, should be screened for JLNS, using an ECG to detect a prolonged QT interval. Genetic testing for JLNS is possible for high-risk individuals.

Individuals with JLNS sometimes have normal or borderline-normal QT intervals on an ECG/EKG. Additional ECGs/EKGs performed during exercise may reveal an abnormal QT interval. ECGs/EKGs of the parents may also reveal a prolonged QT interval.

QUESTIONS TO ASK YOUR DOCTOR

- Am I or my spouse in some way responsible for our son's Jervell and Lange-Nielsen syndrome?
- What is the connection between the auditory and cardiac symptoms of this disorder?
- What types of treatment for Jervell and Lange-Nielsen syndrome are recommended, and at what age should they be applied?
- Can you supply us with the name of an organization that is concerned with individuals who have Jervell and Lange-Nielsen syndrome?

Treatment and management

Since JLNS can result in sudden death, including sudden infant death syndrome (SIDS), treatment is essential. Beta blockers are the most common treatment for the ventricular arrhythmia of JLNS. Treatment with these drugs usually continues for life. Beta blockers such as propranolol are considered to be safe medications. Any side effects from propranolol are usually mild and disappear once the body has adjusted to the drug. However, beta blockers can interact dangerously with many other medications.

Surgery may reduce cardiac arrhythmias in people with JLNS. A mechanical device called a pacemaker or an automatic implanted cardioverter defibrillator (AICD) may be used to regulate the heartbeat or to detect and correct abnormal heart rhythms. Sometimes a pacemaker or AICD is used in combination with beta-blockers.

In 2000, the first cochlear implant in the inner ear of a child with JLNS was reported. The child gained limited hearing and improved speech.

Preventive measures

All individuals who have been diagnosed with JLNS must avoid reductions in blood potassium levels, such as those that occur with the use of diuretics (drugs that reduce fluids in the body). People with JLNS must also avoid a very long list of drugs and medications that can increase the QT interval or otherwise exacerbate the syndrome.

People with JLNS usually are advised to refrain from competitive sports and to practice a "buddy system" during moderate exercise. Family members are advised to learn cardiopulmonary resuscitation (CPR) in case of cardiac arrest.

Prognosis

Cochlear implants may improve the hearing of people with JLNS. The cardiac abnormalities of JLNS usually can be controlled with beta blockers. However, without treatment, there is a high incidence of sudden death due to cardiac events.

Family members of a JLNS individual should be screened with ECGs/EKGs for a prolonged QT interval, since they are at risk of having LQTS. Genetic counseling is recommended for people with JLNS, since their children will inherit a gene causing LQTS.

Resources

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ORGANIZATIONS

- American Heart Association, 7272 Greenville Ave., Dallas, TX 75231, (800) 242-8721, <http://www.heart.org>
- American Society for Deaf Children, 800 Florida Ave., NE #2047, Washington, DC 20002-3695, (800) 942-2732, (410) 795-0965, <http://deafchildren.org>
- Hearing Health Foundation, 363 Seventh Ave., 10th Floor, New York, NY 10001-3904, (212) 257-6140 or (866) 454-3924, info@hhf.org, <http://hearinghealthfoundation.org>
- Sudden Arrhythmia Death Syndromes (SADS) Foundation, 508 E. South Temple, Suite #202, Salt Lake City, UT 84102, (800) 786-7723 or (801) 531-0937, <http://www.sads.org>

Margaret Alic, PhD

Joubert syndrome

Definition

Joubert syndrome is a well-documented but rare autosomal recessive disorder. It is characterized by partial

or complete absence of the cerebellar vermis (the tissue between the two cerebellar hemispheres), causing irregular breathing and severe muscle weakness. Other features of the syndrome include jerky eye movements, abnormal balance and walking, and mental handicap. There may be minor birth defects of the face, hands, and feet.

Description

Marie Joubert, whose name is given to the condition, gave a detailed description of the syndrome in 1969. She wrote about four siblings (three brothers and one sister) in one family with abnormal breathing, jerky eye movements (nystagmus), poor mental development, and ataxia (staggering gait and imbalance). X-ray examination showed that a particular section of the brain, called the cerebellar vermis, was absent or not fully formed. This specific brain defect was confirmed on autopsy in one of these individuals. The initial report also described a sporadic or spontaneous (not inherited) patient with similar findings, in addition to polydactyly. Another name for Joubert syndrome is Joubert-Bolthausen syndrome.

Genetic profile

Joubert syndrome is an autosomal recessive disorder. Autosomal means that both males and females can have the condition; the gene is not in any way linked to the sex of the child. Recessive means that both parents are carriers of a single copy of the changed (mutated) gene. Autosomal recessive disorders occur when a person inherits a mutated gene from both the mother and the father with the same defect, so that neither gene functions correctly. The chance that this will occur in children of carrier parents is 25% (one in four) for each pregnancy. There is a 50% chance with each pregnancy that the child will have one good copy of the gene and one changed or defective copy. These children will not show characteristics of the disorder, but they can pass the defective gene on to their children. There is also a 25% chance with each pregnancy that the child will have two normally functioning genes. These children will not have the disorder and will not be able to pass a defective gene on to the next generation. There have been many instances of siblings each with Joubert syndrome, although the parents appeared free of the disorder.

The cerebellum and brain stem begin to form between the sixth and twelfth week of pregnancy. The birth defects seen in Joubert syndrome appear to develop during this crucial period. The defects will affect balance and coordination later in life. Changes in at least 19 genes (and possibly as many as 30) have been implicated in the development of Joubert syndrome and several related syndromes. These genes include *TMEM67* (*MKS3*), *NPHP1*, *CEP290*

KEY TERMS

Apnea—An irregular breathing pattern characterized by abnormally long periods of the complete cessation of breathing.

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Cerebellum—A portion of the brain consisting of two cerebellar hemispheres connected by a narrow vermis. The cerebellum is involved in control of skeletal muscles and plays an important role in the coordination of voluntary muscle movement. It inter-relates with other areas of the brain to facilitate a variety of movements, including maintaining proper posture and balance, walking, running, and fine motor skills, such as writing, dressing, and eating.

Iris—The colored part of the eye, containing pigment and muscle cells that contract and dilate the pupil.

Nystagmus—Involuntary, rhythmic movement of the eye.

Polydactyly—The presence of extra fingers or toes.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Vermis—The central portion of the cerebellum, which divides the two hemispheres. It functions to monitor and control movement of the limbs, trunk, head, and eyes.

(*NPHP6*), *CC2D2A*, *AH11*, *RPGRIP1L*, *KIF7*, *ARL13B*, *INPP5E*, *TMEM216*, *TCTN1*, *TCTN2*, *TMEM237*, *OFD1*, *CEP41*, *C5orf42*, *TMEM138*, *TMEM231*, and *TCTN3*. A mutation in the *ANIL* gene is responsible for about 11% of cases.

The genes associated with Joubert and related syndromes produce proteins involved in the formation cilia, which are microscopic hairlike projections that develop on cells regulating chemical signaling. Presumably, malformed cilia cannot correctly sense the chemical environment surrounding the cell and direct it to send the correct chemical signals needed for proper development.

Demographics

Joubert syndrome is rare. It appears to occur in one of every 100,000 live births, although the exact incidence is difficult to determine, because the syndrome produces

QUESTIONS TO ASK YOUR DOCTOR

- What are the characteristic symptoms of Joubert syndrome?
- How is Joubert syndrome diagnosed, and at what age does this diagnosis normally take place?
- What treatments are available for Joubert syndrome?
- What is the life expectancy for a person diagnosed with Joubert syndrome, and what factors might affect that prognosis?

a wide variety of symptoms. The disorder is found worldwide, but it is slightly more common in Ashkenazi Jewish, French-Canadian, and Hutterite populations.

Signs and symptoms

The cerebellum is the second largest part of the brain. It is located just below the cerebrum and partially covered by it. The cerebellum consists of two hemispheres, separated by a central section called the vermis and is connected to the spinal cord, through the brain stem.

The cerebellum and vermis normally work to monitor and control movement of the limbs, trunk, head, and eyes. Signals are constantly received from the eyes, ears, muscle, joints, and tendons. Using these signals, the cerebellum can compare what movement is actually happening in the body, with what is intended to happen. Then, it sends an appropriate signal back. The effect is to either increase or decrease the function of different muscle groups, to make movement both accurate and smooth. At birth, infants often have low muscle tone, and as they grow, they are delayed in reaching many gross motor milestones.

In Joubert syndrome, the cerebellar vermis is either absent or incompletely formed. The brain stem is sometimes quite small. The absence or abnormal function of these brain tissues causes problems in breathing and vision as well as severe delays in development.

One characteristic feature of Joubert syndrome is the pattern of irregular breathing, which alternates between deep rapid breathing (almost like panting) and periods of severe apnea (loss of breathing). This is usually noticeable at birth. The rate of respiration may increase more than three times that of normal (up to 200 breaths per minute), and the apnea may last up to 90 seconds. The rapid breathing occurs most often when affected infants are awake, especially when they are excited. The apnea

happens when the infants are awake or asleep. Such abnormal breathing can cause sudden death or coma and requires that these infants be under intensive care. For unknown reasons, the breathing tends to improve with age, usually within the first year of life.

Muscle movement of the eye is also affected in Joubert syndrome. It is common for the eyes to have a quick, jerky motion of the pupil, known as nystagmus. The retina (the tissue in the back of the eye that receives and transmits visual signals to the brain) may be abnormal. Some individuals (most often males) may have a split in the tissue in the iris of the eye. Each of these problems will affect their vision, and eye surgery may not be beneficial.

The central nervous system problem affects the larger muscles of the body as well, such as those of the arms and legs. Many affected infants will have severe muscle weakness and delays in development. They reach normal developmental milestones, such as sitting or walking, much later than normal. For example, some may learn to sit without support at around 19 to 20 months of age. (Normal is at six to eight months.) Most individuals are not able to take their first steps until age four or older. Their balance and coordination are also affected, which makes walking difficult. Many will have an unsteady gait and find it difficult to climb stairs or run, even as they get older.

Cognitive (mental) delays are also a part of the syndrome, although these manifestations can be variable. Most individuals with Joubert syndrome will have fairly significant learning impairment. Some will have little or no speech. Others are able to learn words and can talk with the aid of speech therapy. They do tend to have pleasant and sociable personalities, but problems in behavior can occur. These problems most often are in temperament, hyperactivity, and aggressiveness.

Careful examination of the face, especially in infancy, shows a characteristic appearance. They tend to have a large head and a prominent forehead. The eyebrows look high and rounded, and the upper eyelids may be droopy (ptosis). Their mouth often remains open and looks oval-shaped. The tongue may protrude and rest on the lower lip, or it may quiver slightly. These are all signs of the underlying brain abnormality and muscle weakness. Occasionally, the ears look low-set on the head. As affected individuals age, these features become less noticeable.

Less common features of the syndrome include minor birth defects of the hands and feet. Some individuals with Joubert syndrome have extra fingers on each hand. The extra finger is usually on the pinky finger side (polydactyly). It may or may not include bone and could

just be a skin tag. Some patients will also have extra toes on their feet.

Diagnosis

On an MRI scan, individuals with Joubert syndrome will show a typical “molar tooth” mark (an abnormality that looks like the cross-section of a molar tooth. This indication as well as evidence of an absent or incomplete cerebellar vermis, muscle weakness, and delays in development are diagnostic signs. There may also be irregular breathing and abnormal eye movements. Most individuals are diagnosed by three years of age.

Treatment and management

During the first year of life, many infants with Joubert syndrome require a respiratory monitor for their irregular breathing. For the physical and mental delays, it becomes necessary to provide special assistance and anticipatory guidance. Speech, physical, and occupational therapy are needed throughout life. Genetic testing for four of the most common gene mutations causing Joubert syndrome is available. In conjunction with genetic counseling, it may be helpful to parents in considering future pregnancies and also to other children of these parents who do not show symptoms of the disorder but may be carriers of the defective gene(s).

Prognosis

The unusual pattern of breathing as newborns, especially the episodes of apnea, can lead to sudden death or coma. A number of individuals with Joubert syndrome have died in the first three years of life. For most individuals, the irregular breathing becomes more consistent after the first year. However, many continue to have apnea and require medical care throughout their lives. Although the true lifespan remains unknown, there are some individuals with Joubert syndrome who are in their 30s.

Clinical trials of new therapies for Joubert syndrome are underway. Participation in a U.S. clinical trial is

voluntary and at no cost to the participant. All clinical trials receiving U.S. government funding, and some supported by private industry, are posted at <https://www.clinicaltrials.gov>. Foreign trials are listed at <https://www.orpha.net>.

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Joubert Syndrome and Related Disorders Foundation, 9 Dorenfeld Court, Petaluma, CA president@jsrdf.org, <https://www.jsrdf.org>

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K

Kabuki syndrome

Definition

Kabuki syndrome is a rare disorder characterized by unusual facial features, skeletal abnormalities, and intellectual impairment. Abnormalities in different organ systems can also be present, but they vary from individual to individual. There is no cure for Kabuki syndrome, so treatment focuses on the specific abnormalities, as well as on strategies to improve the overall functioning and quality of life of the affected person.

Description

Kabuki syndrome is a rare disorder characterized by intellectual disability, short stature, unusual facial features, abnormalities of the skeleton, and unusual skin ridge patterns on the fingers, toes, palms of the hands, and soles of the feet. Many other organ systems can be involved in the syndrome, displaying a wide variety of abnormalities, including congenital heart defects, genitourinary anomalies, other facial and visceral abnormalities, and premature breast development in females. Thus, the manifestations of Kabuki syndrome can vary widely among different individuals.

Kabuki syndrome (also known as Niikawa-Kuroki syndrome) was first described in 1980 by Dr. N. Niikawa and Dr. Y. Kuroki of Japan. The disorder received its name from the characteristic long eyelid fissures with eversion of the lower eyelids that is similar to the makeup of actors of Kabuki, a traditional Japanese theatrical form. Kabuki syndrome was originally known as Kabuki makeup syndrome, but the term “makeup” is now often dropped, as it is considered offensive to some families.

Scientific research suggests that Kabuki syndrome may be associated with a change in the genetic material associated with genes *KMT2D* and *KDMA6*.

Genetic profile

Kabuki syndrome is an autosomal dominant syndrome. Studies have shown that an alteration of the *KMT2D* and *KDMA6* genes results in Kabuki syndrome. A review of cases with an alteration of the *KMT2D* gene showed 47% frameshift mutations, 34% nonsense mutations, and 18% pathogenic missense mutations, although variants are also reported. Reports note that 50%–75% of patients with Kabuki syndrome have an alteration of the *KMT2D* gene, while an alteration of the *KDMA6* gene makes up a much smaller percentage. These changes cause a premature stop codon that likely results in the lack of transcription of the entire gene. Located on chromosome 12, *KMT2D* is important in the coding of a protein that is used for spatial and temporal expression of other genes. An alteration in this gene results in a variety of genetic changes related to brain and body development, as seen in the presentation of the signs and symptoms of the disease. Since the finding of this genetic information, an alteration of the *KMT2D* gene denotes the primary Kabuki syndrome and an alteration of the *KDMA6* gene denotes the secondary, type II Kabuki syndrome. Type II Kabuki syndrome shares the same phenotype as Kabuki syndrome, but it is reported to have a dominant pattern of X-linked inheritance.

In almost all cases of Kabuki syndrome, there is no family history of the disease. These cases are thought to represent new genetic changes that occur randomly and with no apparent cause and are termed “sporadic.” However, in several cases the syndrome appears to be inherited from a parent, supporting a role for genetics in the cause of Kabuki syndrome. Scientists hypothesize that an unidentified genetic abnormality that causes Kabuki syndrome is transmitted as an autosomal dominant trait. With an autosomal dominant trait, only one abnormal gene in a gene pair is necessary to display the disease, and an affected individual has a 50% chance of transmitting the gene and the disease to a child.

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance in which only one abnormal gene is needed to display the trait or disease.

Cardinal symptoms—A group of symptoms that define a disorder or disease.

Gastric tube—A tube that is surgically placed through the skin of the abdomen to the stomach so that feeding with nutritional liquid mixtures can be accomplished.

Gastroenterologist—A physician who specializes in disorders of the digestive system.

Kabuki—Traditional Japanese popular drama performed with highly stylized singing and dancing using special makeup and cultural clothing.

Neurologist—A physician who specializes in disorders of the nervous system, including the brain, spine, and nerves.

Demographics

Kabuki syndrome is a rare disorder with an incidence in the Japanese population of about 1 in 32,000 and at least 1 in 86,000 in Australia and New Zealand. The prevalence of the disease may be underestimated, as only a handful of physicians have firsthand experience diagnosing children with Kabuki syndrome. Kabuki syndrome appears to be found equally in males and females. Earlier cases were reported only in Japanese children, but the syndrome is now known to affect other racial and ethnic groups.

Signs and symptoms

The signs and symptoms associated with Kabuki syndrome are divided into cardinal symptoms (i.e., those that are almost always present) and variable symptoms (those that may or may not be present). Cardinal signs and symptoms include typical face, skin-surface abnormalities, skeletal abnormalities, mild to moderate intellectual disability, and short stature.

Diagnosis

The diagnosis of Kabuki syndrome relies on physical exam by a physician familiar with the condition and by radiographic evaluation, such as the use of x-rays or ultrasound to define abnormal or missing structures that are consistent with the criteria for the condition. A person can be diagnosed with Kabuki syndrome if he or she

possesses characteristics consistent with the five different groups of cardinal symptoms.

Although a diagnosis may be made as a newborn, most often the features do not become fully evident until early childhood. Genetic testing via exome sequencing may be available for *KMT2D* and *KDMA6* genes for further diagnosis.

Treatment and management

There is no cure for Kabuki syndrome. Treatment of the syndrome is variable and centers on correcting the different manifestations of the condition and on strategies to improve the overall functioning and quality of life of the affected individual.

For children with heart defects, surgical repair is often necessary. This may take place shortly after birth if the heart abnormality is life threatening, but often physicians will prefer to attempt a repair once the child has grown older and the heart is more mature. For children who experience seizures, lifelong treatment with antiseizure medications is often necessary.

Children with Kabuki syndrome often have difficulties feeding, either because of mouth abnormalities or because of poor digestion. In some cases, a tube that enters into the stomach is surgically placed in the abdomen and specially designed nutritional liquids are administered through the tube directly into the stomach.

People with Kabuki syndrome are at higher risk for a variety of infections, most often involving the ears and the lungs. In cases such as these, antibiotics are given to treat the infection, and occasionally brief hospital stays are necessary. Most children recover from these infections with proper treatment.

Nearly half of people affected by Kabuki syndrome have some degree of hearing loss. In these individuals, formal hearing testing is recommended to determine if they might benefit from a hearing-aid device. A hearing aid is a small mechanical device that sits behind the ear and amplifies sound into the ear of the affected individual. Occasionally, hearing loss in individuals with Kabuki syndrome is severe, approaching total hearing loss. In these cases, early and formal education using American Sign Language as well as involvement with the hearing-impaired community, schools, and enrichment programs is appropriate.

Children with Kabuki syndrome should be seen regularly by a team of healthcare professionals, including a primary care provider, medical geneticist familiar with the condition, gastroenterologist, and neurologist. After growth development is advanced enough (usually late adolescence or early adulthood), consultation with a

QUESTIONS TO ASK YOUR DOCTOR

- Which symptoms of Kabuki syndrome pose the greatest threat to my child's survival and why?
- What prognosis can you suggest for my child, and what factors affect that prognosis?
- Is there any research being conducted on possible treatments or cures for Kabuki syndrome?

reconstructive surgeon may be of use to repair physical abnormalities that are particularly debilitating.

During early development and progressing into young adulthood, children with Kabuki syndrome should be educated and trained in behavioral and mechanical methods to adapt to any disabilities. This program is usually initiated and overseen by a team of healthcare professionals including a pediatrician, physical therapist, and occupational therapist. A counselor specially trained to deal with issues of disabilities in children is often helpful in assessing problem areas and encouraging healthy development of self-esteem. Support groups and community organizations for people with disabilities often prove useful to the affected individuals and their families, and specially equipped enrichment programs should be sought. Furthermore, because many children with Kabuki syndrome have poor speech development, a consultation and regular session with a speech therapist is appropriate.

Prognosis

The abilities of children with Kabuki syndrome vary greatly. Most children with the condition have a mild to moderate intellectual impairment. Some children will be able to follow a regular education curriculum, while others will require adaptations or modifications to their schoolwork. Many older children may learn to read at a functional level.

The prognosis of children with Kabuki syndrome depends on the severity of the symptoms and the extent to which the appropriate treatments are available. Most of the medical issues regarding heart, kidney, or intestinal abnormalities arise early in the child's life and are improved with medical treatment. Since Kabuki syndrome was discovered relatively recently, very little is known regarding the average lifespan of individuals affected with the condition; however, present data on Kabuki syndrome does not point to a shortened lifespan.

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ORGANIZATIONS

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Kallmann syndrome

Definition

Kallmann syndrome (KS) is an inherited disorder of hypogonadotropic hypogonadism (HH), delayed puberty, and anosmia (inability to smell).

Description

HH occurs when the body does not produce enough of two important hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), because of a deficiency of gonadotropin-releasing hormone (GnRH). This deficiency results in underdeveloped gonads and often infertility. Anosmia was first described with HH in 1856, but it was not until 1944 that Kallmann reported the inheritance of the two symptoms together in three separate families. Hence, the syndrome of HH with anosmia was designated Kallmann syndrome (KS). KS is also called isolated gonadotropin-releasing hormone deficiency (IGD) with impaired sense of smell and, occasionally, dysplasia olfactogenitalis of De Morsier.

KS is usually detected in adolescence because of failure to undergo puberty. There are multiple types of KS, with multiple inheritance patterns and features, caused by mutations in different genes. The most common features are HH and anosmia, though a wide range of features can be present in an affected person, including a small penis or undescended testicles in males, kidney abnormalities, cleft lip and/or palate, clubfoot, hearing problems, and central nervous system problems such as synkinesia (involuntary movements), eye-movement abnormalities, and visual and hearing defects.

Embryology

Normally, a structure in the brain called the hypothalamus makes GnRH. This hormone acts on the pituitary gland, another nearby structure in the brain, to produce FSH and LH. Both of these hormones travel to the gonads, where they stimulate the development of sperm in men, and eggs in women. FSH is also involved in the release of a single egg from the ovary once per month. HH results when there is an alteration in this pathway that results in inadequate production of LH or FSH. In KS, the hypothalamus is unable to produce GnRH, and thus the production of LH and FSH is not stimulated and does not occur.

The relationship of HH and anosmia can be explained during the development of an embryo. The cells that eventually make GnRH in the hypothalamus are first found in the nasal placode, part of the developing olfactory system (for sense of smell). The GnRH-producing cells must migrate, or move, from the nasal placode up into the brain to the hypothalamus. These cells migrate by following the path of another type of cell called olfactory neurons. Neurons are specialized cells that are found in the nervous system and have long, tail-like structures called axons. The axons of the olfactory neurons grow from the nasal placode up into the developing front of the brain. Once they reach their final destination in the brain, they form the olfactory bulb, the structure in the brain that helps process odors for the sense of smell. The GnRH-producing cells follow the pathway of the olfactory neurons up into the brain to reach the hypothalamus.

In KS, the olfactory neurons are unable to grow into the brain. As a result, the olfactory bulb does not form, resulting in the inability to smell, and the GnRH-producing cells cannot follow the pathway of the axons and do not reach their final destination in the hypothalamus. Hence, no GnRH is made to stimulate the pituitary to make FSH and LH, resulting in no gonad development or HH.

Genetic profile

Most cases of KS are sporadic, meaning that they are caused by new gene mutations rather than mutations inherited from a parent. However, some cases are inherited in an autosomal dominant pattern, an autosomal recessive pattern, or an X-linked recessive pattern. Most cells of the body contain structures called chromosomes. Chromosomes contain genes, which are instructions for all of the proteins necessary for growth, development, and function. There are 46 chromosomes, or 23 pairs of chromosomes, in each cell. The first 22 chromosomes are the same in men and women and are called the autosomes. The last pair, the sex chromosomes, is different in males and females. Men have an X and a Y chromosome (XY). Females have two X chromosomes (XX). All of the genes of the autosomes and the X chromosomes in females come in pairs.

Autosomal dominant inheritance occurs when only one copy of a gene pair is altered or mutated to cause the condition. In autosomal dominant inheritance, the second normal gene copy cannot compensate, or make up for, the altered gene. People with autosomal dominant inheritance have a 50% chance of passing the gene and the condition on to each of their children.

Autosomal recessive inheritance occurs when both copies of a gene are altered or mutated to cause the condition. In autosomal recessive inheritance, the affected person has inherited one altered gene from his or her mother, and the other altered gene from his or her father. Couples who both have one copy of an altered autosomal recessive gene have a 25% risk with each pregnancy of having an affected child.

X-linked recessive inheritance is thought to be the least common form of KS inheritance but is the best understood at the genetic level. With X-linked recessive inheritance, the altered gene that causes the condition is on the X chromosome. Since men have only one copy of the X chromosome, they have only one copy of each gene on the X chromosome. If that one copy is altered, they will have the condition, because they do not have a second copy of the gene to compensate. Women, however, can have one altered copy of the gene and not be affected, as they have a second copy to compensate. In X-linked recessive conditions, women are generally not affected with the condition. Women who are carriers for an X-linked recessive condition have a 50% chance that each of their sons will be affected.

The genes associated with KS are important for certain areas of brain development in the fetus, especially for the formation and movement of olfactory neurons and the migration of nerve cells that produce GnRH. GnRH directs the production of several other hormones that are responsible for prenatal sexual development, for

puberty, and for the function of ovaries in women and testes in men. Therefore, mutations in these genes cause HH and anosmia.

About half of all individuals with KS have a recognizable gene mutation. Mutations in the following genes account for 25% to 30% of KS cases.

- *KAL1* (*ANOS1*), which instructs the body to make a protein called anosmin-1, causes KS type 1 and most cases of X-linked recessive KS. Anosmin-1 is involved in providing the pathway in the brain along which the olfactory axons grow. Anosmin-1 is also found in other parts of the body, possibly explaining some of the other symptoms sometimes observed with KS.
- *FGFR1*, on chromosome 11, encodes fibroblast growth factor receptor 1 and is associated with KS types 2 and 6.
- *PROKR2* causes KS type 3.
- *PROK2* causes KS type 4.

Other KS-associated genes have been identified that interfere with the migration pathway of cells from the olfactory area to the hypothalamus (brain) include *KAL1*, *NELF*, *FGFR1*, *FGF8*, *PROK2*, *PROKR2*, *HS6ST1*, *CHD7*, *WDR11*, and *SEMA3A*. Genes that primarily interfere with the normal secretion of GnRH or its action on the pituitary include *GNRH1*, *KISS1*, *KISS1R*, *TAC3*, and *TACR3*. This clearly is a complicated system, and some of these genes perform more than one function. As only half of all KS individuals have had a specific gene mutation identified, additional KS-associated genes may be identified in the future.

Demographics

Kallmann syndrome is the most frequent cause of HH and affects approximately one in 30,000 males and one in 120,000 females. KS occurs in people of all ethnic backgrounds.

Signs and symptoms

The signs and symptoms of KS can vary among affected individuals even within the same family. The two features most often associated with KS are HH and the inability to smell and failure to initiate puberty. Males can also have a small penis and undescended testicles at birth (testicles remaining in the body rather than dropping down into the scrotal sac). Clubfoot, cleft lip, and/or cleft palate can also be present at birth. Clubfoot occurs when one or both feet are not properly placed on the legs and can appear turned. Cleft lip and/or cleft palate occur when the upper lip and/or the roof of the mouth fail to come together during development. Kidney abnormalities, most often unilateral renal agenesis (one kidney that does not form), are especially common in males with X-linked

KEY TERMS

Anosmia—Impairment or absence of the sense of smell.

Gonadotropin-releasing hormone (GnRH)—The hormone produced by the hypothalamus that stimulates the release of gonadotropins such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Hypogonadotropic hypogonadism (HH)—Underdevelopment of the gonads due to a deficiency of gonadotropin-releasing hormone.

Hypothalamus—A part of the forebrain that controls heartbeat, body temperature, thirst, hunger, body temperature and pressure, blood sugar levels, and other functions.

Neuron—The fundamental nerve cell that conducts impulses in the brain and nervous system.

Pituitary gland—A small gland at the base of the brain responsible for releasing many hormones, including luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Puberty—The developmental stage in which the gonads begin to function, and secondary sexual characteristics begin to appear.

Synkinesia—Involuntary movement of a part of the body when another part of the body moves.

recessive KS. Choanal atresia (a blocked pathway from the nose at birth) and structural heart defects have also been seen in KS.

Central nervous system problems can occur. These may include nystagmus (involuntary eye movements), ataxia (involuntary body movements), hearing loss, and problems with vision. Synkinesia is especially common in men with the X-linked recessive form of KS. Some people with KS are also mentally limited. Holoprosencephaly, in which the brain fails to develop in two halves, is also seen in some individuals with KS.

Diagnosis

Individuals with KS might not be diagnosed until they fail to undergo the normal stages of puberty. Hormone testing shows that both LH and FSH are decreased.

QUESTIONS TO ASK YOUR DOCTOR

- How is Kallmann syndrome diagnosed?
- Are there prenatal tests for this genetic disorder?
- If my first child was diagnosed with Kallmann syndrome, what are the chances that future children will also have the disorder?
- Are there at-home treatments to help my child to deal with the worst symptoms of Kallmann syndrome?
- What is my child's prognosis?

Affected individuals often do not realize that they cannot smell. MRI can often detect the absence of the olfactory bulb in the brain. Renal ultrasound can determine whether a kidney is missing.

When an isolated case of KS is diagnosed, evaluation of first-degree family members, such as parents and siblings, should be performed. This should include a detailed family history, measurement of hormone levels, assessment of sense of smell, and renal ultrasound to look for kidney abnormalities. This information may help diagnose previously unrecognized cases of KS. Furthermore, this information may be important for genetic counseling and determining who in the family is at risk for KS.

Molecular genetic testing is available for at least four KS-causing mutations, and carrier testing may be available if the KS-causing mutation or mutations in the family have been identified. Prenatal testing and preimplantation genetic diagnosis are possible if the mutation or mutations are known.

Treatment and management

When a child with KS is born with structural abnormalities such as cleft lip and/or palate, clubfoot, or heart defects, surgery is often necessary to repair the defect. Delayed puberty can be treated with sex hormones—estrogen for females, and testosterone for males. Once puberty is achieved, GnRH or LH and FSH can treat hypogonadism. Treatment is usually successful, and infertility can be reversed. However, a small number of people do not respond to treatment.

Prognosis

For people with the most common features of KS—hypogonadism and the inability to smell—the prognosis is excellent. In most cases, hormone treatment can reverse

the delayed puberty and hypogonadism. For individuals with other symptoms of KS, prognosis depends on the severity of the defects. For example, structural heart defects can be quite complex and sometimes cannot be surgically repaired. No specific treatment is available for those affected by intellectual disability.

Clinical trials for treating Kallmann syndrome, including experimental drug treatments and procedures, are underway. Participation in a U.S. clinical trial is voluntary and at no cost to the participant. All clinical trials receiving U.S. government funding, and some supported by private industry, are posted at <https://www.clinicaltrials.gov>. Foreign trials are listed at <https://www.orpha.net>

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ORGANIZATIONS

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Pituitary Foundation, 86 Colston Street, Bristol, UK BS1 5BB, 0117 370 1333, 0117 933 0910, enquiries@pituitary.org.uk, <https://www.pituitary.org.uk>

Pituitary Society. VA Medical Center, 8700 Beverly Boulevard, Room 2051, Los Angeles, CA 90048, (310) 988-9486, <http://www.pituitarysociety.org>

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Karyomapping

Definition

Karyomapping is a method of preimplantation genetic testing (PGT) for detecting abnormalities in a single gene from a single cell taken from an embryo created by in vitro fertilization (IVF). Because karyomapping

was first used to identify mutations that cause monogenic (single-gene or Mendelian) disorders, it is currently referred to as PGT-M to distinguish it from techniques used to identify abnormalities involving entire chromosomes (PGT-A) or structural rearrangements of the parents' chromosomes (PGT-SR). Karyomapping has, however, been shown to detect some structural abnormalities in parental chromosomes as well as single-gene mutations. The name of the procedure comes from the Greek word for seed or kernel, combined with the English word mapping.

Karyomapping should not be confused with karyotyping, which is the process of taking a photograph of an individual's chromosomes in order to count the number of chromosomes and detect any abnormalities in their number or structure.

Description

History

Karyomapping was made possible by the identification of single nucleotide polymorphisms (SNPs) in the early 2000s. Each SNP represents a difference in a single DNA nucleotide. SNPs are the most common type of genetic variation among humans; there are between four and five million SNPs in a person's genome. Most SNPs have no effect on a person's development or health; however, SNPs that occur within or near a gene may affect that gene's function, and these SNPs can serve as markers of genes associated with genetic diseases.

Other advances in technology and genome analysis that contributed to the development of karyomapping include the introduction of polymerase chain reaction (PCR) as a way to obtain a sufficiently large sample of DNA from a single cell, coupled with improved methods of preserving embryos obtained through assisted reproductive technology (ART). As of 2021, all embryos tested by karyomapping are obtained by hormonal stimulation of the mother's ovaries followed by IVF. The resultant embryos are kept in culture until they have reached the blastocyst stage, usually about eight days after fertilization.

Technique

Karyomapping is done for couples who already know themselves to be at risk of having a child with a monogenic disorder, either because they have already had their DNA tested, have relatives affected by the disorder in question, or have already had a child with the disorder. Karyomapping can be done for autosomal recessive disorders (most often for cystic fibrosis, sickle cell anemia, beta-thalassemia, and spinal muscular atrophy), autosomal dominant disorders (Huntington's disease, myotonic dystrophy, and Charcot-Marie-Tooth

disease), and X-linked diseases (fragile X syndrome, hemophilia A, and Duchenne muscular dystrophy).

Karyomapping begins with obtaining a cheek swab or blood or saliva samples from each of the parents and one or more relatives of the couple who may be affected by the disorder or are carriers of it. If the genetic disorder in question is autosomal recessive, it means that each parent carries the defective gene, and DNA samples must be obtained either from an affected child or from the couple's parents. If the genetic disorder is autosomal dominant, only samples from the affected side of the family are needed; that is, samples are needed from the couple and an affected child, or from a parent affected by the disorder. These samples are then analyzed to obtain the SNP profiles of the four parental chromosomes that carry the gene associated with the disorder. Karyomapping examines the chromosomes at 300,000 different SNPs in order to identify a DNA "fingerprint" unique to the chromosome that carries the defective gene.

The next step involves obtaining embryos through a standard IVF cycle. The mother is given some type of hormonal stimulation to produce eggs, which are then removed from the ovaries through the vagina in a process called follicular aspiration. The eggs are then fertilized outside the mother's body and kept in a culture medium for five-to-nine days until the developing embryos reach the blastocyst stage. A blastocyst, which is 0.1 to 0.2 mm in size, consists of an outer layer of cells called the trophoblast (also called the trophectoderm), which will eventually give rise to the placenta, a fluid-filled inner cavity called the blastocoel, and an inner cell mass that will develop into the fetus.

Each of the blastocysts produced in the IVF cycle can then be tested for the DNA fingerprint that indicates the presence of the defective gene. In karyomapping, only one or two cells are removed from the trophoblast for preimplantation testing; this small biopsy sample will not disturb the developing blastocyst. The biopsy is usually done in the local IVF clinic; the actual karyomapping is carried out in a specialized genetic testing laboratory. The turnaround time for the laboratory work is about a week.

A blastocyst that does not carry the DNA fingerprint indicating the defective gene is assumed to be genetically normal and can then be transferred into the mother's uterus for implantation and further development into a healthy fetus. Other blastocysts that are found to be healthy can be frozen for use in a later pregnancy if desired.

Regulation

Karyomapping is regulated in Europe as of 2021 although it (or any other form of preimplantation genetic testing) is not regulated in the United States. The reason for this difference is that countries like France and the

KEY TERMS

Autosome—Any chromosome that is not a sex chromosome. The human genome has 22 pairs of autosomes.

Blastocyst—The phase of human embryonic development that occurs about 5–9 days after fertilization. The blastocyst consists of an outer layer of cells; an inner mass of cells; and a fluid-filled cavity.

Carrier—In genetics, a person who has a genetic mutation associated with a disease and is capable of passing it on. A carrier may or may not display the symptoms of the disease.

Chromosome abnormalities—A general term for abnormalities in either the number or the structure of chromosomes.

Genome—The total amount of genetic information within an organism's chromosomes, including its genes and DNA sequences.

Germline—The population of a complex organism's cells that pass on genetic information to offspring. Germline cells include eggs, sperm, and fertilized eggs.

In vitro fertilization (IVF)—A form of assisted reproduction technology in which a human ovum (egg) is combined with sperm outside the body in a laboratory container ("in vitro" means "in glass").

Karyotype—The complete set of chromosomes in a species or individual organism. The term can also refer to the laboratory technique used to produce an image of an individual's chromosomes.

Mendelian disease—A disease caused by a single mutated gene; also called a single-gene disease.

Monogenic disease—Another term for a single-gene disorder.

Mosaicism—A condition in which two or more genetically different sets of cells occur in the same individual.

Nucleotide—A building block of a nucleic acid (DNA or RNA), consisting of a sugar molecule, a phosphate group, and one of the nitrogen-containing bases (adenine, cytosine, guanine, and thymine in DNA; adenine, cytosine, guanine, and uracil in RNA).

Polymerase chain reaction (PCR)—A method for obtaining a sufficient sample of DNA to analyze by amplifying or making copies of a small segment of DNA through a series of cycles of temperature changes. PCR is sometimes called molecular photocopying.

Preimplantation genetic testing (PGT)—A screening test performed on embryos created by IVF to analyze the genetics of each embryo prior to transfer into the intended mother's uterus.

Single nucleotide polymorphism (SNP)—A germline substitution of a single nucleotide (any of a group of molecules that form the building blocks of DNA or RNA) at a specific position in a person's genome.

United Kingdom have either statutory bodies (the Human Fertilisation and Embryology Authority (HFEA) in the UK) or nationwide public health codes (as in France). The HFEA permits preimplantation testing for over 400 different genetic disorders, while the French Agence de la Biomédecine is more restrictive than its British counterpart.

By contrast, the United States has no government-funded health care program on the national level, nor is IVF (which is a prerequisite for karyomapping) covered by federal programs like Medicare or Medicaid. The exception is Veterans Affairs (VA) coverage of IVF for veterans who lost their fertility as a result of a service-related injury. As of 2021, while 17 states (Arkansas, California, Connecticut, Delaware, Hawaii, Illinois, Louisiana, Maryland, Massachusetts, Montana, New Hampshire, New Jersey, New York, Ohio, Rhode Island, Texas and West Virginia) require health insurance

companies to cover or offer IVF as well as other fertility treatments. Other states have no such provisions.

Another problem is that the United States has no regulatory body responsible for the clinical practice of karyomapping and other forms of PGT. While the Food and Drug Administration (FDA) is tasked with ensuring the effectiveness and safety of drugs and medical devices, it does not regulate how and when they should be used. The Centers for Disease Control and Prevention (CDC) collects data each year on fertility treatments, but its work is limited to data collection and reporting. Federal regulation of PGT would require either the creation of a new agency or assignment of oversight to an existing agency.

Limitations

Karyomapping has several limitations. One is that it is most useful in identifying monogenic disorders,

QUESTIONS TO ASK YOUR DOCTOR

- Have you ever recommended karyomapping to a patient concerned about a single-gene disorder in a planned pregnancy?
- Why do you think that IVF and karyomapping are so expensive?
- Do you think that the FDA or another federal agency should regulate karyomapping in the United States?
- What do you consider the limitations and risks of karyomapping as a diagnostic technique?

although in a few cases it has been found effective in identifying two monogenic disorders in the same family and identifying some forms of structural rearrangement of chromosomes. It cannot, however, be reliably used to screen for abnormalities in the number of chromosome copies, or for simultaneous screening of a panel of single-gene genetic disorders. Karyomapping is also unable to reliably identify mosaicism (the presence of two or more distinct cell lines in the same embryo) because it samples so few cells, and it is known that embryos with mosaicism are less likely to implant successfully in the mother's uterus.

Another limitation is that karyomapping employs PCR amplification of the DNA found in only one or two cells taken from the trophoblast of the blastocyst. While karyomapping is about 95% (some sources say 97%) accurate in identifying healthy embryos for transfer, it cannot absolutely exclude the possibility of misdiagnosis. As a result, the American College of Obstetricians and Gynecologists (ACOG) recommends that karyomapping should be followed up with amniocentesis or chorionic villus sampling of the resulting pregnancy.

The most important limitation for many couples is the cost of the procedure. As karyomapping requires an IVF cycle, the cost of ovarian stimulation, egg retrieval, fertilization, biopsy of trophoblast cells from the blastocyst, freezing of the embryos, the actual karyomapping, and embryo transfer runs as high as \$16,000 as of 2021, with the cost of medications extra. The embryo biopsy charges alone run between \$1000 and \$2200.

Research

There are no clinical trials of karyomapping registered with the NIH as of mid-2021.

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American College of Medical Genetics and Genomics (ACMG),
7101 Wisconsin Avenue, Suite 1101, Bethesda, MD 20814,
(301) 718-9603, (301) 718-9604, acmg@acmg.net, <https://www.acmg.net/>

American College of Obstetricians and Gynecologists (ACOG),
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673-8444, (202) 638-5577, <https://www.acog.org/>

American Society for Reproductive Medicine (ASRM), J.
Benjamin Younger Office of Public Affairs, 726 7th Street
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National Human Genome Research Institute (NHGRI), Building
31, Room 4B09, 31 Center Drive, MSC 2152, 9000
Rockville Pike, Bethesda, MD 20892-2152, (301)
402-0911, <https://www.genome.gov/about-nhgri/Contact>,
<https://www.genome.gov/>

National Society of Genetic Counselors (NSGC), 330 North
Wabash Avenue, Suite 2000, Chicago, IL 60611, (312)
321-6834, nsgc@nsgc.org, <https://www.nsgc.org>

U.S. Food and Drug Administration (FDA), 10903 New
Hampshire Avenue, Silver Spring, MD 20993, (888)
463-6332, <https://www.fda.gov/>

Rebecca J. Frey, PhD

Karyotype

Definition

A karyotype is the arrangement of chromosomes in their matched (homologous) pairs. Human chromosomes are arranged and numbered according to the International System for Human Cytogenetic Nomenclature (ISCN). Karyotype can refer to either the composition of the chromosomes in a cell of an individual or species or to a diagram or photograph of the chromosomes arranged in their pairs.

Description

The normal human karyotype consists of 23 pairs of chromosomes. There are 22 pairs of autosomes—the chromosomes other than the X and Y sex chromosomes. Females normally have two X chromosomes, and males have one X chromosome and one Y chromosome. The karyotype reveals the number of chromosomes; their arrangement, size, and shape; and any structural abnormalities.

Karyotyping is used to examine the chromosomes in cells to identify genetic disorders caused by chromosome abnormalities. Chromosome preparations can be made

KEY TERMS

Acrocentric—A centromere positioned at the top end of a chromosome.

Autosomes—The chromosomes other than the X and Y sex chromosomes.

Banding—Striped patterns that are visible on stained chromosomes and that are distinctive for each chromosome.

Centromere—A constricted region of a chromosome that is involved in cell division and that divides the chromosome into the long arm (q) and the short arm (p).

Chromosomal microarray (CMA)—A more sensitive method for detecting chromosome abnormalities than conventional karyotyping.

Homologous chromosomes—The two members of a chromosome pair, one inherited from each parent.

Metacentric—A centromere in the middle of the chromosome.

Metaphase—The stage in cell division when the chromosomes are arranged along an equatorial plane.

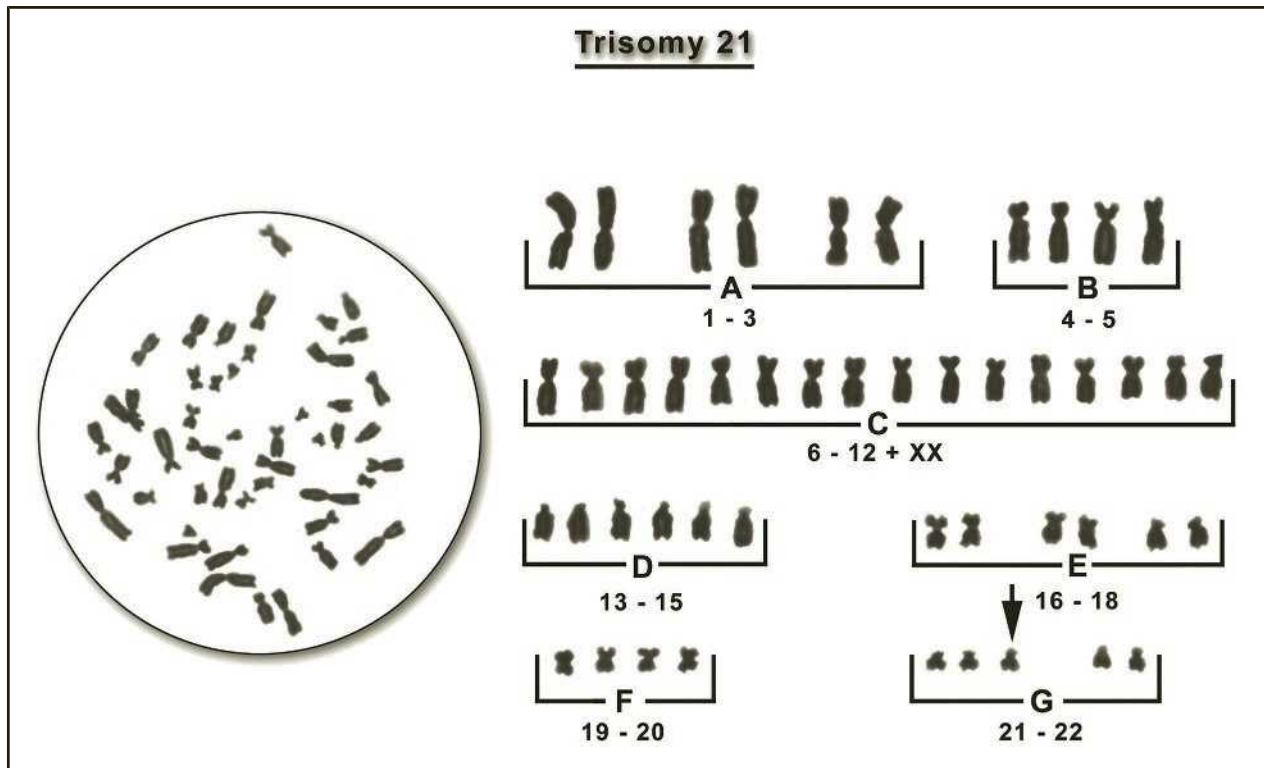
Satellites—Small segments of genetic material at the tips of the short arms of chromosomes 13, 14, 15, 21, and 22.

Submetacentric—A centromere located between the center and the top of the chromosome.

Translocation—The transfer of material in a chromosome to a different position, especially to a nonhomologous chromosome; translocations may be balanced, in which no genetic material is lost or gained, or unbalanced with the loss or gain of genetic material.

from almost any dividing cells, including blood cells, skin cells, amniotic fluid cells (the fluid surrounding an unborn baby), placental tissue or chorionic villi (tissue that forms the placenta and can be used in prenatal diagnosis), bone marrow, or biopsied tissue. Karyotypes are used to identify:

- problems in a developing fetus
- causes of multiple miscarriages or stillbirths
- causes of multiple birth defects
- causes of unusual features or developmental delays in infants and children



Karyotype showing three copies of chromosome 21, which indicates Down syndrome. (Clark Heath/Centers for Disease Control and Prevention)

- chromosome disorders such as Down syndrome, Klinefelter syndrome, Turner syndrome, and trisomy 18
- ambiguous genitalia (a mixture of male and female genitals)
- a “Philadelphia chromosome,” which is usually present in chronic myelogenous leukemia cells
- chromosome abnormalities in other leukemias and cancers

To prepare a karyotype, the cell samples are grown in the laboratory in a dish or tube with rich medium to promote cell division. Chromosomes are individually distinguishable only during a certain stage of cell division known as metaphase. Therefore, a karyotype is made during metaphase and referred to as a metaphase spread. At metaphase, the chromosomes are removed from the cell nucleus, mounted on a slide, stained, and examined and photographed under a microscope. The photographs are then arranged into a karyotype.

Karyotype construction

For the construction of the karyotype, the chromosomes are numbered 1 through 22 from longest to shortest. The 23rd pair is the sex chromosomes and is placed on the karyotype after the 22nd pair. The chromosomes can be separated into groups, based on their length and

the position of the centromere. The centromere is a constricted region of the chromosome that is involved in cell division and is used to define the long arm (q) and the short arm (p) of each chromosome. Group A consists of chromosome pairs 1, 2, and 3. These are the longest chromosomes, and their centromeres are located at the center of each chromosome (metacentric). Group B consists of chromosome pairs 4 and 5. These are long, but their centromeres lie toward the top of each chromosome (submetacentric). Group C consists of chromosome pairs 6, 7, 8, 9, 10, 11, and 12 and the X chromosome(s). These are of medium length, and their centromeres are located either in the middle or toward the top of the chromosome. Group D consists of chromosome pairs 13, 14, and 15. These are of medium length, and their centromeres lie at the top of the chromosome (acrocentric). Additionally, D group chromosomes have satellites (small fragments of genetic material at the tip of the short arm). Group E consists of chromosome pairs 16, 17, and 18. These are relatively short chromosomes, and their centromeres are located in the center or toward the top of the chromosome. Group F consists of chromosomes 19 and 20. These are short chromosomes with centromeres located in the center. Lastly, group G consists of chromosome pairs 21, 22, and the Y chromosome. These are short chromosomes with their centromeres at the top.

QUESTIONS TO ASK YOUR DOCTOR

- Will my cells be karyotyped?
- What cells will be used for karyotyping?
- How will the cells be obtained?
- What method will be used for karyotyping?
- What information will my karyotype provide?

Chromosome pairs 21 and 22 have satellites. The Y chromosome does not have satellites.

Chromosomes in a metaphase preparation are stained to reveal patterns of light and dark stripes called bands. Staining the chromosomes with Giemsa dye is referred to as “G-banding.” Each numbered chromosome is unique in its banding pattern, although there may be slight normal familial variations. Banding makes it easier to identify the chromosomes and visualize any differences or abnormalities. For example, banding makes it much easier to see if a chromosome is missing a piece, if two chromosomes are attached to each other, or if a piece of one chromosome is joined to another chromosome (a translocation).

Chromosome complements are described by ISCN formulas. The basic formula for describing a karyotype is the total number of chromosomes followed by the sex chromosome complement. Thus, a typical female karyotype is written as 46,XX, and a typical male karyotype is written as 46,XY.

Formulas for abnormal karyotypes

Common formulas for abnormal karyotypes are as follows:

- A plus or minus sign before a chromosome number indicates that an entire chromosome is extra or missing. Therefore, the total number of chromosomes will be more or less than 46. For example, Down syndrome is caused by an extra chromosome 21. The karyotype of a male with Down syndrome is 47,XY,+21.
- Chromosomes may have extra or missing regions of the short arm (p) or long arm (q). For example, Wolf-Hirschhorn syndrome is caused by a missing part of the end of the short arm of chromosome 4. The karyotype of a female with this syndrome is 46,XX,del(4)(p16). The “del” means “deletion,” (4) indicates that chromosome 4 is affected, and (p16) indicates the missing region of the short arm.
- There are many types of balanced and unbalanced translocations. Balanced translocations are exchanges of

regions between two different chromosomes without a gain or loss of genetic material. A Robertsonian translocation occurs when two entire acrocentric chromosomes are attached. A common example is a translocation involving chromosomes 13 and 14. A male with a balanced Robertsonian translocation of chromosomes 13 and 14 has the karyotype 45,XY,der(13;14). Thus, there are only individual chromosomes. The “der” stands for derivative, since the new 13;14 chromosome is considered a derivative.

Newer methods

High-resolution chromosome studies are performed with chromosomes from cells in which cell division has been stopped at an earlier stage, called pro-metaphase. These chromosomes appear longer, and 700–1,200 bands can be seen, compared with the 300–600 bands that are visible with routine metaphase banding. High-resolution karyotyping allows for a more detailed analysis of chromosome structure.

A chromosomal microarray (CMA) is much more sensitive than traditional karyotyping. There are various CMA methods that can be applied to all of the chromosome, to a specific chromosome, or to a specific region of a chromosome. CMA can detect losses or gains of genetic material at single-gene resolution, known as copy number variations. Fluorescent in situ hybridization (FISH) is another technique that can detect small changes, such as deletions, in chromosomes.

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- American Association for Clinical Chemistry, 1850 K St. NW, Suite 625, Washington, DC 20006-2213, (202) 857-0717 or (800) 892-1400, (202) 887-5093, <https://aacc.org>

Renee A. Laux, MS
and Margaret Alic, PhD

Karyotype analysis see **Karyotype**
 Keller syndrome see **FG syndrome**

Keppen-Lubinsky syndrome

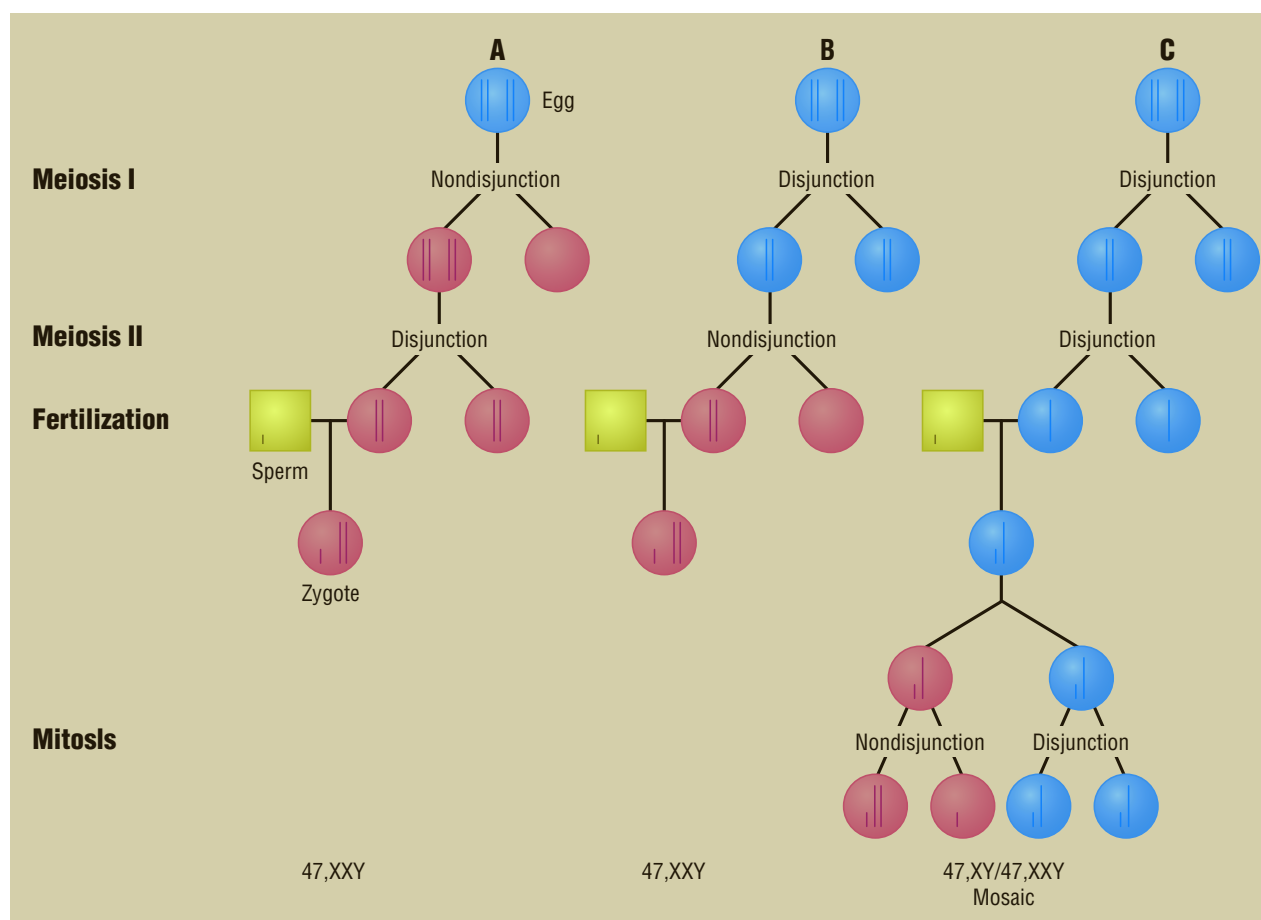
Definition

Keppen-Lubinsky syndrome, often referred to by its acronym (KPLBS) or as Lubinsky syndrome, is a rare autosomal dominant heterozygous genetic disorder. The first case of KPLBS was reported in 2001; therefore, research on it is limited. Research as of 2015 showed that the gene mutation associated with KPLBS leads to a severe impairment of the functioning of the potassium channel the gene codes for, classifying the mutation as a channelopathy. The result of this mutation in the human body leads to severe developmental delay, a dysmorphic appearance, and cognitive disability.

Description

KPLBS is a genetic disorder that directly mutates the *KCNJ6* gene that encodes an integral membrane protein and the inward-rectifier potassium channel. The encoded integral membrane protein is a cellular membrane protein that regulates the amount of potassium that goes in and out of a cell. This is very important for the overall function of the cell. The balance between intracellular and extracellular potassium, for example, is necessary for the regulation of heart rate and the activity of part of the nervous system.

In addition to altering the function of the integral membrane protein structure, the KPLBS mutation also affects the inward-rectifier potassium channel, which plays a role in the regulation of potassium into the cell more so than out of the cell. When this intra-extracellular balance of potassium is altered, many functions of the cell can become either overactive or underactive, depending on the interruptions resulting from the



Nondisjunction, failure of paired chromosomes to separate, can result at different stages of meiosis or mitosis. When nondisjunction occurs in the first (A) or second (B) phase of meiosis the resulting karyotype will be 47,XXY. If the chromosomes fail to separate during mitosis (C) a mosaic karyotype (46,XY/47,XXY) will result. (Gale)

imbalance. This includes a change in the sodium-potassium pump, which plays a major role in the conductivity of both afferent and efferent nerve cells. Researchers have suggested that this alteration of the ratio of sodium to potassium that occurs when the inward-rectifier potassium channels are not working correctly may cause cell death due to the influx of sodium.

Inward-rectifier potassium channels are found throughout the human body in cells including, but not limited to, the following:

- blood cells
- osteoclasts
- endothelial cells
- glial cells
- epithelial cells
- oocytes

The role of potassium in these cells is to mediate the passive and active electrical properties of the cells' signaling, and it may link cellular metabolic state and membrane excitability in vivo as well. When these processes are not functioning correctly, the cell they correlate to will not be able to do its encoded job, leading to the overall dysfunction of the human body as seen in KPLBS. Studies of these channels suggest the importance of potassium channels in differentiation of cells in the embryonic stage, particularly adipocytes. The alteration of differentiation of embryonic adipocytes is suggested to be the underlying reason for the generalized lipodystrophy seen in all three of the cases of KPLBS reported as of 2015.

Genetic profile

KPLBS is an autosomal dominant heterozygous *de novo* mutation in the *KCNJ6* gene located on chromosome 21q22. This also maps to the Down syndrome critical region between *DIRK1A* and *DSCR4*, which is indicative of the resulting mental impairment seen in cases of KPLBS in addition to the musculoskeletal abnormalities. Studies have shown two patterns of mutations of this particular gene that lead to the syndrome. By sequencing exomes of three unrelated individuals diagnosed with KPLBS, the study by Masotti et al. (2015) found that two individuals shared an in-frame heterozygous deletion of three nucleotides, leading to the loss of one amino acid the three nucleotides code for. The third individual was heterozygous for a missense mutation, in which an amino acid change from glycine to serine occurs. This missense of one amino acid for another also changes the nucleotide the triplet codon is meant to code for and results in the overall impairment of the gene. All three cases outlined caused the mutation of the gene

KEY TERMS

Channelopathy—A disorder of channels.

De novo—An alteration in a gene that is present for the first time in one family member as a result of a mutation in a germ cell (egg or sperm) of one of the parents or in the fertilized egg itself.

Lipodystrophy—A medical condition characterized by abnormal or degenerative conditions of the body's adipose tissue.

Microcephaly—A condition of abnormal smallness of the head usually associated with mental defects.

Philtrum—The vertical groove on the median line of the upper lip.

Tetraparesis—Muscle weakness affecting all four limbs.

coding for the inwardly rectifying potassium channel and, due to the heterogeneous nature of this mutation, both genes that coded for the channel were mutated.

Demographics

The Office of Rare Diseases, the National Institutes of Health, and Orphanet, a consortium of European partners, have classified KPLBS as a rare disease, based on their individual parameters. Studies note that as few as three male children have been diagnosed with this syndrome. Of the children, the first was the second child of parents with an American and Hispanic background, the second was the third child of parents with Italian backgrounds, and the third was the second child of Jewish parents with Yemenite backgrounds.

Signs and symptoms

Inspection of a child born with KPLBS will reveal normal growth parameters at birth followed by failure to thrive and poor postnatal growth. After infancy, signs and symptoms of KPLBS are seen more so in the facial features than in the rest of the body. A highly arched superior palate leads to a short philtrum, a tented upper lip, a smaller jaw, and a mouth in the open position. A change in orbital structure causes large, prominent eyes. Generalized lipodystrophy causes a decrease in fat cells in the facial region, causing a hypoplastic nose and giving the face an overall aged appearance from wrinkled skin typically in the forehead and the chin, tightly adhered facial skin, and mask-like facies. Neurological signs and symptoms include, but are not limited to, intellectual disability, decreased intelligence and cognitive function,

QUESTIONS TO ASK YOUR DOCTOR

- How often should my child be monitored for growth or intellectual disability?
- What treatments are available to us for improving my child's quality of life?
- Will the changes in my child's facial features alter the food he or she can eat?
- Are there any support groups established for us to join?

hypertonia/hyperreflexia, and spastic tetraparesis. Other signs and symptoms include respiratory dysfunction, scoliosis, and possible seizures.

Diagnosis

Diagnosis of KPLBS is highly correlated with the signs and symptoms of the mutation seen upon physical and radiological examination of the patient. Neurological examination, brain MRI, and cognitive function tests are also instrumental in the diagnosis of KPLBS. Specific diagnosis can be made via exome sequencing and confirmed by Sanger sequencing. Laboratory tests are typically negative.

Treatment and management

Although there are minimal studies outlining treatment specifically for KPLBS, there have been some animal studies performed for the opioid treatment of pain related to the *KCNJ6* gene. Treatment and management of certain signs and symptoms such as scoliosis, seizures, and spasticity may be provided for a person diagnosed with this syndrome. These may include cognitive therapy, occupational or physical therapy, and pain management. Genetic counseling is recommended for parents considering future offspring following a diagnosis of a child with KPLBS.

Treatment and management of the symptoms associated with the syndrome are more available than treatment for the gene mutation itself. The treatment of life-threatening symptoms of the syndrome, such as respiratory dysfunction, seizures, and changes in structure affecting nutritional status, have a higher priority than non-life-threatening symptoms such as scoliosis, hypertonia, hyperreflexia, and tetraparesis. Cases reported over the last 15 years have shown children being treated with tracheostomy and ventilation for respiratory dysfunction,

percutaneous endoscopic gastrostomy for nutritional deficiencies, and tendon release surgeries for spasticity.

Prognosis

Due to the limited cases of KPLBS in adulthood, the prognosis of this genetic disorder was unknown as of 2015.

Resources

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ORGANIZATIONS

Genetic Alliance, 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008-2369, (202) 966-5557, (202) 966-8553, info@geneticalliance.org, <http://www.geneticalliance.org>

Genetic Disease Foundation, 1425 Madison Ave., Box 1498, New York, NY 10029, (212) 659-6704, <http://www.geneticdiseasefoundation.org>

Taryn Terry, DC, MSACN, BA

Klinefelter syndrome

Definition

Klinefelter syndrome is a chromosome disorder in males. People with this condition are born with at least one extra X chromosome.

Description

Klinefelter syndrome is a condition where one or more extra X chromosomes are present in a male. Boys with this condition appear normal at birth. They enter puberty normally, but by mid-puberty have low levels of testosterone causing small testicles and the inability to make sperm. Affected males may also have learning disabilities and behavior problems such as shyness and

KEY TERMS

Chromosome—A microscopic thread-like structure found within each cell of the body, consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Gonadotrophin—Hormones that stimulate the ovary and testicles.

Testosterone—Hormone produced in the testicles that is involved in male secondary sex characteristics.

immaturity and are at an increased risk for certain health problems.

Genetic profile

Chromosomes are found in the cells in the body. Chromosomes contain genes, structures that tell the body how to grow and develop. Chromosomes are responsible for passing on hereditary traits from parents to child. Chromosomes also determine whether the child will be male or female. Normally, a person has a total of 46 chromosomes in each cell, two of which are responsible for determining that individual's sex. These two sex chromosomes are called X and Y. The combination of these two types of chromosomes determines the sex of a child. Females have two X chromosomes (the XX combination); males have one X and one Y chromosome (the XY combination).

In Klinefelter syndrome, a problem very early in development results in an abnormal number of chromosomes. Most commonly, a male with Klinefelter syndrome will be born with 47 chromosomes in each cell, rather than the normal number of 46. The extra chromosome is an X chromosome. This means that rather than having the normal XY combination, the male has an XXY combination. Because people with Klinefelter syndrome have a Y chromosome, they are all male.

Approximately one-third of all males with Klinefelter syndrome have other chromosome changes involving an extra X chromosome. Mosaic Klinefelter syndrome occurs when some of the cells in the body have an extra X chromosome and the others have normal male chromosomes. These males can have the same or milder symptoms than non-mosaic Klinefelter syndrome. Males with more than one additional extra X chromosome, such as

48,XXXY, are usually more severely affected than males with 47,XXY.

Klinefelter syndrome is not considered an inherited condition. The risk of Klinefelter syndrome reoccurring in another pregnancy is not increased above the general population risk.

Demographics

Klinefelter syndrome is one of the most common chromosomal abnormalities. About one in every 500 to 1,000 males is born with this disorder. Approximately 3% of the infertile male population has Klinefelter syndrome.

Signs and symptoms

The symptoms of Klinefelter syndrome are variable, and not every affected person will have all of the features of the condition. Males with Klinefelter syndrome appear normal at birth and have normal male genitalia. From childhood, males with Klinefelter syndrome are taller than average with long limbs. Approximately 20%–50% have a mild intention tremor, an uncontrolled shaking. Many males with Klinefelter syndrome have poor upper body strength and can be clumsy. Klinefelter syndrome does not cause homosexuality. Approximately one-third of males with Klinefelter syndrome have breast growth, some requiring breast reduction surgery.

Most boys enter puberty normally, though some can be delayed. The Leydig cells in the testicles usually produce testosterone. With Klinefelter syndrome, the Leydig cells fail to work properly, causing the testosterone production to slow. By mid-puberty, testosterone production is decreased to approximately half of normal. This can lead to decreased facial and pubic hair growth. The decreased testosterone also causes an increase in two other hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH). Normally, FSH and LH help the immature sperm cells grow and develop. In Klinefelter syndrome, there are few or no sperm cells. The increased amount of FSH and LH causes hyalinization and fibrosis, the growth of excess fibrous tissue, in the seminiferous tubules, where the sperm are normally located. As a result, the testicles appear smaller and firmer than normal. With rare exception, men with Klinefelter syndrome are infertile because they cannot make sperm.

While it was once believed that all boys with Klinefelter syndrome were intellectually disabled, doctors now know that the disorder can exist without intellectual disability. However, children with Klinefelter syndrome frequently have difficulty with language, including learning to speak, read, and write. Approximately 50% of males with Klinefelter syndrome are dyslexic.

QUESTIONS TO ASK YOUR DOCTOR

- Why does Klinefelter syndrome affect only males?
- Can Klinefelter syndrome be diagnosed by prenatal tests?
- What information can a genetic counselor provide our family about Klinefelter syndrome?
- Will my son be able to live a normal life if he has been diagnosed with Klinefelter syndrome?

Some people with Klinefelter syndrome have difficulty with social skills and tend to be more shy, anxious, or immature than their peers. They can also have poor judgment and do not handle stressful situations well. As a result, they often do not feel comfortable in large social gatherings. Some people with Klinefelter syndrome can also have anxiety, nervousness, and/or depression.

The greater the number of X chromosomes present, the greater the disability. Boys with several extra X chromosomes have distinctive facial features, more severe intellectual disability, deformities of bony structures, and even more disordered development of male features.

Diagnosis

Diagnosis of Klinefelter syndrome is made by examining chromosomes for evidence of more than one X chromosome present in a male. This can be done in pregnancy with prenatal testing such as a chorionic villus sampling or amniocentesis. Chorionic villus sampling is a procedure done early in pregnancy (approximately 10–12 weeks) to obtain a small sample of the placenta for testing. An amniocentesis is done further along in pregnancy (from approximately 16–18 weeks) to obtain a sample of fluid surrounding the baby for testing. Both procedures have a risk of miscarriage. Usually these procedures are done for a reason other than diagnosing Klinefelter syndrome. For example, a prenatal diagnostic procedure may be done on an older woman to determine if her baby has Down syndrome. If the diagnosis of Klinefelter syndrome is suspected in a young boy or adult male, chromosome testing can also be on a small blood or skin sample after birth.

Treatment and management

There is no treatment available to change chromosomal makeup. Children with Klinefelter syndrome may benefit from a speech therapist for speech problems or other educational intervention for learning disabilities.

Testosterone injections started around the time of puberty may help to produce more normal development including more muscle mass, hair growth, and increased sex drive. Testosterone supplementation will not increase testicular size, decrease breast growth, or correct infertility.

Prognosis

While many men with Klinefelter syndrome go on to live normal lives, nearly 100% of these men will be sterile (unable to produce a child). However, a few men with Klinefelter syndrome have fathered a child through the use of assisted fertility services. Males with Klinefelter syndrome have an increased risk of several conditions such as osteoporosis, autoimmune disorders such as lupus and arthritis, diabetes, and both breast and germ cell tumors.

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ORGANIZATIONS

- American Association for Klinefelter Syndrome Information and Support (AAKSIS), c/o Roberta Rappaport. 3796 Ogden Ln., Mundelein, IL 60060, (888) 466-5747, aaksis@sbcglobal.net, <http://www.aaksis.org>
- AXYS, PO Box 872, Pine, CO 80470, (888) 999-9428, info@genetic.org, <http://www.genetic.org>

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Klippel-Feil syndrome

Definition

Individuals with Klippel-Feil syndrome (KFS), also called Klippel-Feil sequence, were originally described as having a classic triad of webbed neck (very short

neck), low hairline, and decreased flexibility of the neck. More commonly, KFS features include abnormal joining or fusion of two or more vertebrae (bones) of the cervical spine (neck bones).

Description

KFS is characterized by the extensive fusion of multiple cervical vertebrae (the uppermost bones of the spine). There may be complete fusion or multiple irregular bony segments in the bones of the upper back (cervical and often upper thoracic spine). Premature and extensive arthritis and osseous (bony) spurring affecting the joints of the spine (facet joints) are common in individuals with KFS.

There are three morphologic classifications of KFS.

- Type 1 exhibits fusion of the lower skull (head) and the first bone of the spine (the first cervical vertebrae [C1]). The second and third spinal bones (cervical vertebrae C2 and C3) are also usually fused together in type 1. The normal cervical spine has seven bones or vertebrae. Normally half of the ability of humans to bend their heads forward (flexion) and backward (extension) occurs in the joints between the base of the skull and the uppermost spinal bone. The other half of the motions of flexion and extension occur in the rest of the upper spine. Therefore, the danger is due to the excessive motion of the neck between the joints that are fused.
- Type 2 has fusion of bones (vertebrae) below the second cervical bone (C2). Type 2 also has an abnormal skull and upper spinal bone connection.
- Type 3 has an open space between two fused segments of spinal bones.

Genetic profile

As of 2015, genetic mutations in *GDF6*, *GDF3*, and *MEOX1* genes had been found to cause KFS. A 2008 study reported mutations at the *GDF6* gene locus in some familial and sporadic cases of KFS. The *GDF6* gene encodes a member of the bone morphogenetic protein (BMP) family and another family of secreted signaling molecules. It is required for normal formation of some bones and joints in the limbs, skull, and axial skeleton. Mutations in this gene are believed to play a role in the development of KFS signs and symptoms.

Demographics

As of 2015, it was estimated that KFS occurred in 1 in 40,000 to 42,000 newborns around the world. The incidence rate of KFS seems to be slightly higher in females. There have been some reports of KFS being more common among infants born with fetal alcohol

KEY TERMS

Degenerative disc disease—Narrowing of the disc space between the spinal bones (vertebrae).

Fetal alcohol syndrome—Syndrome characterized by distinct facial features and varying mental retardation in an infant due to impaired brain development resulting from the mother's consumption of alcohol during pregnancy.

Hypoplasia—Incomplete or underdevelopment of a tissue or organ.

Microtia—Small or underdeveloped ears.

Ossicles—Any of the three bones of the middle ear, including the malleus, incus, and stapes.

Radiculopathy—A bulging of disc material often irritating nearby nerve structures resulting in pain and neurologic symptoms; a clinical situation in which the radicular nerves (nerve roots) are inflamed or compressed. This compression by the bulging disc is referred to as a radiculopathy. This problem tends to occur most commonly in the neck (cervical spine) and low back (lumbar spine).

Scoliosis—An abnormal, side-to-side curvature of the spine.

Torticollis—Twisting of the neck to one side that results in abnormal carriage of the head and is usually caused by muscle spasms. Also called wry neck.

syndrome (FAS) because FAS affects bone development of the fetus.

Signs and symptoms

The first clinical signs are the classic triad of webbed neck, low hairline, and decreased flexibility of the neck. However, the presence of abnormalities of the cervical spine found with x-rays is the hallmark diagnosis. Other signs and symptoms may be found, but vary from person to person.

Some patients may exhibit wry neck or torticollis, which is a twisting of the neck to one side that results in abnormal carriage of the head. The individual may have differences between the two sides of his face, known as facial asymmetry. Patients may also have scoliosis (abnormal curves of the spine).

A variety of miscellaneous abnormalities may clinically manifest themselves in KFS. Deafness occurs in about 30% of the cases. Ear abnormalities such as very small ear lobes (microtia), or deformed bones within the

ear (ossicles), may be present. They may even have a small or absent internal ear.

Abnormalities of the blood vessels such as a missing radial artery in the forearm may decrease the size of the thumbs (thenar hypoplasia). Anomalies of the right subclavian artery (artery under the clavicle or collar bone) have been reported as well as higher incidences of artery anomalies of the upper neck (cervical vertebrae). Anomalies of the genital areas and urinary system are also common.

Individuals diagnosed with KFS frequently have problems with cervical nerves and nerves that go from the neck to the arms and hands. Individuals can have pain that starts in their neck and travels into the arms if the nerve roots coming off of the spinal cord are irritated or pinched.

Diagnosis

KFS is usually diagnosed in early childhood or adolescence. Observing the clinical signs of having the classic triad of webbed neck, low hairline, and limited cervical ranges of motion initiates the diagnosis. When further testing is done, such as x-ray, the diagnosis is confirmed by the fusion of multiple cervical vertebrae.

Treatment and management

If the individual has a very mild case of KFS, then the person can lead a normal life with only minor restrictions. These restrictions, such as avoiding contact sports that would place the neck at risk, are necessary because of the instability of the cervical spine. This is due to the increased motion between the fused cervical vertebrae.

Symptoms, such as pain, that occur with the arthritis and degeneration of the joints may also result. The individuals should be treated with pain medication and possible cervical traction. If neurological symptoms occur, the treatment of choice is fusion of the symptomatic area. However, due to the severe consequences of not having the preventive surgery, surgery is still the treatment most performed.

Prognosis

There have been reports of death following minor trauma because of injuries to the spinal cord in the cervical spine. Most commonly, individuals with Klippel-Feil will develop pain. Some diseases are acquired or occur because of the increased motion of the vertebrae. Degenerative disc disease, or destruction of the cushion-like disc between the vertebrae, is also very common and affects the entire lower cervical spine. Spondylotic osteophytes, or bone spurs in the spine, form as a result of this degeneration. This laying down of new bone may lead to narrowing of the canal through which the spinal cord travels (spinal stenosis).

Because of the instability of the spinal cord, surgery may prevent a dangerous and fatal accident. Pain that originates in the neck and travels into the arms (radiculopathy) is common near the sites of the surgical fusion of vertebrae. One study found that 25% of the individuals who had surgery would have had neurological problems within ten years, therefore requiring additional surgery.

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ORGANIZATIONS

- March of Dimes, 1275 Mamaroneck Ave., White Plains, NY 10605, (914) 997-4488, <http://www.marchofdimes.org>
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), 1 AMS Circle, Bethesda, MD 20892-3675, (301) 495-4484 or (877) 226-4267, (301) 718-6366, NIAMSinfo@mail.nih.gov, <http://www.niams.nih.gov>
- National Institute of Neurological Disorders and Stroke (NINDS), PO Box 5801, Bethesda, MD 20824, (301) 496-5751 or (800) 352-9424, <http://www.ninds.nih.gov>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Klippel-Trenaunay-Weber syndrome

Definition

Klippel-Trenaunay-Weber syndrome (KTWS) is most often defined by the presence of three classic characteristics: vascular abnormalities, prominent varicose veins or darkened skin patches, and limb enlargement.

Description

KTWS was first described by Drs. Klippel and Trenaunay in 1900. The condition is also known by the names Klippel-Trenaunay syndrome (KTS) and angioosteohypertrophy syndrome.

Vascular abnormalities in KTWS may involve the capillary, venous, arterial, and lymphatic systems. Limb enlargement resulting in asymmetry of the limbs is quite common. This usually affects the lower limbs, but occasionally the upper limbs as well. Vein enlargement and varicose veins are also typically a part of KTWS. Other occasional abnormalities in KTWS may involve the fingers and toes, other skin changes, glaucoma, mental delays, seizures, and blood platelet problems.

Genetic profile

In most cases, KTWS occurs by chance alone. There is usually no family history and very little chance of the condition occurring again, even to the same parents. In 2004, researchers reported that abnormalities in the *VG5Q* gene on chromosome 5 were found to cause a susceptibility to KTWS. *VG5Q* is a gene known to be important for blood vessel development, so abnormalities within it might naturally lead to some symptoms of KTWS.

A few families with multiple people who may have KTWS have been noted. One study described a family with three people who were suspected to have KTWS, in three separate generations. Each person had different symptoms seen in KTWS. This family history suggests autosomal dominant inheritance in rare cases of KTWS. In dominant inheritance, an affected individual has a 50% chance of having an affected child with KTWS, regardless of that child's gender. It is also common to see families with histories of the condition in this type of inheritance pattern.

Demographics

KTWS is a relatively uncommon condition that is found worldwide, affecting males and females equally. Additionally, it appears to affect people of all ages, though the average age that children may come for medical care is four years.

Signs and symptoms

Vascular abnormalities

Problems may occur as a result of an abnormal communication between a group of blood vessels and the skin. An abnormal grouping of blood vessels may reach the skin, causing the appearance of a large hemangioma on the skin. Additionally, the blood vessel walls may enlarge or swell, causing large, blood-filled spaces within the

body. Internal bleeding can be a serious complication in some cases. There may also be swelling or masses of tissue from problems in the lymphatic system. These may disturb neighboring tissues and internal organs.

Veins and arteries may join abnormally, which can cause an improper flow of blood between the body's vein and artery systems. The deep veins can be incorrectly developed, sometimes being smaller than usual or even duplicated. Ultimately, this can disrupt the proper circulation of blood between various parts of the body.

Varicose veins are common in KTWS. People may have prominent veins that involve their feet or entire legs.

The lymphatic system, meant to help blood and fluid circulate, can be problematic in those with KTWS. Lymphatic fluid can collect abnormally, causing an enlargement and swelling of surrounding tissues. Smaller swellings can occur in various parts of the body like the neck, armpits, or other locations where the lymph nodes are naturally located.

Skin abnormalities

Abnormal capillary formations can cause dark patches on the skin, which look similar to a hemangioma. These are usually reddish in color and can be large. They are most often seen on the lower limbs, but in 17%–21% of people with KTWS the entire limb or one side of the body is affected. The dark skin patches usually have an irregular and linear border to them. When seen on the torso of someone's body, they do not usually cross from the left to right sides. Other skin abnormalities can include smaller streaks and patches of dark skin.

Limb abnormalities

Limb enlargement is a very common sign of KTWS. In the vast majority of people, one leg is larger than the other. In others, an arm or a combination of both the arm and leg are affected. About 70% of people with KTWS have lengthening of an extremity, and an increase in thickness occurs in at least 50%.

Enlargement and vascular abnormalities usually occur together in the same limb. The enlargement of the limbs is presumed to be due to a combination of factors: underlying bone overgrowth, lymphatic swelling, muscle overgrowth, and thickened skin.

Other limb abnormalities can include enlargement of the fingers or toes, webbing between these digits, extra digits, or missing digits.

Other signs of KTWS

Glaucoma can be seen in KTWS, either first appearing at birth or in early childhood. Seizures can be

part of the condition and, rarely, intellectual disability as well.

Individuals with extensive vein or lymphatic abnormalities can develop a blood-clotting problem in which their platelet count is lower than usual. This is sometimes incorrectly referred to as the Kasabach-Merritt syndrome, which actually occurs when the blood platelet count is extremely low.

Diagnosis

As of early 2015, there was no clinical genetic testing available for KTWS. Research taking place in the United States and Belgium offers screening of genes that may be implicated in the condition, but it is only offered as part of a research study. Most people with KTWS are diagnosed because of signs and symptoms they have.

Children may first come to medical attention for KTWS at birth or shortly afterward because they are born with dark patches on their skin or a limb that is larger than the other. A careful evaluation by a team of physicians, including a pediatrician, medical geneticist, and a dermatologist, can help to identify whether the diagnosis is KTWS.

KTWS has occasionally been suspected during a pregnancy in cases where significant limb enlargement was seen on a prenatal ultrasound. One study reported a case from 1999 where a prenatal ultrasound showed that the developing baby had limb and digit enlargement with increased blood flow and fluid-filled sacs.

In this case, suspecting KTWS helped to determine the best type of delivery for the baby and the mother. The baby was born by a Caesarean section, which helped reduce the complications to him and his mother from his limb enlargement and fluid collections. When the baby was born, he was found to have large red skin patches on the affected limb, and KTWS was highly suspected.

There are symptoms of KTWS that overlap with other conditions. Sturge-Weber syndrome usually has dark skin patches and vascular abnormalities, glaucoma, seizures, and mental delays. However, significant limb enlargement is not usually a part of Sturge-Weber syndrome.

Parkes-Weber syndrome involves vascular abnormalities, but these differ from those seen in KTWS. For example, Parkes-Weber syndrome does not usually involve the lymphatic system. Additionally, Parkes-Weber syndrome can have symptoms that affect the heart, which are not typically seen in KTWS.

Treatment and management

There is no known cure for KTWS. However, treatments are available to help with some symptoms of the condition. These typically involve a large team of

specialists that may include a pediatrician, vascular surgeon, orthopedist, orthopedic surgeon, hematologist, medical geneticist, genetic counselor, ophthalmologist, neurologist, social worker, and therapist.

Custom-made compression stockings can be worn to reduce swelling, create a barrier for minor trauma, and help blood drain from an enlarged body part. Parents can find it a challenge to encourage a young child to wear such stockings, but they may work well for older children and adults. Compression stockings do not usually permanently reduce the size of the enlarged limb.

Swelling can also be reduced with manual drainage, a gentle massage of the affected area. A physical therapist, occupational therapist, or massage therapist typically performs this. Air-driven pumps can also help reduce swelling. The affected limb is covered in an air-filled plastic sleeve, which places gentle pressure to stimulate fluid movement from the swollen limb.

Some people have seen reduction in the redness of their skin patches through laser treatments using pulses of light. It may require a series of these treatments, and skin changes may still be noticeable or even unchanged after the treatment is finished.

If there is increased bleeding or a low amount of platelets is suspected, blood testing can check the platelet level. This can be carefully monitored through a series of blood tests, and in some cases a blood transfusion may be required. If a patient has internal bleeding that causes damage to some internal organs or tissues, surgery to control this bleeding or remove affected tissues may be needed.

In some cases, bacterial infections can warrant the use of antibiotics to stop the infection.

Ultrasounds, x-rays, magnetic resonance imaging (MRI) scans, lymphoscintigraphy, and angiography can help obtain details about limb enlargement. These all attempt to gain information about the specific tissues or organs affected by limb enlargement and abnormal blood flow.

Surgical treatments may be needed for some with KTWS, though the goal is often to avoid this whenever possible. Abnormal blood vessels may need to be repaired by removing them or rejoining them. Varicose veins may need to be removed, but these can sometimes return even after treatment. Women with KTWS who are pregnant may have bleeding complications depending on the location of any vascular abnormalities, and should be monitored closely during their pregnancies.

Minor leg length differences can sometimes be treated with a shoe insert that is worn on the foot of the shorter leg. If a leg causes a significant asymmetry, a procedure called epiphysiodesis may be necessary. This

KEY TERMS

Angiography—Procedure that shows the system of blood vessels and the blood flow in a portion of the body. Requires an injection of dye to help see the vessels.

Arterial—Term used to describe an artery or the entire system of arteries.

Caesarean section—Surgical method to deliver a baby that requires making an incision in the mother's abdomen to remove the infant.

Capillary—Very narrow tube that carries liquid like blood or lymphatic fluid.

Glaucoma—An eye disease that usually involves high pressure in the eye, which can lead to vision problems or blindness if left untreated.

Hemangioma—Abnormality resulting from a collection of vascular tissue like blood vessels, which can cause a dark reddish patch on the skin.

Lymphoscintigraphy—Procedure that helps to look at the lymph nodes in the body. Requires an injection of radioactive material to help see the lymph nodes and lymphatic system.

Magnetic resonance imaging (MRI) scan—Procedure that shows internal organs and tissues of the body using magnetic fields and signals.

Platelet—Cell in the blood that helps with clotting.

Ultrasound—Procedure that shows internal organs and tissues of the body using sound waves.

Venous—Term used to describe a vein or the entire system of veins.

X-ray—Procedure that shows internal organs and tissues of the body using radiation.

surgical treatment can stop bone growth in an affected leg, but requires destroying a portion of the underlying bone to do it. It must be timed well to coordinate with the normal bone growth that occurs in childhood and adolescence.

In rare cases, limb or digit amputation may be needed to improve function for a person with KTWS. This is typically done when other helpful options have not been successful.

Seizures can occur in KTWS, and these may be treated with antiseizure medications. Glaucoma may be identified from a careful eye examination and treated with eye drops, pills, ointments, or laser therapy to reduce the pressure in the eye and maintain vision.

Mental retardation is rare in KTWS, but may be assessed by a child development team or early childhood program. Extra assistance is sometimes available through early intervention programs and special education in schools. Social workers are useful to connect families to helpful resources.

A psychologist, genetic counselor, or therapist can be helpful for some with KTWS. Living with visible skin changes can be difficult, and some may find it easier to talk to an objective person or to talk with other affected families in a support group.

Prognosis

Prognosis can vary widely in KTWS. Complications, especially the vascular abnormalities, can be serious and cause death if symptoms are severe enough and treatment is not successful. The exact expected lifespan for the average person with KTWS is unknown, but is highly dependent on the symptoms experienced.

The best way to improve one's prognosis is to utilize a team of specialists that are familiar with KTWS. Through early identification and monitoring of symptoms, treatments can be started sooner and appropriate medical decisions can be made to help the individual and the family.

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ORGANIZATIONS

Klippel-Trenaunay Syndrome Support Group, (513) 722-7724, support@k-t.org, <http://k-t.org>
National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

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Kniest dysplasia

Definition

Kniest dysplasia is a form of dwarfism caused by a mutation in gene *COL2A1*, which plays a role in the normal formation of collagen tissue needed for growth.

Description

Kniest dysplasia is a rare form of congenital dwarfism. It is caused by mutations in the gene responsible for the formation of the eye's vitreous body (the gel portion inside the eyeball) and cartilage. As the human skeleton is formed, it is largely made of cartilage; therefore, a lack of cartilage seriously delays the growth of bone, as well as formation of the nose, ears, and other connective tissues that support the body.

Intelligence is not usually affected by Kniest dysplasia.

Genetic profile

Kniest dysplasia is inherited through an autosomal dominant pattern, which means that a child may inherit the disorder even if only one parent has the gene for it. The disorder is caused by mutations in the *COL2A1* gene, which is involved in the formation of collagen needed to make the gel within the eye (vitreous body) and cartilage.

Demographics

Kniest dysplasia is rare, but the exact incidence of the disorder is unknown.

Risk factors

A person is at risk for inheriting Kniest dysplasia if one parent carries the gene mutation; however, most cases develop with a new mutation that is not carried by either parent. A person who has Kniest dysplasia has a 50% chance of having a child with the disorder.

Because the ligaments are not held as tightly as in an unaffected person, the neck is vulnerable to injury in activities such as sports or in the event of an automobile accident.

Signs and symptoms

Signs that a person has Kniest dysplasia may include:

- Height. Short stature, 42–58 inches in adulthood
- Limbs. Short arms and legs with bones that are broad at either end and more narrow in the middle, sometimes referred to as “dumbbell-shaped”

KEY TERMS

Myopia—Nearsightedness.

Trachea—Also called windpipe; a tube in the upper airway.

- Fingers. Long with knob-like protrusions
- Feet. Clubfoot may be present
- Joints. Unusually large, painful, and unable to move freely
- Spine. Kyphoscoliosis (rounded back that curves to one side) and flattened vertebrae
- Face. Round, flat with eyes that bulge and are wide set
- Mouth. Cleft palate may be present at birth
- Respiratory. Infants may have difficulty breathing due to a weak trachea
- Ears. Frequent ear infections
- Eyes. Severe nearsightedness and retinal detachment

Diagnosis

Examination

On examination, a baby may exhibit some of the characteristics described such as clubfoot. Most infants will show slow growth compared to other children their age.

Tests

An x-ray examination may reveal the characteristic Swiss cheese pattern of cartilage in people with Kniest dysplasia.

Procedures

Kniest dysplasia may be diagnosed in pregnancy via chorionic villus sampling (CVS) or amniocentesis. The disorder may also appear in a sonogram performed toward the latter part of the second trimester of pregnancy.

Treatment and management

Traditional

People with Kniest dysplasia must be monitored medically throughout their lives because the disorder leaves them vulnerable to many medical conditions. In some cases, curvature of the spine is corrected through spinal fusion surgery. Eye exams are an important part of routine care, and the ophthalmologist will check these individuals for detached retina, cataracts (which may develop at an early age), or worsening myopia. Hearing

QUESTIONS TO ASK YOUR DOCTOR

- What are the major medical concerns my child will face?
- What supportive measures can be undertaken to enhance the quality of life for my child?

should be monitored. Some people with Kniest dysplasia require ear tube insertion to deal with the frequent ear infections.

Surgery poses a special risk to individuals with Kniest dysplasia because their loose ligaments make them more susceptible to neck injury. Additionally, their reduced lung capacity and airway stability add further risk. It is important for a thorough anesthesia evaluation to be performed prior to any procedure requiring anesthesia.

An orthopedist will provide routine care to people with Kniest dysplasia because of complications in the joints, such as the hips and knees, related to impaired collagen development. Hip replacements are sometimes performed to treat extensive arthritis. Kniest dysplasia cannot be prevented; however, maintaining a schedule of medical monitoring may catch some of its complications, such as retinal detachment, at an earlier stage. People with Kniest dysplasia will most likely require regular visits to primary care providers and to an ophthalmologist, orthopedist, and rheumatologist.

Home remedies

Because of the looseness of the ligaments and poorly developed cartilage, individuals with Kniest dysplasia must approach any athletic or physical activity with extreme caution.

Prognosis

Kniest dysplasia affects a variety of body systems, and the effects often worsen as the individual ages. Joints may become more swollen over time. The spine may become more curved. Problems with hearing and vision may also worsen; retinal detachment may lead to blindness.

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ORGANIZATIONS

- Human Growth Foundation, 997 Glencove Ave., Suite 5, Glenhead, NY 11545, (800) 451-6434, hgf1@hgfound.org, <http://www.hgfound.org>
- MAGIC Foundation, 6645 W. North Ave., Oak Park, IL 60302, (708) 383-0808 or (800) 362-4423, ContactUs@magicfoundation.org, <http://www.magicfoundation.org>

Rhonda Cloos, RN

Knobloch syndrome see **Encephalocele**

Konigsmark syndrome see **Hereditary hearing loss and deafness**

Krabbe disease

Definition

Krabbe disease, also called globoid cell leukodystrophy, is an inherited enzyme deficiency that leads to the loss of myelin, the substance that wraps nerve cells and speeds cell communication. Most affected individuals start to show symptoms before six months of age and have progressive loss of mental and motor function. Death occurs at an average age of 13 months. Other less-common forms exist with onset in later childhood or adulthood.

Description

Myelin insulates and protects the nerves in the central and peripheral nervous system. It is essential for efficient nerve cell communication (signals) and body functions such as walking, talking, coordination, and thinking. As nerves grow, myelin is constantly being built, broken down, recycled, and rebuilt. Enzymes break down, or metabolize, fats, carbohydrates, and proteins in the body including the components of myelin.

Individuals with Krabbe disease are lacking the enzyme galactosylceramidase (GALC), which metabolizes a myelin fat component called galactosylceramide and its by-product, psychosine. Without GALC, these substances are not metabolized and accumulate in large globoid cells. For this reason, Krabbe disease is also called globoid cell leukodystrophy. Accumulation of galactosylceramide and psychosine is toxic and leads to the loss of myelin-producing cells and myelin itself. This results in impaired nerve function and the gradual loss of developmental skills such as walking and talking.

Risk factors

People at risk for Krabbe disease are those who have a family history of the condition.

Genetic profile

Krabbe disease is an autosomal recessive disorder. Affected individuals have two nonfunctional copies of the *GALC* gene. Parents of an affected child are healthy carriers and therefore have one normal *GALC* gene and one nonfunctional *GALC* gene. When both parents are carriers, each child has a 25% chance to inherit Krabbe disease, a 50% chance to be a carrier, and a 25% chance to have two normal *GALC* genes. The risk is the same for males and females. Brothers and sisters of an affected child with Krabbe disease have a 66% chance of being a carrier.

The *GALC* gene is located on chromosome 14. Over 70 mutations (gene alterations) known to cause Krabbe disease have been identified. One specific *GALC* gene deletion accounts for 45% of disease-causing mutations in those with European ancestry and 35% of disease-causing mutations in those with Mexican ancestry.

Demographics

Approximately 1 in every 100,000 infants born in the United States and Europe will develop Krabbe disease. A person with no family history of the condition has a 1 in 150 chance of being a carrier. Krabbe disease occurs in all countries and ethnic groups, but no cases have been reported in the Ashkenazi Jewish population. A Druze community in Northern Israel and two Moslem Arab villages near Jerusalem have an unusually high incidence of Krabbe disease. In these areas, about one person in every six is a carrier.

Signs and symptoms

Ninety percent of individuals with Krabbe disease have the infantile type. These infants usually have normal development in the first few months of life. Before six months of age, they become irritable, stiff, and rigid.

They may have trouble eating and may have seizures. Development regresses leading to loss of mental and muscle function. They also lose the ability to see and hear. In the end stages, these children usually cannot move, talk, or eat without a feeding tube.

Ten percent of individuals with Krabbe disease have juvenile or adult type. Children with juvenile type begin having symptoms between three and ten years of age. They gradually lose the ability to walk and think. They may also have paralysis and vision loss. Their symptoms usually progress slower than in the infantile type. Adult Krabbe disease has onset at any time after age ten. Symptoms are more general including weakness, difficulty walking, vision loss, and diminished mental abilities.

Diagnosis

There are many tests that can be performed on an individual with symptoms of Krabbe disease. The most specific test is done by measuring the level of GALC enzyme activity in blood cells or skin cells. A person with Krabbe disease has GALC activity levels that are 0% to 5% of the normal amount. Individuals with later onset Krabbe disease may have more variable GALC activity levels. This testing is done in specialized laboratories that have experience with this disease.

The fluid of the brain and spinal cord (cerebrospinal fluid) can also be tested to measure the amount of protein. This fluid usually contains very little protein, but the protein level is elevated in infantile Krabbe disease. Nerve-conduction velocity tests can be performed to measure the speed at which the nerve cells transmit their signals. Individuals with Krabbe disease will have slowed nerve conduction. Brain imaging studies such as computerized tomography (CT scan) and magnetic resonance imaging (MRI) are used to get pictures from inside the brain. These pictures will show loss of myelin in individuals with Krabbe disease.

DNA testing for *GALC* mutations is not generally used to make a diagnosis in someone with symptoms, but it can be performed after diagnosis. If an affected person has identifiable known mutations, other family members can be offered DNA testing to find out if they are carriers. This is helpful since the GALC enzyme test is not always accurate in identifying healthy carriers of Krabbe disease.

If an unborn baby is at risk to inherit Krabbe disease, prenatal diagnosis is available. Fetal tissue can be obtained through chorionic villus sampling (CVS) or amniocentesis. Cells obtained from either procedure can be used to measure GALC enzyme activity levels. If both parents have identified known *GALC* gene mutations, DNA testing can also be performed on the fetal cells to

QUESTIONS TO ASK YOUR DOCTOR

- What kind of nervous system damage has Krabbe disease caused?
- What are the treatment options?
- Is stem cell transplant possible?
- What are the likely outcomes?

determine if the fetus inherited one, two, or no *GALC* gene mutations.

Some centers offer preimplantation diagnosis if both parents have known *GALC* gene mutations. In vitro fertilization (IVF) is used to create embryos in the laboratory. DNA testing is performed on one or two cells taken from the early embryo. Only embryos that did not inherit Krabbe disease are implanted into the mother's womb. This is an option for parents who want a biological child but do not wish to face the possibility of terminating an affected pregnancy.

Treatment and management

The treatment team for a child with Krabbe disease should include a neurologist, general surgeon to place certain types of feeding tubes, and a hematologist if bone marrow or stem cell transplants are being considered. Physical and occupational therapists can help plan for daily care of the child and provide exercises to decrease muscle rigidity. Genetic testing is recommended for persons with a family history of Krabbe disease who are planning to have children.

Traditional

Once a child with infantile Krabbe disease starts to show symptoms, there is little effective treatment. Supportive care can be given to keep the child as comfortable as possible and to counteract the rigid muscle tone. Medications can be given to control seizures. When a child can no longer eat normally, feeding tubes can be placed to provide nourishment.

Alternative

Affected children who are diagnosed before developing symptoms (such as through prenatal diagnosis) can undergo bone marrow transplant or stem cell transplant. The goal of these procedures is to destroy the bone marrow which produces the blood and immune system cells. After the destruction of the bone marrow, cells from a healthy donor are injected. If successful, the healthy cells travel to the bone

marrow and reproduce. Some children have received these transplants and had a slowing of their symptoms' progression or even improvement of their symptoms. However, these procedures are not always successful, and research is being done in order to reduce complications.

Scientists are also researching gene therapy for Krabbe disease. This involves introducing a normal *GALC* gene into the cells of the affected child. The goal is for the cells to integrate the new *GALC* gene into its DNA and copy it, producing functional *GALC* enzyme. This is still in research stages and is not being performed clinically.

Prognosis

Prognosis for infantile and juvenile Krabbe disease is very poor. Individuals with infantile type usually die at an average age of 13 months. Death usually occurs within a year after the child shows symptoms and is diagnosed. Children with juvenile type may survive longer after diagnosis but death usually occurs within a few years. Adult Krabbe disease is more variable and difficult to predict, but death usually occurs two to seven years after diagnosis.

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ORGANIZATIONS

Hunter's Hope Foundation, 6368 W. Quaker St., PO Box 643, Orchard Park, NY 14127, (716) 667-1200, info@huntershope.org, <http://www.huntershope.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, <http://rarediseases.org>

United Leukodystrophy Foundation, 224 N. Second St., Suite 2, DeKalb, IL 60115, (800) 728-5483, office@ulf.org, <http://www.ulf.org>

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L1 syndrome

Definition

L1 syndrome, formerly known as X-linked hydrocephaly, is a genetic disorder resulting in hydrocephaly. Hydrocephaly is the accumulation of cerebrospinal fluid (CSF) in fluid-filled cavities, called ventricles, that are located deep in the core of the brain. This disorder results from an X-linked mutation causing an alteration in the L1 cell adhesion molecule (L1CAM).

Description

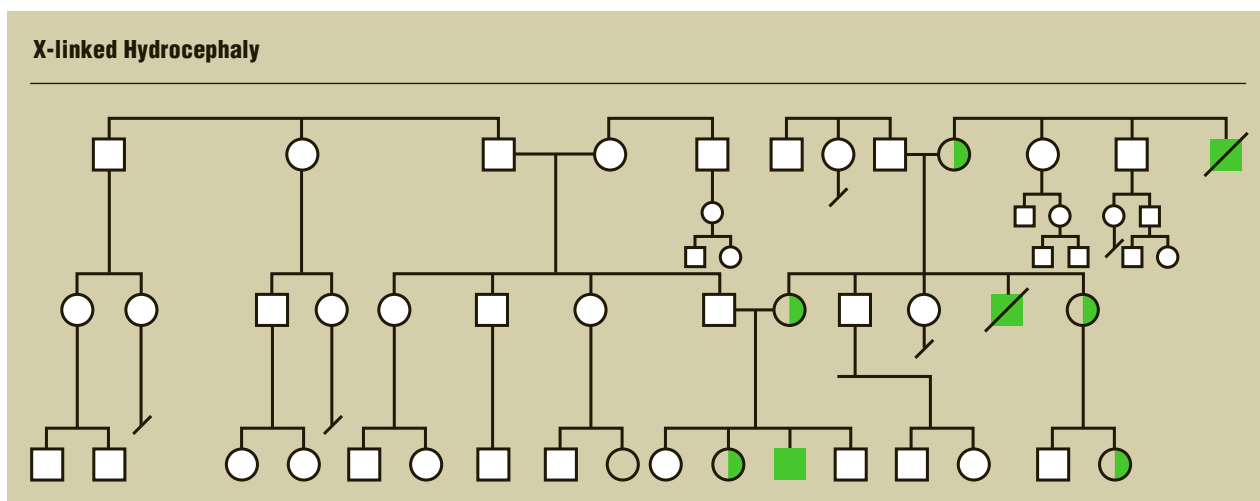
Cell adhesion molecules (CAMs) provide the traffic signals that guide the cells of developing organs to migrate to their proper places and make the appropriate connections with the cells with which they interact. The L1CAM protein is embedded in the membrane of nerve cell axons, which are projections from the nerve cell body that carry impulses to sometimes distant targets. As a developing axon grows toward its target, its leading end is capped by a growth cone similar in function to that of a plant root. The growth cone of a developing axon is rich in L1CAM. The L1CAM protein has a large, complex extracellular domain (portion of the protein outside the nerve cell), a transmembrane domain within the nerve cell membrane, and a small intracellular domain (portion inside the nerve cell). The extracellular domain acts as a feeler and binds to CAMs that are either on the surface of other cells or floating in the extracellular fluid. The binding of the L1CAM protein to various CAMs in its environment sends signals into the nerve cell that direct the projecting axon to grow to the appropriate length, follow the course required for it to reach its target, and stop when appropriate.

The L1CAM protein is critical for proper development of several long fiber tracts in the forebrain. These include the corpus callosum, which is a thick fiber bridge that connects the left and right cerebral hemispheres, and the cerebrospinal tract, which extends from the motor control region of the cerebral cortex down to the spinal cord.

The developing axon often extends many cell diameters away from the cell body and must interact with CAMs from many different sources to ensure that it follows the correct route to its target. The complex extracellular domain of the L1CAM protein interacts with a variety of CAMs in the environment to serve several important functions. Because of the many functions L1CAM serves, the specific brain changes and functional handicaps that are seen in any individual patient with an L1CAM mutation depend on which of L1CAM's functions are lost and which are spared by the specific mutation that occurs in the *L1CAM* gene. Most families have their own unique L1CAM mutation. Some mutations abolish all of L1CAM's functions, while others change only a small piece of the L1CAM protein. Therefore, there is marked variability between patients in terms of which brain structures are most affected and what the primary physical and behavioral symptoms will be. Because of this variability, patients with different L1CAM mutations have been given diagnoses such as X-linked hydrocephaly (XLH), X-linked spastic paraplegia type 1 (SPG1), hydrocephaly with stenosis of the aqueduct of Sylvius (HSAS), X-linked agenesis of the corpus callosum (XLACC), and MASA syndrome (mental impairment, aphasia, shuffling gait, adducted thumbs). Because these patients all presented with such different combinations of brain changes and functional handicaps, it was originally thought that these were all distinct disorders with different biological causes. An effort has been made to unite these disorders under the general heading "L1CAM spectrum" to reflect the fact that these are not distinct disorders, but merely alternative possible consequences of L1CAM mutations.

Genetic profile

The *L1CAM* gene is located close to the end of the long arm of the X chromosome, in the band referred to as Xq28. Since the *L1CAM* gene is on the X chromosome, usually only males are affected. This is because females have two X chromosomes, while males only have one. In



X-linked hydrocephaly: pedigree analysis chart (Gale)

a female, if one X chromosome has an *L1CAM* mutation on it, the nonmutated *L1CAM* gene on the other X chromosome can usually provide enough good L1CAM protein to support normal brain development. Males, on the other hand, having only one X chromosome, cannot compensate for an X-linked gene mutation.

The inheritance pattern for L1CAM spectrum disorders follows the typical X-linked inheritance pattern. Males are usually the only ones affected, and most females who carry L1CAM mutations are unaffected. There may be several affected brothers in a single family. In addition, in a family in which the L1CAM mutation has been passed through several generations, the normally developed mothers of affected males may have affected brothers, or the normally developed sisters of affected males may have affected sons. If a female carries a mutation in L1CAM, she has a 50% chance of passing the mutation to each of her children. Therefore, approximately half her sons will be affected, and approximately half her daughters will be carriers. There is no known case in which an affected male has reproduced.

L1CAM mutations exhibit 100% penetrance, meaning that any male who has the L1CAM mutation will be affected, albeit with varying degrees of severity. This contrasts with some other disorders, in which some family members are unaffected despite having the same gene mutation that has been seen in other affected family members.

Demographics

The incidence of hydrocephaly from all causes is approximately 1 in 2,000 live births in the general population. The X-linked form is thought to account for approximately 5% of the total cases of hydrocephaly, or approximately 1 in 30,000 males. In very rare cases a

female may be affected, usually mildly. There are no systematic data comparing the incidence of L1CAM spectrum disorders in different races.

Signs and symptoms

Most patients with mutations in L1CAM exhibit intellectual disability, the degree of which can vary from mild to severe. The vast majority also exhibit hydrocephaly, which can be mild and not require any medical intervention, or severe enough to be life-threatening. The most severe cases of hydrocephaly are associated with stenosis (narrowing or pinching closed) of the aqueduct of Sylvius. The aqueduct of Sylvius (also called the cerebral aqueduct) is a narrow channel connecting the third ventricle, located deep in the midbrain, to the fourth ventricle, located underneath the cerebellum in the posterior part of the brain. The brain's cerebrospinal fluid (CSF) is made by cells lining the first two ventricles, called the lateral ventricles, which are located in the forebrain. The CSF normally flows from the first two ventricles, through the third ventricle, then into the fourth ventricle, before flowing out of the brain. Stenosis of the aqueduct of Sylvius stops the outflow of CSF and causes an accumulation of fluid and pressure, primarily in the first two ventricles. Since there is no mechanism to stop CSF production in the lateral ventricles, this form of hydrocephaly is progressive. The pressure can become so great that it stretches the developing skull bones, which are still not fully hardened, resulting in the child having a head that is visibly enlarged (macrocephaly). In the process, the brain tissue is pressed against the skull, with predictably devastating effects on brain function. Many of the more severely hydrocephalic patients are either stillborn or die within one year of birth.

KEY TERMS

Adducted thumbs—Thumbs clasped across the palm.

Aphasia—Impairment of the ability to comprehend or communicate through speech, writing, or signs due to brain dysfunctions.

Brain ventricles—A set of four connected cavities that are located deep in the core of the brain. Cerebrospinal fluid (CSF) is made by cells lining the walls of the first two ventricles, then flows through the third, then through the fourth ventricle, before flowing out of the brain. The fluid-filled cavities provide mechanical cushion for the brain, and the CSF provides nutrients to, and carries metabolic wastes away from, the cells of the brain.

Cell adhesion molecule—Any one of several thousand proteins that together control the cell-to-cell communication that must take place in order for cells to migrate to their proper places, develop into the proper types of cells, and make the appropriate connections with other cells.

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides

communications between the right and left cerebral hemispheres.

Corticospinal tract—A bundle of long nerve fibers that runs from the motor control region of the cerebral cortex to the spinal cord, where it connects to nerves that control movement in the legs.

Hydrocephaly—An increase of cerebrospinal fluid in the brain.

Macrocephaly—An unusually large head.

Penetrance—The frequency with which a heritable trait is manifested by individuals carrying the principal gene or genes conditioning it, usually expressed as a percentage.

Spastic paraplegia—Inability to walk, due to lack of proper neural control over the leg muscles.

Stenosis—The constricting or narrowing of an opening or passageway.

Ventriculoperitoneal shunt—A tube equipped with a low pressure valve, one end of which is inserted into the lateral ventricles, the other end of which is routed into the peritoneum, or abdominal cavity.

X-linked—A genetic trait that is carried on the X chromosome.

Approximately 80% of patients with *L1CAM* mutations exhibit adducted thumbs (clasped across the palm). A smaller percentage exhibit aphasia (lack of speech) or problems with leg control that range from walking with a shuffling gait to spastic paraplegia that leaves them unable to walk at all.

The most common finding in brain imaging studies is the absence (agenesis) or underdevelopment (hypoplasia) of the corpus callosum. The corpus callosum is a large fiber tract that projects between the left and right hemispheres of the brain and enables information to be transferred from one hemisphere to the other. It is uncertain whether the abnormalities in the corpus callosum are an important cause of these patients' intellectual disability. It is most likely that the pressure exerted on the developing brain tissue by the hydrocephaly is a more consistent and important cause of the intellectual disability seen in these patients. Another brain structure seen to be underdeveloped in some patients with *L1CAM* mutations is the corticospinal tract. The corticospinal tract begins in the motor control region of the cerebral cortex and runs downward to connect with the spinal cord neurons that control the legs. Abnormal development of the corticospinal tract is

probably the cause of the shuffling gait/spastic paraplegia seen in some patients with *L1CAM* mutations.

Diagnosis

In the more severely hydrocephalic patients, hydrocephaly can be seen by ultrasound at 20 weeks gestation, or approximately halfway through the fetal period. For less severely affected patients, some degree of hydrocephaly is usually noted within a year after birth, along with a general developmental delay. These babies do not roll over, sit up, or reach for objects as early as babies typically do. In rarer cases, some mildly affected patients are not diagnosed until an age at which speech problems or problems with their walking gait can be observed. Adducted thumbs, when present, are noticeable from birth or sometimes upon ultrasound analysis.

Genetic testing involves a search for mutations in the *L1CAM* gene in patients with *L1CAM* spectrum disorders. The sequence of the *L1CAM* gene from the affected patient is compared to the normal *L1CAM* sequence. DNA is usually obtained from a blood sample for postnatal diagnosis. For prenatal diagnosis, DNA can be

QUESTIONS TO ASK YOUR DOCTOR

- How beneficial will modes of treatment such as physical, occupational, or speech therapy be for my child?
- What are the risks and benefits of shunting?
- What is the level of severity of my child's case of L1 syndrome?
- Which family members should undergo genetic testing?

extracted from amniotic fluid cells obtained by amniocentesis, or from chorionic villus sampling (CVS).

Treatment and management

In the most severely hydrocephalic cases, the baby must be delivered by cesarian section because the head has grown too large by the end of the pregnancy for the baby to be delivered vaginally. For the more severely affected patients, a ventriculoperitoneal shunt can be used to reduce the pressure inside the brain. The shunt is a tube inserted into the lateral ventricles that allows the CSF to drain into the peritoneum, or abdominal cavity. This provides a means for the CSF to flow out of the brain in cases of HSAS in which the aqueduct of Sylvius has been closed and the CSF cannot flow out of the brain by the usual channel. Shunting markedly reduces the pressure on the brain and has saved many patients' lives. However, shunting will not prevent these patients from having intellectual disability or other L1CAM spectrum features.

Other methods for managing cases of L1CAM spectrum disorders are focused on the specific features the individual patient exhibits. Special education is almost always necessary, with the specific program designed to accommodate the degree of cognitive disability seen in the individual patient. Physical therapy and mechanical aids such as walkers can be used to help patients with milder degrees of spastic paraplegia. Speech therapy has also benefited some of the less severely aphasic patients. There is generally little improvement when these therapies are applied to more severely affected patients.

Prognosis

The prognosis for patients with L1CAM mutations is highly variable. The most severe cases of L1CAM mutations involve fetal demise, presumably because of the pressure exerted on the developing brain by the hydrocephaly. However, in less severe cases, the lifespan is

determined primarily by general health and care factors. A number of patients with less severe L1CAM spectrum disorders have lived at least into their 50s.

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ORGANIZATIONS

- Hydrocephalus Association, 4340 East West Hwy., Suite 905, Bethesda, MD 20814-4447, (301) 202-3811 or (888) 598-3789, (301) 202-3813, info@hydroassoc.org, <http://www.hydroassoc.org>
- National Hydrocephalus Foundation, 12413 Centralia Rd., Lakewood, CA 90715-1653, (562) 924-6666 or (888) 857-3434, info@nhfonline.org, <http://nhfonline.org>
- National Institute of Neurological Disorders and Stroke, PO Box 5801, Bethesda, MD 20824, (301) 496-5751 or (800) 352-9424, <http://www.ninds.nih.gov>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06801, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>
- Pediatric Hydrocephalus Foundation, 66 Caroline St., 2nd Floor, Woodbridge, NJ 07095, (732) 634-1283, (847) 589-1250, <http://www.hydrocephaluskids.org/wordpress>

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Lamellar ichthyosis see **Ichthyosis**

Langer-Saldino achondrogenesis

Definition

Langer-Saldino achondrogenesis is a rare genetic disorder that affects the development of bones and

connective tissues (fibrous tissues, such as tendons and cartilage that support body tissues and organs). Although it is a genetic disorder, it is not inherited. This condition is often fatal in infancy. Typical symptoms include a small body with short limbs and poor lung development.

Description

Achondrogenesis is a collection of disorders that affect the development of bone and connective tissues. There are at least three types of achondrogenesis:

- Houston-Harris achondrogenesis, also known as type 1A
- Parenti-Fraccaro achondrogenesis, also known as type 1B
- Langer-Saldino achondrogenesis, also known as type II (or type 2)

Symptoms of the three types are somewhat similar, and all three result from genetic mutations.

Mutations in the *COL2A1* (collagen, type II, alpha 1) gene are associated with Langer-Saldino achondrogenesis. Mutations in this gene affect the body's ability to make a type of collagen. Collagen is a fibrous protein that is the main constituent of bones and connective tissues. Specifically, this gene produces type II collagen, which is the primary protein in cartilage. Type II collagen is necessary for the development of bones and connective tissues. In Langer-Saldino achondrogenesis, type II collagen protein is not formed, bones and connective tissues do not develop as they should, and the affected individual has a range of skeletal and other problems.

Langer-Saldino achondrogenesis is fatal. The presence of a mutated *COL2A1* gene may result in stillbirth. Infants who are born with the disorder often have hydrops fetalis, a condition in which massive fluid accumulation causes the limbs to swell and makes breathing difficult. Babies with hydrops fetalis often die. Those rare children who survive infancy typically live no longer than their early teens.

Symptoms of Langer-Saldino achondrogenesis

Short trunk
Extremely short limbs
Short neck supporting a comparatively large head
Distinctive facial features, including a small chin and large forehead
Narrow chest with short ribs
Underdeveloped lungs
Hydrops fetalis
Incomplete bone development in the backbone and in the hips
Cleft palate in some cases
Large abdomen

(Gale)

KEY TERMS

Amino acids—Building blocks of proteins.

Collagen—Fibrous protein that is the main constituent of bones and connective tissues.

Connective tissues—Fibrous tissues, such as tendons and cartilage that support body tissues and organs.

Hydrops fetalis—A condition in which massive fluid accumulation causes the limbs to swell and breathing to be difficult.

Hypochondrogenesis—A condition similar to Langer-Saldino achondrogenesis caused by different mutations in the *COL2A1* gene.

Micromelia—Extremely short arms and legs.

Procollagen—A collagen precursor formed by the twisting together of three pro-alpha1(II) chains.

Vitreous humor of the eye—The clear gel inside the eyeball.

Genetic profile

Langer-Saldino achondrogenesis is caused by spontaneous mutations in the *COL2A1* gene. This means that an affected child did not inherit the mutation; rather, the mutation developed in the egg or sperm cell, or during early embryonic development. Individuals with this disorder do not live into their reproductive years, so the disorder is not passed down from one generation to the next.

The *COL2A1* gene, located on the long arm (q) of chromosome 12 at 12q13.11, carries the blueprint for making certain components of type II collagen. These components are called pro-alpha1(II) chains, and three of them twist together into a coil-like structure known as procollagen. The procollagen molecules then go through another step involving an enzyme to become long strands that form a meshwork in the spaces around cells. These long strands are known as mature type II collagen fibers. The strong meshwork of the type II collagen fibers provides the framework to support large body structures, including muscles, organs, and skin, and is important in skeletal development. Type II collagen is also found in the vitreous humor of the eye (the clear gel inside the eyeball).

Scientists know of at least 18 different mutations in the *COL2A1* gene that can lead to Langer-Saldino achondrogenesis. These mutations all result in the substitution of a single glycine amino acid (a building block of protein) with another amino acid at one of several different positions in the collagen protein chain. These substitutions all prevent the production of mature type II collagen

fibers. Different mutations in the *COL2A1* gene can result in various other genetic disorders.

Demographics

Langer-Saldino achondrogenesis is a rare genetic disorder that affects individuals of various ethnicities and geographic areas with the same frequency. It is similar to hypochondrogenesis, which is caused by mutations in the same gene and has similar symptoms; thus, the National Institutes of Health report the incidence of the two diseases as a combined number. Langer-Saldino achondrogenesis and hypochondrogenesis together affect 1 in 40,000–60,000 newborns.

Signs and symptoms

Typical symptoms of Langer-Saldino achondrogenesis include:

- a short trunk
- extremely short limbs (micromelia)
- a short neck supporting a comparatively large head
- distinctive facial features, including a small chin and large forehead
- a narrow chest with short ribs
- underdeveloped lungs
- hydrops fetalis
- incomplete bone development in the backbone and in the hips
- a large abdomen
- a cleft palate in some cases

In addition, babies with achondrogenesis are born in the breech position (feet first) more often than healthy babies.

Diagnosis

Since Langer-Saldino achondrogenesis results from a spontaneous rather than an inherited mutation, the patient's family history is not helpful in its diagnosis. Often, the first signs of a potential problem arise during traditional prenatal care, when a technician notices fetal anomalies during an ultrasound examination. These anomalies may include severe micromelia, a narrow chest, and a lack of bone development in the spine and pelvis.

Examination

The doctor will review the ultrasound to confirm the anomalies. If achondrogenesis is not identified before birth, x-rays at birth verify the extent of skeletal abnormalities, although a visual examination of the infant

QUESTIONS TO ASK YOUR DOCTOR

- What treatments are available to make my child as comfortable as possible?
- I have a child with Langer-Saldino achondrogenesis. What are the chances that I will have a second child in the future with this disorder?
- We lost a child to Langer-Saldino achondrogenesis. What alternatives are available to ensure that our next child does not have this disorder?
- What would be the benefit of having DNA testing to determine which type of achondrogenesis my child has?
- Is prenatal testing available for Langer-Saldino achondrogenesis?

may be sufficient. A DNA analysis may be ordered to confirm the specific type of achondrogenesis.

Treatment and management

No cure is available for Langer-Saldino achondrogenesis. Doctors are sometimes, but not always, able to assist with a patient's breathing problems. Physical therapy may be helpful in assisting with overall body movement. Treatments for many symptoms, however, are not available.

Prognosis

Prenatal death is common. Infants who are born with this disorder often die shortly after birth, typically due to underdeveloped lungs. Rarely, individuals survive into childhood, and rarer still, into their early teens. There is no way to prevent Langer-Saldino achondrogenesis. It is a disorder that results from a spontaneous genetic mutation. If this condition is diagnosed during pregnancy, parents should consult their doctor for advice and referrals so they can prepare for the birth or otherwise determine how they wish to respond to the diagnosis.

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International Skeletal Dysplasia Registry. UCLA–OHRC, 615 Charles E. Young Dr. S, Los Angeles, CA 90095-7358, (310) 825-8998, AZargaryan@mednet.ucla.edu, <http://ortho.ucla.edu/body.cfm?id=279>
 National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

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Larsen syndrome

Definition

Larsen syndrome (LRS) is an inherited condition characterized by congenital dislocation of multiple body joints along with other unusual features of the face, hands, and bones.

Description

This condition was first described in 1950 by Larsen, Schottstaedt, and Bost, who compiled information on six people with sporadic cases of LRS. It is named for Loren Larsen, the orthopedic surgeon who was the first author of the original study.

LRS has been called both a skeletal dysplasia (a condition caused by abnormalities of bone structure) and a hypermobility syndrome (a condition involving abnormally loose joints). It is most likely caused by inherited abnormalities of connective tissue that affect both bone and joint structure. It is sometimes classified as an *FLNB*-related disorder because it is now known to be caused by mutations in the *FLNB* gene. Other disorders in the *FLNB*-related group include atelosteogenesis, types 1 and 3, boomerang dysplasia, and spondylocarpotarsal syndrome (SCT).

Present at birth are multiple dislocations of the elbows, hips, and, most commonly, the knees. Persons with LRS have other distinctive physical features that

can include a prominent forehead, widely spaced eyes, long cylindrical fingers, and short bones of the hand. Sometimes present are other birth defects such as structural heart defects, cleft palate, cataracts, extra bones of the wrist, and abnormalities of the vertebrae.

Most people have moderate symptoms that can be treated, allowing for a relatively normal lifespan. However, a small number of babies have a severe form of the condition and die at birth.

Genetic profile

There are likely to be multiple causes for LRS. Both recessive and dominant patterns of inheritance have been described thus far.

Some cases are sporadic, meaning the affected person is the first in the family to have the condition. Many sporadic cases are thought to be caused by new dominant mutations (spontaneous changes in the genetic material). A person with sporadic LRS has a change in the genetic material that is not present in either parent but can be passed on, with 50/50 odds in each child, to his or her offspring.

Patients have been reported who have affected brothers or sisters but unaffected parents. Most of these cases probably represent a recessive form of LRS in which a person must have two copies of a genetic change in order to be affected. The parents of a person with a recessive condition must each have one copy of the genetic change in order to have an affected child.

There are rare instances in which a person with LRS appears to have the recessive form but then gives birth to an affected child. These cases are most likely dominant rather than recessive. It can be difficult to be certain of the inheritance pattern in some families, and genetic counselors must be careful to address both forms of inheritance when discussing chances of recurrence.

The autosomal dominant form of LRS is thought to be caused by mutations in a gene called *FLNB* on the short arm of chromosome 3 at 3p14.3. The *FLNB* gene codes for a protein called filamin B, which is important in the formation and development of cartilage in the fetus before birth. The *FLNB* mutation associated with LRS results in an abnormal protein that interferes with the normal production of cartilage and the later maturation of cartilage into bone as the child grows older.

Another dominantly inherited condition called atelosteogenesis type 3 (AOIII) has features that overlap with those of LRS, and is caused by mutations in the same gene. As of 2015, at least six different mutations of the *FLNB* gene had been identified as causing AOIII.

Demographics

LRS is an extremely rare genetic condition that occurs in about 1 in every 100,000 to 250,000 births, although some researchers suspect that it is underdiagnosed because the symptoms can be confused with those of other skeletal or joint disorders.

Signs and symptoms

The symptoms of LRS vary widely from person to person and can range from lethal to very mild, even among members of the same family.

Typical characteristics at birth are multiple joint dislocations that can include hips, elbows, wrists, and knees. Babies can be born with their knees in hyperextension with their ankles and feet up by their ears, a deformation called genu recurvatum. Clubfoot is common, and persistent flexion, or contractures, of such other joints as the wrist and fingers can also occur.

Persons with LRS often have distinctive facial features. Common findings, in addition to a large forehead and wide-spaced eyes, are flat cheekbones and a flat bridge of the nose, which is sometimes indented and called “saddle nose.” The hands are often short, but the fingers are long and lack the normal tapered ends.

Other birth defects can occur but are not present in all people. Cleft palate, cataracts, and heart defects of the valves or between the upper or lower chambers occur occasionally.

Often, babies have poor muscle tone (hypotonia), giving them a “rag doll” appearance. Respiratory problems are frequently seen at birth because of laxity of the trachea. Feeding and swallowing difficulties are common.

Abnormalities of the bones are frequent. Underdevelopment and abnormal shape of some of the vertebral bones can lead to problems such as scoliosis or kyphosis. Abnormalities of the epiphyses (centers of bone growth) can develop in childhood. Height is often reduced, and an adult height of 4–5 ft (1.2–1.5 m) is not uncommon. The joints between the bones of the ear may be abnormal and may cause conductive hearing loss.

Hypermobility of joints lasts throughout life and may lead to early-onset arthritis and recurrent dislocations, which may necessitate joint replacement at an early age. Cervical spine instability is a very serious complication of LRS, as it can cause compression of the spinal cord and lead to paralysis or death.

The condition does not affect intelligence, and children can expect to have normal school experiences, with

KEY TERMS

Arthrogryposis—Abnormal joint contracture.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Clubfoot—Abnormal permanent bending of the ankle and foot; also called talipes equinovarus.

Congenital—Refers to a disorder that is present at birth.

Connective tissue—A group of tissues responsible for support throughout the body; includes cartilage, bone, fat, tissue underlying skin, and tissues that support organs, blood vessels, and nerves throughout the body.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Deformation—An abnormal form or position of a part of the body caused by extrinsic pressure or mechanical forces.

Epiphysis (plural, epiphyses)—The end of long bones, usually terminating in a joint.

Hypermobility—Unusual flexibility of the joints, allowing them to be bent or moved beyond their normal range of motion.

Joint dislocation—The displacement of a bone from its socket or normal position.

Kyphosis—An abnormal outward curvature of the spine, with a hump at the upper back.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Scoliosis—An abnormal side-to-side curvature of the spine.

Skeletal dysplasia—A group of syndromes consisting of abnormal prenatal bone development and growth.

the exception of physical education, which will need to be adapted to each child's needs.

Diagnosis

LRS should be suspected in any baby having multiple joint dislocations at birth. Babies suspected of

QUESTIONS TO ASK YOUR DOCTOR

- At what point in fetal or child development can Larsen syndrome be diagnosed?
- What tests or other measures are used to diagnose Larsen syndrome?
- What are the stages that normally occur in the development of Larsen syndrome in a child?
- Are there parent or research organizations that can provide me with additional information about my child's Larsen syndrome?

having the condition warrant a complete evaluation by a medical geneticist (a physician specializing in genetic syndromes).

LRS is sometimes misdiagnosed as another condition called arthrogryposis, which involves multiple joint contractures. LRS can be distinguished from this and other syndromes involving joint dislocations or contractures because of the unusual constellation of features found in the face and hands. Extra bones of the wrist, often seen in LRS, are extremely rare in other syndromes.

Some people have very mild symptoms and may not have joint dislocations or other problems at birth. The diagnosis can be missed in these people unless they are carefully evaluated.

A person with dominantly inherited LRS has a 50% chance with each pregnancy of having a child with the same disorder. Genetic counseling can help couples sort out their options for parenthood. Some couples choose to adopt rather than take the chance of an affected child, others go ahead with a pregnancy, and others choose to have prenatal diagnosis. The usual form of prenatal diagnosis available to date is ultrasound.

Fetal ultrasound performed by a specialist at 18–20 weeks of pregnancy can sometimes reveal signs of LRS. Some symptoms that can be noted during fetal ultrasound include knee dislocations and hyperextension; club feet; fixed flexion of elbows, wrists, and fingers; and some of the characteristic facial features. Physical findings from ultrasound can suggest, but do not confirm, the diagnosis of LRS in a fetus. As of 2015, the diagnosis could be confirmed before birth by molecular genetic testing, either sequence analysis of the entire coding region or deletion/duplication analysis. There is a test for the *FLNB* gene by itself, as well as genetic panel tests that check for 30 or more genes associated with skeletal and joint abnormalities.

Treatment and management

Treatment varies according to the symptoms of a particular child. Joint problems require long-term orthopedic care. Dislocations, clubfeet, and joint contractures are treated with intensive physical therapy, splints, casting, and/or surgery. Physical therapy is also important after joint surgery to build up muscles around the joint and preserve joint stability. Occupational therapy may be helpful for children with wrist and finger contractures.

Respiratory problems at birth may necessitate oxygen or assistive breathing devices. If not alleviated by medication or special feeding techniques, eating and swallowing problems may require tube feeding. Heart problems, cleft palate, and cataracts often warrant surgical correction. Special care is needed if laxity of the trachea is present because of an increased risk for respiratory problems during and after surgery.

People with chronic pain associated with hypermobile joints often can be helped by techniques taught in a pain management clinic.

Magnetic resonance imaging of the neck is recommended in childhood to screen for cervical vertebral problems. Early diagnosis and surgical stabilization of the spine can help patients avoid paralysis and death from spinal cord compression. Scoliosis is usually treated by bracing or by a surgically placed metal rod. Artificial hip and knee replacements may be needed in early-to-mid adulthood because of degeneration of unstable joints.

Regular medical examinations are crucial to assess the condition of the bones, joints, spine, heart, and eyes. Hearing should be evaluated on a periodic basis, especially in children, because of the potential for conductive hearing loss. Ophthalmologic examinations are recommended periodically to screen for cataracts.

Prognosis

The effects of the syndrome vary markedly from person to person. Therefore, prognosis is based on the findings in a given individual. The usual causes of early death are either severe respiratory problems or compression of the cervical spine from vertebral instability.

If careful and consistent orthopedic treatment is initiated early, prognosis can be good, with a normal lifespan. Weak and unstable joints and limited range of motion from contractures may cause walking difficulties and restrict other physical activities. Knee or hip replacement may be needed in early adult life. Contact sports and heavy lifting should be avoided, as anything that puts extra strain or pressure on the joints can cause harm. Swimming is a good activity because it helps strengthen muscles without joint strain.

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- Arthritis Foundation, 1330 W. Peachtree St., Suite 100, Atlanta, GA 30309, (404) 872-7100, <http://www.arthritis.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>
- Scoliosis Research Society, 555 E. Wells St., Suite 1100, Milwaukee, WI 53202, (414) 289-9107, (414) 276-3349, info@srs.org, <http://www.srs.org>

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Late-onset multiple carboxylase deficiency
see **Biotinidase deficiency**

Laterality sequence

Definition

Laterality sequence refers to a variable group of developmental anomalies in which some or all of an affected individual's internal organs form on the opposite side of the body than is standard. The heart, stomach, and spleen may form on the right side of the body instead of the left. The liver and gallbladder may form on the left side of the body instead of the right. Laterality refers to a side of the body. A sequence is a chain of events that occurs as a result of a single abnormality or problem.

Description

All humans display a characteristic placement of internal organs, with the heart, stomach, and spleen toward the left and the liver and gallbladder on the right. This placement of organs is called situs solitus. Very early in fetal development, the embryo forms a left-right axis that determines which side is left and which side is right. The axis can then instruct the body to form organs toward one side or the other. When the left-right axis does not form correctly, all or some of the organs form in the wrong location and result in a laterality sequence defect.

The first documented cases of laterality sequence occurred in the 1600s with Fabricius's description of an individual's symptoms of reversed liver and spleen and Marco Severino's recognition of dextrocardia. Laterality sequence defects range in features and descriptions. Features of laterality sequence anomalies include abnormal placement of all or some organs, dextrocardia (heart on the right side of the body), asplenia (no spleen), polysplenia (multiple spleens), complex congenital heart defects, intestinal malrotation, abnormal lung formation, symmetrical liver, midline abnormalities, and neural tube defects. Other terms for laterality sequence defects include situs inversus, situs inversus viscerum, situs transverses, heterotaxy, situs ambiguous, isomerism sequence, asplenia syndrome, Ivemark syndrome, polysplenia syndrome, partial situs inversus, and dextrocardia.

Genetic profile

Laterality sequence defects can occur due to genetic or multifactorial causes. Most cases of laterality sequence defects are sporadic and multifactorial. Multifactorial conditions result from the combination of environmental and genetic factors that contribute to the development of laterality sequence defects. First-degree relatives of an individual affected by a multifactorial condition have an increased risk that is based on family studies. A family that has one child with an isolated case of a laterality sequence, with no other affected children, runs a 3%–5% risk of having a future child affected by a laterality sequence defect.

Although all of the genes that are known to be involved in laterality sequence defects encode proteins that help determine the laterality of an individual, the inheritance pattern of inherited laterality sequence defects depends on the specific gene defect. New genetic mutations that cause laterality defects are still being discovered. Genes currently associated with laterality defects include *ZIC3* (also known as *HTX1*, zinc finger protein *ZIC3*, Xq26.2), *CRELD1* (Cysteine-rich with EGF-like domains located at 3p25.3), *DNAH11*, *LEFTB* (formerly *LEFTY2*), *CRC* (CRYPTIC located on chromosome 2),

EBAF (transforming growth factor beta 1q42.1), *NKX2* (homeobox protein Nkx-2.55 5q34), and *ACVR2B* (encoding activin receptor IIB located at 3p22-p21.3).

Most cases of inherited laterality defects travel through the family in an autosomal recessive manner. In an autosomal recessive condition, two copies of the mutant, or nonworking, gene are needed for a person to develop the symptoms of laterality sequence. In these cases, each parent carries one copy of a mutant gene. Individuals with only one copy of a nonworking gene for a recessive condition are known as carriers and have no problems related to the condition. However, when two people with the same mutant recessive gene have children together, there is a 25% chance with each pregnancy for the child to inherit two mutant copies, one from each parent. That child then has no working copies of the gene and, therefore, has the signs and symptoms associated with genetic defects. Gene mutations that result in autosomal recessive forms of laterality defects include *DNAH11*. *DNAH11*, located on the short arm of chromosome 7 (7p21), is expressed in the node of the embryo at day 7.5 and is involved in left-right axis determination of the organs. Mutations in the coding region of *DNAH11* account for situs inversus totalis.

Additional autosomal recessive laterality defects can also be a feature of other inherited conditions, such as Kartagener syndrome and Ivemark syndrome. Kartagener syndrome is an autosomal recessive disorder characterized by bronchiectasis, sinusitis, dextrocardia, and infertility that can be caused by several different genetic locations and mutations. Approximately 25% of individuals affected by situs inversus have Kartagener syndrome. Ivemark syndrome refers to the congenital absence of the spleen, usually accompanied by complex cardiac malformations, malposition and maldevelopment of the abdominal organs, and abnormal lobation of the lungs.

Some cases of laterality sequence defects are inherited in an autosomal dominant pattern. In an autosomal dominant inheritance pattern, the genes that cause laterality sequence are carried on one of the 22 pairs of numbered autosomal chromosomes, rather than on the X or Y sex chromosomes. Furthermore, in autosomal dominant conditions, only one copy of the mutant, or nonworking, gene is necessary for the development of laterality sequence. An individual who inherits a normal gene copy from one parent and an abnormal gene copy from the other parent is likely to have a lateral sequence anomaly. The children of an individual with one normal gene copy and one mutated copy have a 50% chance of inheriting laterality sequence. One known form of laterality sequence that is found inherited in an autosomal dominant manner occurs in patients with a nonworking copy

of *CFC1*. *CFC1* is located on chromosome 2 and is involved in the formation of the left-to-right axis in human development. Accordingly, individuals who have one nonworking copy of *CFC1* have randomized organ positioning (heterotaxia). In addition to the forms of laterality sequence described earlier, as of 2015 there had been eight other genes described that were known to be associated with the autosomal recessive form of this condition.

Some cases of laterality sequence defects are inherited in an X-linked recessive pattern. As opposed to genes that are carried on one of the 22 pairs of numbered autosomal chromosomes, X-linked genes are found on the sex chromosomes called X. Females have two X chromosomes, while males have a single X chromosome and a single Y chromosome. When a female inherits a mutated gene on the X chromosome, she is known as a carrier. She often has no problems related to that condition because the gene on her other chromosome continues to function properly. However, males only inherit one copy of the information stored on the X chromosome. When a male inherits a mutated copy of the gene that causes an X-linked recessive condition, he will experience the symptoms associated with the disease. The chance for a carrier female to have an affected son is 50%, while the chance to have an unaffected son is 50%. The chance for a carrier female to have a daughter who is also a carrier for the condition is 50%, while the chance for her to have a daughter who is not a carrier is 50%. An affected male has a 100% chance of having carrier daughters and a 0% chance of having affected sons. In 1997, an X-linked recessive form of laterality sequence caused by mutations in *HTX1* located on the long arm of the X chromosome (Xq26.2) was described. In the same year, it was determined that the gene is a zinc finger protein, and it was named *ZIC3*. The gene is known as both *ZIC3* and *HTX1*. *ZIC3* is involved in the development of the left-right axis, and mutations account for approximately 1% of individuals affected by heterotaxy. Accordingly, mutations in *ZIC3* cause inability of the embryo to establish normal left-right asymmetry.

Demographics

Laterality sequence defects occur in about 1 in every 8,500–25,000 live births. It occurs in individuals of all ethnic backgrounds. An equal number of males and females are affected by laterality sequence defects.

Signs and symptoms

Different laterality sequence defects can be described by the positioning of the various organs and associated malformations.

KEY TERMS

Complete situs inversus—A laterality defect resulting in a mirror image of the normal organ formation with heart, spleen, and stomach on the right side, and the liver and gallbladder on the left.

Dextrocardia—Right-sided positioning of the heart.

Heterotaxy—Random organ positioning in an individual that can result in multiple malformations with severe heart defects, livers found in the middle of the body, spleen abnormalities, and intestines turned in the opposite direction from normal (gastrointestinal malrotation).

Left-right axis—The developmental feature in a fetus that determines which side of the body is left and which side is right; it conducts the location and positioning of the fetus's internal organs.

Situs solitus—Normal organ placement in the body with the heart, stomach, and spleen placed toward the left, and the liver and gallbladder on the right.

Complete situs inversus or situs transversus is a laterality defect resulting in a mirror image of the normal organ formation with heart, spleen, and stomach on the right side and the liver and gallbladder on the left side. The normal pulmonary anatomy is reversed so that the left lung has three lobes and the right lung has two lobes. The remaining internal structures also are a mirror image of the normal.

Heterotaxy or situs ambiguous refers to random positioning of individual organs that can result in multiple malformations with severe heart defects, livers found in the middle of the body, spleen abnormalities, and intestines turned in the opposite direction than is standard (gastrointestinal malrotation). Often, structures normally found on one side of the body are duplicated or absent. Two primary subtypes of heterotaxy are based on the presence or absence of certain organs. In classic right isomerism, or asplenia, patients have a right atrium on both sides of the body, a centrally located liver, no spleen, and three lobes in both lungs. In left isomerism, or polysplenia, patients have left atria on both sides, multiple spleens, and two lobes in both lungs.

Dextrocardia refers to right-sided positioning of the heart. There are various forms of dextrocardia, ranging from a normally configured heart that is positioned farther to the right than normal to mirror-image dextrocardia, in which the positions of the heart chambers and major vessels are exactly the reverse of the standard arrangement.

Laterality sequence defects caused by mutations in *DNAH11* are characterized by situs inversus viscerum; intrauterine growth retardation; congenital heart defects, such as transposition of the great vessels, ventricular septal defect, atrial septal defect, truncus communis, and dextrocardia; right pulmonary isomerism; and right spleen. Mutations in *DNAH11* may also be associated with Kartagener syndrome, which includes bronchiectasis, sinusitis, dextrocardia, and infertility.

Laterality sequence defects caused by mutations in *CFC1* result in visceral heterotaxy, including a variable group of congenital anomalies that include complex cardiac malformations and situs inversus or situs ambiguous.

Laterality sequence defects caused by mutations in *ZIC3* include a variable group of congenital anomalies that include complex cardiac malformations (corrected transposition of great arteries, ventricular septal defect, and patent ductus arteriosus), dextrocardia, situs inversus, asplenia, polysplenia, situs inversus viscerum, pulmonic stenosis, and poor growth (intrauterine growth retardation). Some individuals with mutations in *ZIC3* have been found to have isolated heart defects only. Female carriers have been described with uterine septums and hypertelorism (wide-spaced eyes).

Diagnosis

Laterality defects may be discovered before birth and in infancy because of associated heart defects or other health problems. Laterality defects may remain asymptomatic in childhood and are discovered by chance in adult life as affected individuals seek medical attention for an unrelated condition. Clinical testing for many of the genes associated with laterality defects is available; however, diagnosis is still primarily based on imaging through means such as ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT) scan.

Some symptoms of laterality sequence defects such as heart defects, poor growth (intrauterine growth retardation), and possibly organ reversal may be identified through a screening ultrasound around 18 weeks gestation of pregnancy. Accuracy of diagnosis of laterality sequence defects depends on the position, size, and maturity of the fetus, as well as an adequate volume of amniotic fluid and mother's size. A fetal echocardiogram can also help characterize a heart defect or placement before birth. If there is a known gene mutation present in an affected family member, prenatal diagnosis may be available through tests, such as amniocentesis.

QUESTIONS TO ASK YOUR DOCTOR

- Will my child require any operations to treat this condition?
- What form of laterality sequence does my child have?
- What are the chances of having another affected child?
- Are all forms of laterality sequence genetic?
- What types of medical complications will my child have as he or she gets older?
- Will my child's lifespan be shortened because of this diagnosis?

Diagnosis of a laterality sequence defect in infancy is most often made as a result of a heart defect or other serious medical issue related to the organ positioning and/or number of organs. Laterality sequence defects can be verified through use of x-rays, ultrasound, or CT scan. The location and relationships of the abdominal organs, veins of the liver, heart arteries and veins, heart chambers, and heart valves should be reviewed carefully.

Diagnosis in adulthood is based on clinical manifestations and exams such as abdominal and thoracic radiography and electrocardiogram. CT is the preferred examination for definitive diagnosis of situs inversus with dextrocardia because it provides good detail for confirming visceral organ position, cardiac position, and great vessel branching. MRI is usually reserved for difficult cases or for patients with associated cardiac anomalies. The features of laterality sequence defects are variable and require thorough evaluation of the internal organs for full diagnosis.

Treatment and management

The treatment and management of laterality sequence defects depend on the type of defect. Infants and children with laterality defects can have congenital heart defects and other associated birth defects that require surgery. Many adults with incidental detection of their laterality sequence anomalies do not need special treatment or management unless they are ill or need surgery. The recognition of situs inversus is important for preventing surgical mishaps that result from the failure to recognize reversed anatomy or an atypical history. The reversal of the organs may lead to some confusion, as many signs and symptoms are opposite from the standard side. Laterality sequence defects can also complicate

organ transplantation operations, as donor organs most likely come from normal individuals whose organs and vessels are a mirror image of the transplanted patients'. Accordingly, in the event of a medical problem, the knowledge that the individual has a laterality defect can increase the time and accuracy of diagnosis and increase the safety of surgery.

Prognosis

Many patients with laterality sequence defects such as total situs inversus present with no significant medical problems and have normal life expectancy. Total organ reversal results in normal relationships between the left-right positions of the organs and their blood supplies. In other forms of laterality sequence defects, such as those associated with Kartagener's syndrome, issues such as chronic respiratory problems and infertility can occur. Infants affected by complex cardiac defects may die as a result of their congenital heart defects. Prognosis in isolated dextrocardia depends on the congenital cardiac defects present. Women have been described with a uterine septum that can result in difficulties maintaining a pregnancy.

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Congenital Heart Information Network (C.H.I.N.), PO Box 3397, Margate City, NJ 08402, (609) 823-4507, <http://tchin.org>

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Laurence-Moon-Bardet-Biedel syndrome see
Bardet-Biedl syndrome

Lebers hereditary optic neuropathy see
Lebers hereditary optic atrophy

Leber congenital amaurosis

Definition

Leber congenital amaurosis (LCA) is a group of autosomal recessive-inherited eye disorders that lead to blindness at birth or within the first few years of life. Other manifestations of the disease may include hearing loss, intellectual disability, and decreased physical coordination.

Description

Vision is an important and complex sense by which the qualities of an object, such as color, shape, and size, are perceived through the detection of light. For proper vision, a critical series of biological steps must occur; if any of the steps in the process is abnormal, visual impairment or blindness may occur.

The process of vision begins with light that bounces off an object and passes through the outer coverings and lens of the eye and projects onto a layer of cells at the back of the eye called the retina. The retina contains two kinds of specialized cells types, called the rods and cones, that are responsible for sensing visual stimuli. When rods and cones are stimulated by light, impulses are conducted through the optic nerve to a region in the back of the brain known as the occipital lobe. The occipital lobe contains the visual cortex, the area of the brain that processes visual stimuli and integrates signals sent by the retina to obtain a composite image of an object.

Leber congenital amaurosis is the term for a group of inherited conditions in which the rod and cone receptors in the retina are defective or missing. Without the proper function of these specialized cells, light cannot be sensed normally.

LCA is often referred to by other names, such as congenital absence of the rods and cones, congenital retinal blindness, congenital retinitis pigmentosa, Leber congenital tapetoretinal degeneration, or Leber congenital tapetoretinal dysplasia. The disorder was first described in

1869 by the German ophthalmologist Theodor Leber, who subsequently showed that it was an inherited defect. Although similarly named, LCA should not be confused with another disorder of sight, Leber optic atrophy, which was also first described by Theodor Leber.

Genetic profile

Mutations in any one of at least 14 different genes may result in LCA. Each of the known genes produces proteins, which are located within the retinal rod and cone cells. These proteins participate in the detection of an incoming stimulus of light and the subsequent transmission of signals out of the retinal cells to the visual cortex of the brain. Six identified mutations likely account for less than half of all diagnosed cases of LCA; thus, there are additional mutations resulting in LCA that remain to be identified.

The most common genes associated with LCA are *RPE65*, *CEP290*, *CRB1*, and *GUCY2D*. Mutations in the genes *CRX* and *IMPHD1* also cause LCA, but as autosomal dominant mutations. Approximately 30% of LCA cases are due to unknown causes, and because so many genes are associated with LCA and the symptoms are so variable, it is very difficult to test for the disease.

LCA is a genetic condition and can be inherited or passed on in a family. The genetic defects for the disorder are all inherited as autosomal recessive traits, meaning that two mutant genes of the same group are needed to display the disease. A person who carries one mutant gene does not display the disease and is called a carrier. A carrier has a 50% chance of transmitting the gene to his or her children, who must inherit the same defective gene from each parent to display the disease. Since there are different genes that are responsible for causing LCA, two individuals with different types of LCA will have an unaffected child, as it is impossible for the child to inherit two of the same type of defective genes from his or her parents.

Location of genetic abnormality for specific types of Leber congenital amaurosis

Type	Abnormal	Mutant gene	Gene location
LCA1	Retinal-specific guanylate cyclase	RETGC/GUC2D	17p13.1
LCA2	Retinal pigment epithelium specific protein	RPE65	1p31
LCA3	Unknown	Unknown	14q24
LCA4	Arlhydrocarbon-interacting protein-like 1	AIPL1	17p13.1
LCA5	Unknown	Unknown	6q11-q16
LCA due to CRX defect	Cone-rod homeobox protein	CRX	19q13.3

(Gale)

Demographics

Although LCA affects approximately 1 in 80,000 people, it is considered one of the most common causes of childhood blindness. It can affect males and females equally. LCA has been reported to account for at least 5% of all cases of inborn blindness, but several reports suggest that is an underestimation. In 1957, scientific investigators reported that one form of LCA was responsible for 10% of blindness in Sweden. Several years later, similar rates of LCA were found in people living in the Netherlands. While this suggests that the geographical distribution of LCA is not uniform and may be higher in certain ethnic groups, a comprehensive study has never been performed.

Signs and symptoms

Because there are 13 types of LCA, there is considerable variation in the symptoms experienced by an affected infant. Most infants with LCA are often blind at birth or lose their sight within the first few years of life; however, some people with LCA may have residual vision. In these patients, visual acuity is usually limited to the level of counting fingers or detecting hand motions or bright lights, and patients are extremely farsighted. There may be some small improvement in vision during the first decade of life as the visual system reaches maturity, but it is uncommon for children to be able to navigate without assistance or to be able to read print.

Other symptoms of LCA may include crossed eyes, sluggish pupils, rapid involuntary eye movements, unusual sensitivity to light, and the clouding of the lenses of the eyes. Many children with LCA habitually press on their eyes with their fists or fingers. This habitual pressing on the eyes is known as an oculo-digital reflex and may represent an instinctual attempt to provide the developing visual cortex of the brain with a stimulus to replace the loss of normal visual stimuli. As a result of this behavior, the eyes may become thin and conical in shape and appear sunken or deep. In some cases, LCA is associated with hearing loss, epilepsy, decreased coordination, kidney problems, or heart abnormalities. Intellectual disability is present in approximately 20% of individuals affected with LCA.

Diagnosis

Infants are usually brought to medical attention within the first six months of life when parents notice a lack of visual responsiveness and the unusual roving eye movements characteristic of the disease. As with any evidence of loss of vision, a prompt and thorough evaluation is initiated to determine the cause of the visual defect, and steps may include physical tests designed to measure

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are needed to display the trait or disease.

Braille—An alphabet represented by patterns of raised dots that are felt with the fingertips. It is the main method of reading used by the blind.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Electroretinography (ERG)—A diagnostic test that records electrical impulses created by the retina when light strikes it.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Occipital lobe—An anatomical subdivision, located at the back of the brain, that contains the visual cortex.

Oculo-digital reflex—A reflex causing an individual to press on his or her eyes with fingers or fists.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Visual cortex—The area of the brain responsible for receiving visual stimuli from the eyes and integrating it to form a composite picture of an object.

brain and eye function, CT scans (a method using x-rays controlled by a sophisticated computer) of the brain and eye, and even tests to look for genetic and metabolic causes of blindness.

Eye examinations of infants with LCA usually reveal a normal-appearing retina. By early adolescence, however, various changes in the retinas of patients with LCA become readily apparent; blood vessels often become narrow and constricted, and a variety of color changes can occur in the retina and its supportive tissue.

One of the most important tests in diagnosing LCA is called electroretinography (ERG). This test measures electrical impulses that are produced in the retina when

light is sensed by the rod and cone cells. It is useful in distinguishing whether blindness is due to a problem in the retina versus a problem in the visual cortex of the brain. When ERG tests are performed on people with LCA, there is no recordable electrical activity arising from the eye, indicating that the problem is based in the retina rather than in the brain.

Thus, an absence of activity on ERG, combined with the absence of diagnostic signs of other conditions that result in blindness, point to a diagnosis of LCA. Although several abnormal genes have been identified as responsible for LCA, genetic analysis and prenatal diagnosis is rarely performed outside of research studies.

Treatment and management

Currently, there is no treatment for LCA; thus, patient and family education and adaptive assistance is critical. Some people with remaining vision may benefit from vision-assistance technology such as electronic, computer-based, and optical aids, but severely visually impaired individuals often utilize traditional resources such as canes and companion-guide dogs. Orientation and mobility training, adaptive training skills, job placement, and income assistance are available through hospital physical and occupational therapy programs and various community resources. It should be noted that up to 20% of patients with LCA may have associated intellectual disability and require additional adaptive and vocational assistance.

Most people with LCA are unable to read print and instead utilize Braille, an alphabet represented by raised dots that can be felt with the fingertips. People with LCA often attend schools specially designed to meet the needs of visually impaired students and may require modifications to their home and work environments in order to accommodate their low or absent vision. Because almost all patients with LCA are legally blind, they are not able to drive or operate heavy machinery. Genetic counseling may assist affected individuals with family planning.

Scientists have several isolated mutant genes that can each cause LCA. Ongoing scientific research is directed toward understanding how these genes function in the retina and toward locating the remaining genes that cause LCA. With this information, scientists can better develop a means of prevention and treatment.

Gene Therapy

There has been some success in the treatment of LCA with the use of gene therapy. In 2008, a clinical trial reported on the safety and efficacy of introducing the

QUESTIONS TO ASK YOUR DOCTOR

- Relatives in my family have LCA—is it possible that I could be a carrier?
- My child has been diagnosed with LCA. What form of the disease does he or she have, and is there a course of treatment?
- Can I pass LCA to my children?

functional form of the human *RPE65* gene into the eyes of patients in whom LCA is caused by a mutation in the *RPE65* gene. In the three patients treated, no side effects were reported, and vision was improved for up to one and a half years.

In a 2009 study, 12 patients ranging in age from 8 to 44 with *RPE65* LCA were also treated with gene therapy to introduce a functional *RPE65* gene. They showed improvement, especially the younger patients.

In both of these trials, the adeno-associated virus (AAV) was used to introduce the *RPE65* gene, and there was some concern that antibodies made in the body against the AAV vector could compromise the treatment and the patients' health. In animal studies in which AAV antibodies were injected along with the AAV2-hRPE65v2, treatment did not show any complications. In later human trials, AAV antibody levels were measured and showed little to no change post treatment, suggesting that this form of gene therapy has little risk of producing harmful side effects.

A 2015 clinical study using gene therapy to treat 12 LCA patients with gene therapy to replace *RPE65* measured visual function three years after treatment and found no associated improvement that could be detected with ERG. The final conclusion was that gene therapy of LCA had mild effects on improving retinal sensitivity within the first 6–12 months, but that these effects were temporary.

Prognosis

While children born with LCA may have variable symptoms and differing levels of visual acuity, they can lead productive and healthy lives with adaptive training and assistance. In those patients who do not have associated problems with their brain, heart, or kidney, lifespan is approximately the same as in the general population; otherwise, the prognosis is variable and depends on the extent of the complication.

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ORGANIZATIONS

- American Association for Pediatric Ophthalmology and Strabismus, 655 Beach St., San Francisco, CA 94109-1336, (415) 561-8505, (415) 561-8531, aapos@aao.org, <http://www.aapos.org>
- Foundation Fighting Blindness, 7168 Columbia Gateway Dr., Suite 100, Columbia, MD 21046, (410) 423-0600, (800) 683-5555, info@fightblindness.org, <http://www.blindness.org>

Oren Traub, MD, PhD
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Leber hereditary optic atrophy

Definition

Leber hereditary optic atrophy is a painless loss of central vision (blurring of objects and colors appearing less vivid) that usually begins between the ages of 25 and 35 (but can occur at any age) and leads to legal blindness. Other minor problems may be present such as tremors, numbness or weakness in the arms and legs, or loss of ankle reflexes. It was first described in 1871 by Theodore Leber and is the most common cause of optic atrophy.

Description

Leber hereditary optic atrophy is also called Leber hereditary optic neuropathy or LHON. The beginning of visual blurring in both eyes is called the acute phase of LHON. In about half of patients, both eyes are

affected at the same time. In the remainder of patients, central vision is lost in one eye over a period of a few weeks, followed by the second eye a month or two later. Once both eyes are affected, a few weeks usually pass before the eyesight stops getting worse. Other less common patterns of central vision loss in LHON can be very sudden loss in both eyes, or very gradual loss occurring over several years. After the acute phase, there is rarely any significant change in eyesight during the remainder of the person's life. People with LHON are usually left with some peripheral vision, which is seeing around the edges, or out of the corner of the eye. This final phase is called the atrophic phase because the optic discs are atrophic (cells have wasted away) and rarely change.

The optic disc is the center part of the retina (back of the eye) and is where the clearest vision—both in detail and color—comes from. The retina interprets what a person sees, and sends this message to the brain, along the pathway known as the optic nerve. In LHON, both the retina and the optic nerve stop working properly. The rest of the eye works normally, so that light enters the eye through the pupil (black circle in the center of the iris, the colored part of the eye) as it should. However, in LHON patients, even though the light is focused on the retina properly, this information is not converted into signals for the brain to process. When a person wears prescription glasses, the purpose is to help focus light properly on the retina. In LHON, light is already focused as it should be, so glasses will not improve vision. Magnifying glasses and telescopes do help, however, because they make things look bigger. When a person looks through a magnifier or telescope, they use more of their retina to see, and some undamaged cells of the retina may be able to provide some information to the brain.

Suddenly losing vision can be a shock. Patients diagnosed with LHON may feel they have no useful sight left, and often, their family and friends treat them as the stereotypic blind person. In reality, LHON usually leaves an affected person with some useable vision. A variety of visual aids are available to enhance this.

Genetic profile

In 60% of patients with LHON, there is a positive family history of LHON, while the remaining cases are considered sporadic (occur by chance), where only one person in the family has LHON. In 1988, it was discovered that LHON is caused by a mutation in a mitochondrial gene. Mitochondria are the energy-producing organelles (structures) of cells. They have their own genetic material called mitochondrial DNA, which is separate from the usual genetic material contained in

KEY TERMS

Acute phase—The initial phase of LHON, when visual blurring begins in both eyes and central vision is lost.

Atrophic phase—The final phase of LHON where cells in the optic disc and optic nerve have atrophied, resulting in legal blindness. Peripheral vision remains.

Central vision—The ability to see objects located directly in front of the eye. Central vision is necessary for reading and other activities that require people to focus on objects directly in front of them.

Heteroplasmy—When all copies of mitochondrial DNA are not the same, and a mix of normal and mutated mitochondrial DNA is present.

Homoplasmy—When all copies of mitochondrial DNA are the same, or have the same mutation.

Leber hereditary optic atrophy or Leber hereditary optic neuropathy (LHON)—Discovered in 1871 by Theodore Leber, the painless loss of central vision in both eyes, usually occurring in the second or third decade of life, caused by a mutation in mitochondrial DNA. Other neurological problems, such as tremors or loss of ankle reflexes, may also be present.

Lifetime risk—A risk that exists over a person's lifetime; a lifetime risk to develop disease means that the chance is present until the time of death.

Mitochondria—Organelles within the cell responsible for energy production.

Mitochondrial inheritance—Inheritance associated with the mitochondrial genome that is inherited exclusively from the mother.

Multiple sclerosis (MS)—A progressive degeneration of nerve cells that causes episodes of muscle weakness, dizziness, and visual disturbances, followed by periods of remission.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Ophthalmologist—A physician specializing in the medical and surgical treatment of eye disorders.

Optic disc—The region where the optic nerve joins the eye; also referred to as the blind spot.

Optic nerve—A bundle of nerve fibers that carries visual messages from the retina in the form of electrical signals to the brain.

Peripheral vision—The ability to see objects that are not located directly in front of the eye. Peripheral vision allows people to see objects located on the side or edge of their field of vision.

Pupil—The opening in the iris through which light enters the eye.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

the center of the cell (or nucleus). Each mitochondrion has several copies of its circular DNA. DNA is the chemical that makes up genes. Genes code for certain traits, and in some cases, can code for disease. Mutations in the DNA of a mitochondria may be present in all copies (called homoplasmy), or may be present in a portion of the mitochondria's DNA (called heteroplasmy). About 15% of individuals with LHON are heteroplasmic, which means some of their mitochondrial DNA has a mutation, and some does not. This may have a bearing on the chance to develop symptoms, and on the risk of transmission.

There are three specific DNA changes or mutations that are found in the majority (90%–95%) of LHON cases. The remaining LHON patients have other various mitochondrial mutations. In genetics, mutations are

designated in such a way as to tell a scientist where they are located in the mitochondrial DNA and what the DNA alteration is: for example, G11778A means the mutation is located at position 11778 and DNA change is G [guanine] to A [adenine], a change in the base pairs that make up DNA.

Not all persons who have one of these mutations will develop LHON, since it is thought that additional genetic or environmental factors are necessary to develop central vision loss. In general, males with one of these mutations have a 40% lifetime risk to develop symptoms of LHON, while females have a 10% risk, although the actual risk varies slightly from mutation to mutation. In addition, the older a person in whom a mutation has been identified becomes without symptoms, the less likely they will lose their vision at all. If a person is going to experience vision

loss from LHON, the majority of people with a mutation express symptoms by the age of 50 years.

Environmental factors that can reduce the blood supply to the retina and optic nerve and “trigger” the vision loss in LHON to begin include heavy drinking or smoking, exposure to poisonous fumes such as carbon monoxide, high levels of stress, and certain medications. A person in whom a mutation has been identified is considered more susceptible to some of these exposures and is advised not to smoke and to moderate their alcohol intake if they are asymptomatic.

The other important concept to understand in relation to mitochondrial disease is that mitochondria are only inherited from the mother. Therefore, a woman with a mitochondrial mutation (whether she has symptoms or not) will pass it to all of her offspring. Sons who inherit the mutation will not pass it to any of their children, while daughters who inherit the mutation will pass it to all of their children. This is in contrast to nuclear DNA, where half the genetic material is inherited from each parent.

Demographics

Males have LHON more often than females; however, females may develop LHON at a slightly older age and may have more severe symptoms, including a multiple sclerosis-like illness. Multiple sclerosis is a progressive degeneration of nerve cells that causes episodes of muscle weakness, dizziness, and visual disturbances, followed by remission. The onset of LHON usually occurs by age 50 if a mitochondrial DNA mutation is present, although it can present as late as the sixth or seventh decade of life.

Signs and symptoms

Symptoms of LHON include a painless sudden loss of central vision, in both visual detail and color, in both eyes over a period of weeks to months. Peripheral vision (seeing out of the corner of the eye) remains. Additional symptoms involving the neurological system may be present such as tremors, numbness or weakness in the arms or legs, or loss of ankle reflexes. Symptoms vary by gender and type of mutation present. The following mutations are frequently identified and well understood:

- G11778A—the most common mutation and usually the most severe vision loss
- T14484C—usually has the best long-term prognosis or outcome
- G3460A—has an intermediate presentation

Persons who have a multiple sclerosis-like illness can have any of the three mutations. This phenomenon—where different mutations give different

clinical outcomes—is called a genotype-phenotype correlation. The word *genotype* describes the specific findings in DNA, while the word *phenotype* is used to describe the clinical presentation.

Diagnosis

Suspicion of LHON is usually made by an ophthalmologist after a complete eye examination. Genetic testing for the presence or absence of mitochondrial mutations can then be performed from a small blood sample. After a symptomatic person with LHON in a family has been identified as having a mitochondrial mutation, other asymptomatic at-risk relatives can also be tested. At-risk relatives include the affected persons’ mother, siblings, and the offspring of any females found to have the mutation. Testing for asymptomatic children who are at risk is not currently offered since no treatment is available for LHON; these individuals could opt for testing upon becoming a legal adult (i.e., reaching 18 years of age). Prenatal diagnosis for LHON was as of 2021 not available in the United States, but may be offered elsewhere. With genetic testing for LHON, it is important to remember that the presence of a mitochondrial mutation does not predict whether the condition will occur at all, the age at which it will begin, the severity, or the rate of progression.

Treatment and management

There is no proven treatment available for LHON, although some studies report benefit from various vitamin therapies or other medications. Management of LHON is supportive, utilizing visual aids such as magnifiers.

Prognosis

The loss of central vision tends to remain the same (legally blind) over a lifetime once a person with LHON has reached the atrophic phase.

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ORGANIZATIONS

International Foundation for Optic Nerve Disease (IFOND), PO Box 777, Cornwall, NY 12518, (675) 206-7250, IFONDORG@gmail.com, <http://www.ifond.org>

United Mitochondrial Diseases Foundation, 8085 Saltsburg Rd., Suite 201, Pittsburgh, PA 15239, (888) 317-8633 or (412) 793-8077, (412) 793-6477, info@umdf.org, <http://www.umdf.org>

Catherine L. Tesla, MS, CGC

Leigh Syndrome

Definition

Leigh syndrome is a rare inherited neurometabolic disorder characterized by degeneration of the central nervous system (CNS; brain, spinal cord, and optic nerve), meaning that the CNS gradually loses its ability to function properly.

Description

First described in 1951, Leigh syndrome is usually diagnosed between the ages of three months and two years. The disorder worsens rapidly; the first signs may be loss of head control, poor sucking ability, and loss of previously acquired motor skills, meaning that the control of particular groups of muscles. Loss of appetite, vomiting, seizures, irritability, and/or continuous crying may accompany these symptoms. As the disorder worsens, other symptoms such as heart problems, lack of muscle tone (hypotonia), and generalized weakness may develop, as may lactic acidosis, a condition by which the body produces too much lactic acid. These symptoms eventually result in death. In rare cases, Leigh syndrome may begin late in adolescence or early adulthood, and in such cases, the progression of the disease is slower than with the classical form.

Leigh syndrome usually develops in three stages. The first is between eight and 12 months and involves vomiting and failure to thrive. The second is in infancy,

characterized by loss of motor ability, eye problems, and respiratory irregularity. The third stage occurs between two and 10 years of age and is characterized by hypotonia and feeding difficulties. Several different types of genetic enzyme defects are thought to cause Leigh syndrome, meaning that the disorder may be caused by defective enzymes, the proteins made by the body to speed up the biochemical reactions necessary to sustain life.

Commonly known as Leigh's disease, Leigh syndrome is also known as Leigh necrotizing encephalopathy, necrotizing encephalomyelopathy of Leigh's, and subacute necrotizing encephalopathy (SNE). When it occurs in adolescence and adulthood, it may be called adult-onset subacute necrotizing encephalomyelopathy.

Genetic profile

Leigh syndrome can be caused by mutations in one of more than 75 different genes. In most cases, Leigh syndrome is inherited as an autosomal recessive genetic trait. However, X-linked recessive, autosomal dominant, and mitochondrial inheritance can also occur. Several different types of genetic metabolic defects are thought to lead to Leigh syndrome. A deficiency of one or a number of different enzymes may be the cause.

Classic Leigh syndrome

The usual form of Leigh syndrome is inherited as an autosomal recessive genetic trait. The syndrome has been linked to multiple defects in the genes that cause either a deficiency of the enzyme pyruvate dehydrogenase or an abnormality in other enzymes that make pyruvate dehydrogenase work. Other cases of autosomal recessive Leigh syndrome are associated with other genetic enzyme deficiencies (i.e., NADH-CoQ and cytochrome C oxidase). All of these different genetic defects seem to have a common effect on the central nervous system.

In autosomal recessive inheritance, a single abnormal gene on one of the autosomal chromosomes (one of the 22 nonsex chromosomes) from both parents can cause the disease. Both of the parents must be carriers in order for the child to inherit the disease, but neither of the parents will have the disease (since it is recessive).

A child whose parents are carriers of the disease has a 25% chance of having the disease; a 50% chance of being a carrier of the disease, meaning that he or she is not affected by the disease but can pass the defective gene on to future children; and a 25% chance of receiving both normal genes, one from each parent, and being genetically normal for that particular trait.

KEY TERMS

Apnea—An irregular breathing pattern characterized by abnormally long periods of the complete cessation of breathing.

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Central nervous system (CNS)—In humans, the central nervous system is composed of the brain, the cranial nerves, and the spinal cord. It is responsible for the coordination and control of all body activities.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Hypotonia—Low or poor muscle tone, resulting in floppy limbs.

Lactic acidosis—A condition characterized by the accumulation of lactic acid in bodily tissues. The cells of the body make lactic acid when they use sugar as energy. If too much of this acid is produced, the person starts feeling ill with symptoms such as stomach pain, vomiting, and rapid breathing.

Metabolism—The total combination of all of the chemical processes that occur within cells and tissues of a living body.

Mitochondria—Organelles within the cell responsible for energy production.

Motor skills disorder—A disorder that affects motor coordination or its development and the control of particular groups of muscles that perform activities.

Necrosis—Death of a portion of tissue differentially affected by disease or injury.

Neurometabolic disorder—Any disorder or condition that affects both the CNS and the metabolism of the body.

X-linked Leigh syndrome

Evidence exists for an X-linked recessive form of Leigh syndrome, which has been linked to a specific defect in a gene called *E1-alpha*, a part of the enzyme pyruvate dehydrogenase.

X-linked recessive disorders are conditions that are coded on the X chromosome. All humans have two chromosomes that determine their biological sex: females have XX, and males have XY. X-linked recessive (also called sex-linked) inheritance affects the genes located

on the X chromosome. It occurs when an unaffected mother carries a disease-causing gene on at least one of her X chromosomes. Because females have two X chromosomes, one from each parent, they are usually unaffected carriers. The X chromosome that does not have the disease-causing gene compensates for the X chromosome that does. Generally, for a woman to have symptoms of the disorder, both X chromosomes would have the disease-causing gene. That is why women are less likely than men to show such symptoms.

If a mother has a female child, the child has a 50% chance of inheriting the disease gene and being a carrier who can pass the disease gene on to her children. On the other hand, if a mother has a male child, he has a 50% chance of inheriting the disease-causing gene, because he has only one X chromosome. If a male inherits an X-linked recessive disorder, he is affected. All of his daughters will also be carriers.

Mitochondrial Leigh syndrome

Leigh syndrome may be inherited in some cases from the mother as a DNA mutation inside mitochondria. Hundreds of tiny mitochondria are contained in every human cell. They control the production of cellular energy and carry the genetic code for this process inside their own special DNA, called mitochondrial DNA (mtDNA). The mtDNA instructions from the father are carried by sperm cells, and during fertilization, these instructions break off from the sperm cell and are lost. All human mtDNA, therefore, comes from the mother. An affected mother passes it to all of her children, but only daughters can pass the mutation on to the next generation.

When mutations occur on mtDNA, the resulting defective genes may outnumber the normal ones. Until mutations are present in a significant percentage of the mitochondria, symptoms might not occur. Uneven distribution of normal and mutant mtDNA in different tissues of the body means that different organ systems in individuals from the same family may be affected, and a variety of symptoms may result in affected family members. In about 20% of people with Leigh syndrome, the cause is mtDNA mutations.

Adult-onset Leigh syndrome

In cases of adult-onset Leigh syndrome, the disorder may be inherited in yet another way, as an autosomal dominant genetic trait. In autosomal dominant inheritance, a single abnormal gene on one of the autosomal chromosomes (one of the 22 nonsex chromosomes) from either parent can cause the disease. One of the parents will have the disease (since it is dominant) and will be the carrier. Only one parent needs to be a carrier in order for

the child to inherit the disease. A child who has one parent with the disease has a 50% chance of also having the disease.

Demographics

Leigh syndrome is rare. Overall, it affects about one in 40,000 newborns; the rate is much higher in some sub-populations, including in the Faroe Islands and some areas of Quebec, Canada. The classic form of the disorder accounts for approximately 80% of cases and affects males and females in equal numbers. In both X-linked Leigh syndrome and adult-onset Leigh syndrome, almost twice as many males as females are affected.

Signs and symptoms

The symptoms of developmental delay, hypotonia, and lactic acidosis are present in almost all cases of Leigh syndrome. Other symptoms vary widely and include the following:

- **Respiratory:** Hyperventilation, breathing arrest (apnea), shortness of breath (dyspnea), and respiratory failure. Respiratory disturbance may occur in as many as 70% of cases.
- **Neurological:** Muscle weakness, clumsiness, shaking, failure of muscular coordination (ataxia), and seizures.
- **Ocular:** Abnormal eye movements, sluggish pupils, and blindness.
- **Cardiovascular:** Heart disease and malformation. In adult-onset cases, progression of the disease is slower than with the classical form.

Diagnosis

The diagnosis of Leigh syndrome is usually made by clinical evaluation and a variety of tests.

Advanced imaging techniques

The main body part affected is the nerve cells (gray matter) of the brain with areas of dead nerve cells (necrosis) and cell multiplication (capillary proliferation) in the lowest part of the brain (brain stem). A CT scan or magnetic resonance imaging of the brain may reveal these abnormalities. Cysts may be present in the outer portion of the brain (cerebral cortex) as well.

Laboratory testing

Biochemical findings are high levels of pyruvate and lactate in the blood and slightly low sugar (glucose) levels in the blood and cerebrospinal fluid (CSF), a clear fluid that bathes the brain and spinal cord. Laboratory tests may reveal high levels of acidic waste products in the blood, indicative of lactic acidosis, as well as high levels of

QUESTIONS TO ASK YOUR DOCTOR

- What are the changes that will occur in my child's body as a result of Leigh syndrome?
- What are the genetic causes of this disorder?
- What types of treatment are available for my child as he or she grows through infancy and childhood as a result of Leigh syndrome?
- How long do patients with Leigh syndrome typically live?

pyruvate and alanine. The enzyme pyruvate carboxylase may be absent from the liver. An inhibitor of thiamine triphosphate (TTP) production may be present in the blood and urine of affected individuals. Blood glucose may be somewhat lower than normal. Some children with the disorder may have detectable deficiencies of the enzymes pyruvate dehydrogenase complex or cytochrome C oxidase.

Related disorders

Symptoms of other disorders are very similar to those of Leigh syndrome, and comparisons may be useful to distinguish between them. These disorders are the following:

- Wernicke encephalopathy
- Kufs disease
- Batten disease
- Tay-Sachs disease
- Sandhoff disease
- Niemann-Pick disease
- Alpers disease

Prenatal testing

Genetic counseling may be beneficial for families with a history of Leigh syndrome. Prenatal testing is available to assist in prenatal diagnosis. Prior testing of family members is usually necessary for prenatal testing.

Either chorionic villus sampling (CVS) or amniocentesis may be performed for prenatal testing. CVS is a procedure to obtain chorionic villi tissue for testing. Examination of fetal tissue can reveal information about the changes that lead to Leigh syndrome. CVS can be performed at 10 to 12 weeks of pregnancy.

Amniocentesis is a procedure that involves inserting a thin needle into the uterus, into the amniotic sac, and

withdrawing a small amount of amniotic fluid. DNA can be extracted from the fetal cells contained in the amniotic fluid and tested. Amniocentesis is performed at 15 to 18 weeks of pregnancy.

Tissue obtained from CVS or in amniotic fluid that shows evidence of the genetic abnormalities responsible for Leigh syndrome confirms the diagnosis. Other forms of prenatal testing may be available for Leigh syndrome.

Treatment and management

The most common treatment for the disorder is the prescription of thiamine or vitamin B1. This may result in a temporary improvement of the symptoms and slightly slow the progress of the disease.

Patients who lack the pyruvate dehydrogenase enzyme complex may benefit from a high-fat, low-carbohydrate diet.

To treat lactic acidosis, oral sodium bicarbonate or sodium citrate may be prescribed. To control severe lactic acidosis, intravenous infusion of tris(hydroxymethyl)aminomethane (THAM) may be beneficial. Both treatments help reduce abnormally high acid levels in the blood and the accumulation of lactic acid in the brain.

If eye problems occur, the individual with Leigh syndrome may benefit from treatment from an ophthalmologist.

Treatment should include assistance with locating support resources for the family and the individual with Leigh syndrome.

Prognosis

Prognosis for individuals with classical Leigh syndrome is poor. Death usually occurs within a few years, although patients may live to be six or seven years of age. Some patients have survived to the mid-teenage years. Children who survive the first episode of the disease might not fully recover physically and neurologically. They are likely to face successive bouts of devastating illness that ultimately cause death.

In 2021, scientists used genetic engineering to develop a model for Leigh disease that allows them to reproduce some of the developmental effects of a specific gene mutation, *SURF1*. Although it is a long way from this model to a cure for Leigh syndrome, this is the first workable model that allows researchers to experiment with possible protective measures or gene therapy for the disorder.

Clinical trials for Leigh syndrome, including experimental drug treatments and procedures, are underway. Participation in a U.S. clinical trial is voluntary and at no cost to the participant. All clinical trials receiving

U.S. government funding, and some supported by private industry, are posted at <https://www.clinicaltrials.gov>. Foreign trials are listed at <https://www.orpha.net>

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Muscular Dystrophy Association, 161 N. Clark, Suite 3550, Chicago, IL 60601, (800) 572-1717, mda@mdausa.org, <https://www.mda.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <https://rarediseases.org>

United Mitochondrial Disease Foundation (UMDF), 8085 Saltsburg Road, Suite 201, Pittsburg, PA 15239, (412) 793-8077 or (888) 317-8633, (412) 793-6477, info@umdf.org, <https://www.umdf.org>

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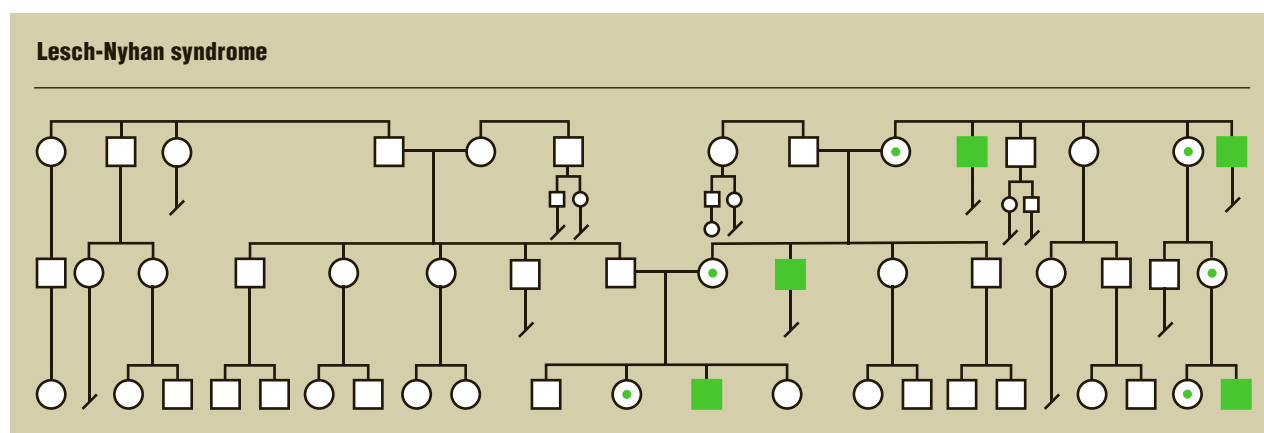
Leopard syndrome see **Multiple lentigines syndrome**

Leprechaunism see **Donohue syndrome**

Lesch-Nyhan syndrome

Definition

Lesch-Nyhan syndrome (LNS) is a rare genetic disorder that primarily affects males. Males with this syndrome develop physical handicaps, behavioral symptoms, mental retardation, and kidney problems. LNS is caused by a total absence of a purine-recycling enzyme known as hypoxanthine-guanine phosphoribosyltransferase. Self-injury is a classic feature of this genetic disease.



Lesch-Nyhan syndrome: pedigree analysis chart (Gale)

Description

Lesch-Nyhan syndrome was first described in 1964 by two American physicians, Dr. Michael Lesch and Dr. William Nyhan; its biochemical cause was identified in 1967. The syndrome is caused by a severe change (mutation) in the *HPRT1* gene. This gene is responsible for the production of an enzyme called hypoxanthine-guanine phosphoribosyltransferase (HPRT), which catalyzes a reaction necessary to prevent the buildup of uric acid. The enzyme enables cells to recycle purines, which are organic molecules critical to the structure of both DNA and RNA. A number of mutations in the *HPRT1* gene result in the absence or very low levels of HPRT enzyme activity, which in turn leads to markedly elevated uric acid levels in the blood—a condition called hyperuricemia. This buildup of uric acid is toxic to the body and is related to the symptoms associated with the disease. Absence of HPRT enzyme activity is also thought to alter the chemistry of certain parts of the brain, including the basal ganglia, affecting neurotransmitters (chemicals used for communication between nerve cells), acids, and other chemicals. This change in the nervous system is also related to the symptoms associated with Lesch-Nyhan syndrome.

Males with Lesch-Nyhan syndrome develop neurological problems during infancy. Infants with Lesch-Nyhan syndrome have weak muscle tone (hypotonia) and are unable to develop normally. Affected males develop uncontrollable writhing movements (athetosis) and muscle stiffness (spasticity) over time. Lack of speech is also a common feature of Lesch-Nyhan syndrome. The most dramatic symptom of Lesch-Nyhan syndrome, however, is the compulsive self-injury seen in 85% of affected males. This self-injury does not indicate that patients with LNS are insensitive to pain. The self-mutilating behavior involves the biting of the

patient's own lips, tongue, and fingertips, as well as head banging. These behaviors may lead to serious injury and scarring.

Some boys with LNS develop a rare blood disorder known as megaloblastic anemia, which results from impairment of DNA synthesis during the production of red blood cells. In this form of anemia, the red blood cells grow larger without dividing, resulting in enlarged but dysfunctional blood cells in the bone marrow, a lower than normal red blood cell count in the bloodstream, and low hemoglobin levels.

LNS is a disorder with some phenotypic variability even in the same family; some patients are only mildly impaired, have normal intelligence, and do not always manifest self-injurious behaviors while others show profound developmental delays with muscle contractures and progressive loss of kidney function. The overall severity of the disorder depends on the way in which the mutations in the *HPRT1* gene affect the activity levels of the HPRT enzyme. There are more than 615 mutations in the *HPRT1* gene that had been identified as of 2015.

There is a less severe genetic disorder related to LNS called Kelley-Seegmiller syndrome or HPRT-related gout; it is also caused by mutations in the *HPRT1* gene. This syndrome involves only partial deficiency (at least 8% of normal levels) of the HPRT enzyme rather than a complete lack of it. People with Kelley-Seegmiller syndrome typically suffer from gout and kidney stones but do not have the neurological symptoms associated with LNS.

A third group of patients, with mutations in the *HPRT1* gene that result in HPRT enzyme levels between 1.5% and 8% of normal, develop a milder form of LNS called HPRT deficiency, neurologic variant. This condition is marked by uric acid overproduction and neurological symptoms that may range from simple clumsiness in voluntary movements to major muscular dysfunction.

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman’s abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Athetosis—A condition marked by slow, writhing, involuntary muscle movements.

Basal ganglia—A group of nuclei (specialized clumps of cells) at the base of the forebrain responsible for control of voluntary muscle movement.

Chorea—Involuntary rapid or jerky movements.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother’s vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Hypotonia—A condition marked by poor muscle tone, often accompanied by low muscle strength. Hypotonia in infants is sometimes called “floppy baby syndrome.”

Lithotripsy—A procedure for treating kidney stones that involves the use of external shockwaves to break down the stones into small pieces that can be passed in the patient’s urine.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Neurotransmitter—Chemical in the brain that transmits information from one nerve cell to another.

Palsy—Uncontrollable tremors.

Purines—A group of organic compounds that are important building blocks of RNA and DNA. Two of the four nucleobases found in DNA (adenine and guanine) are purines.

Spasticity—Increased muscle tone or stiffness, which leads to uncontrolled and awkward movements.

Genetic profile

Mutations in the *HPRT1* gene, which is located on the long arm of the X chromosome at Xq26.1, are responsible for deficient activity of the HPRT enzyme (less than 1.5% of normal levels in patients with full-blown LNS). There have been many different mutations identified in the *HPRT1* gene. These mutations may differ in severity within the same family. Because the *HPRT1* gene is located on the X chromosome, Lesch-Nyhan syndrome is considered an X-linked disorder and affects only males.

A person’s sex is determined by their chromosomes. Males have one X chromosome and one Y chromosome; females have two X chromosomes. Males who possess a severe mutation in the *HPRT1* gene on their single X chromosome will develop Lesch-Nyhan syndrome.

Females who possess a mutation in one of their *HPRT1* genes will not develop LNS; instead, they are carriers. This difference is due to the fact that most females have another X chromosome without the mutation that prevents them from getting the disease. If a woman is a carrier, she has a 50% risk with each pregnancy to pass on her copy of the X chromosome with the mutation.

She has a 25% risk of giving birth to an affected son, a 25% risk of having a carrier daughter, a 25% chance of having an unaffected son, and a 25% chance of having an unaffected daughter. Males with LNS do not pass on their defective X chromosome because they do not reproduce due to the characteristics of the disease.

Demographics

Lesch-Nyhan syndrome affects approximately 1 in 380,000 live births. It occurs among members of all races and ethnic groups. Almost always, only male children are affected. Women carriers usually do not have any symptoms in childhood or adolescence. Women carriers occasionally develop inflammation of the joints (gout) as they get older.

Signs and symptoms

LNS is not usually diagnosed until the affected child shows signs of developmental delay or self-inflicted injuries. At birth, males with Lesch-Nyhan syndrome appear completely normal. Development is usually normal for the first few months. Symptoms develop between three

to six months of age. Sand-like crystals of uric acid in the baby's diapers may be one of the first symptoms of the disease. The baby may be unusually irritable. Typically, the first sign of nervous system impairment is hypotonia, often reflected in the baby's inability to lift the head or sit up at an appropriate age. Many patients with Lesch-Nyhan never learn to walk. By the end of the first year, writhing motions (athetosis), and spasmodic movements of the limbs and facial muscles (chorea) are clear evidence of defective motor development.

The compulsive self-injury associated with Lesch-Nyhan syndrome begins on average at three years of age. The self-injury begins with biting of the lips and tongue. As the disease progresses, affected individuals frequently develop finger biting and head banging. The self-injury can increase during times of stress.

Males with Lesch-Nyhan disease may develop kidney damage due to kidney stones. Blood in the urine (hematuria) is another frequent sign of LNS. Swollen and tender joints (gout) are another common problem.

Diagnosis

The diagnosis of Lesch-Nyhan syndrome is based initially on the distinctive pattern of symptoms. Measuring the amount of uric acid in a person's blood or urine cannot definitively diagnose Lesch-Nyhan syndrome. It is diagnosed by measuring the level of activity of the HPRT enzyme through a blood test called an enzyme assay. When the activity of the enzyme is very low, it is diagnostic of Lesch-Nyhan syndrome. LNS can also be diagnosed by molecular testing. This is also a blood test. Molecular genetic testing checks for changes (mutations) in the *HPRT1* gene. Results from DNA testing are not only helpful in making the diagnosis but may also serve to guide the family's decisions about future pregnancies. Both enzyme assays and molecular genetic testing for mutations in the *HPRT1* gene were readily available in North America and Europe as of 2015.

Prenatal diagnosis is possible by DNA testing of fetal tissue drawn by amniocentesis or chorionic villus sampling. Fetuses should be tested if the mother is a known carrier of a mutation in her *HPRT1* gene. A woman is at risk of being a carrier if she has a son with Lesch-Nyhan syndrome or if someone in her family has Lesch-Nyhan syndrome. Any woman who may be a carrier should have DNA testing.

Treatment and management

There are no known treatments for the neurological defects of Lesch-Nyhan. A medication called allopurinol

QUESTIONS TO ASK YOUR DOCTOR

- What genetic changes in my son's body are responsible for his Lesch-Nyhan syndrome?
- What changes in my son's physical and mental conditions resulting from his Lesch-Nyhan syndrome are likely to occur as he grows older?
- How can we control my son's self-destructive behaviors that result from Lesch-Nyhan syndrome?
- What is the probability of our having a second child with Lesch-Nyhan syndrome?

(Zyloprim) can lower blood uric acid levels but does not affect the behavioral problems and developmental delays. Drugs that are used to relieve the neurological symptoms in patients with LNS include haloperidol (Haldol), diazepam (Valium), lorazepam (Ativan), and phenobarbital (Luminal). Muscular symptoms may be treated with baclofen (Lioresal).

Patients with LNS who develop kidney stones may be treated with lithotripsy, a procedure that uses shock waves to break down kidney stones into pieces small enough to pass in the urine.

Some patients with Lesch-Nyhan syndrome have their teeth removed to prevent self-injury. Restraints are recommended to reduce self-destructive behaviors.

Prognosis

With strong supportive care, infants born with Lesch-Nyhan can live into their early 30s with symptoms continuing throughout life; however, many patients die in the first decade of life. Few live beyond age 40.

At present, there are no preventive measures for Lesch-Nyhan syndrome. However, recent studies have indicated that this genetic disorder may be a good candidate for treatment with gene replacement therapy. Unfortunately, the technology necessary to implement this therapy did not exist as of 2015.

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ORGANIZATIONS

Alliance of Genetic Support Groups, 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008, (202) 966-5557, (202) 966-8553, <http://www.geneticalliance.org>
 LND Net (Lesch-Nyhan Disease support group), <http://lndnet.ning.com>
 National Institute of Neurological Disorders and Stroke, PO Box 5801, Bethesda, MD 20824, (301) 496-5751 or (800) 352-9424, <http://www.ninds.nih.gov>
 National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Leukodystrophy

Definition

Leukodystrophy is a collection of about 15 rare genetic disorders that affect the brain, spinal cord, and peripheral nerves. It is characterized by abnormal growth or development of the white matter covering nerve fibers in the brain.

Description

Leukodystrophy comes from the Greek words "leuko" meaning "white" (referring to the white matter of the nervous system) and "dystrophy" meaning "abnormal growth or development." The white matter is the myelin sheath and is an extremely complex substance composed of at least ten chemicals. The myelin sheath protects the axon (a long and single-nerve cell process that acts as a wire to conduct impulses away from the cell body) much the way insulation protects an electric wire.

Each type of leukodystrophy affects one of the chemicals that make up the myelin sheath. Leukodystrophies include Alexander's disease; childhood ataxia with

central nervous system hypomyelination (CACH), also known as vanishing white matter disease; cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); cerebrotendinous xanthomatosis (CTX); metachromatic leukodystrophy; ovariroleukodystrophy syndrome; and Van der Knapp syndrome, also called vacuolating leukodystrophy with subcortical cysts, 4H leukodystrophy, and hereditary diffuse leukoencephalopathy with neuroaxonal spheroids (HDLS), which is an adult-onset leukodystrophy.

Additional leukodystrophies include adrenoleukodystrophy (ALD)/adrenomyeloneuropathy (AMN), Aicardi-Goutieres syndrome, canavan disease (spongy degeneration), Krabbe disease (globoid cell leukodystrophy), neonatal adrenoleukodystrophy, Pelizaeus-Merzbacher disease (X-linked spastic paraplegia), Refsum disease, and Zellweger syndrome.

Genetic profile

Genes are the blueprint for the human body that directs the development of cells and tissue. Mutations in some genes can cause genetic disorders such as leukodystrophy. Every cell in the body has 23 pairs of chromosomes, 22 pairs of which are called autosomes and contain two copies of individual genes. The twenty-third pair of chromosomes are called the sex chromosomes because they determine a person's sex. Males have an X and a Y chromosome, while females have two X chromosomes.

Most leukodystrophies have an autosomal recessive pattern of inheritance that affects males and females. This excludes HDLS, which is inherited in an autosomal dominant pattern. People with only one abnormal gene are carriers, but since the gene is recessive, they do not have the disorder. Their children will be carriers of the disorder but not show symptoms of the disease. Both parents must have one of the abnormal genes for a child to have symptoms of an autosomal recessive leukodystrophy. When both parents have the abnormal gene, there is a 25% chance that each child will inherit both abnormal genes and have the disease. There is a 50% chance that each child will inherit one abnormal gene and become a carrier of the disorder but not have the disease itself. There is a 25% chance that each child will inherit neither abnormal gene and not have the disease or be a carrier.

Mutations in specific genes that code for proteins that are crucial in the structure and function of the myelin sheath will cause leukodystrophy. Alexander's disease, for example, is due to a mutation in the *GFAP* gene that codes for a glial protein that acts to build the sheath

around the nerves. Vanishing white matter disease is due to a mutation in one or more of the genes *EIF2B1–EIF2B5*, all of which code for proteins that regulate the synthesis of other proteins. Van der Knapp syndrome, in 75% of cases, is due to a mutation in the *MLC1* gene, which also codes for a protein in glial cells of the brain, specifically astrocytes. In addition, metachromatic leukodystrophy is associated with a mutation in the *ARSA* gene, which is important for proteins necessary to break down lysosomes. Alterations of the *POLR3A* and *POLR3B* genes are associated with five types of leukodystrophies, including 4H leukodystrophy.

Demographics

Leukodystrophies appear to affect all racial and ethnic groups and all geographic populations. However, metachromatic leukodystrophy has been found in a higher frequency in highly inbred groups, such as the Habbanite Jewish population, and is reported in 1 in 40,000 to 1 in 160,000 people worldwide.

Signs and symptoms

The most common signs seen in most leukodystrophies include gradual changes in an infant or child who previously appeared healthy. These changes may appear in body tone, movements, gait, speech, the ability to eat, hearing, vision, behavior, and memory. Specific signs and symptoms for individual leukodystrophies include the following:

- Metachromatic, with the most common and most severe form occurring between the ages of six months and two years with symptoms such as irritability, decreased muscle tone, muscle wasting, and difficulty learning to walk and talk. Onset symptoms in older children and adults include deterioration of intellectual performance and behavioral or psychiatric problems. Blindness, seizures, and paralysis occur as the disease progresses.
- Alexander's disease, which usually begins in infancy (6 to 24 months of age), affects mostly males. Initial signs are physical retardation and intellectual disability, and as the disease progresses, enlargement of the brain and head, spasticity, and seizures. In children and adults, symptoms are the same but occur less frequently and progress more slowly.
- CACH is usually diagnosed in infancy, and initial symptoms include motor and speech difficulties that progressively worsen. Later symptoms include difficulty swallowing, seizures, and coma.
- CADASIL can be diagnosed in children and adults but usually shows up around age 45. The initial symptom is

KEY TERMS

Arteriopathy—Damage to blood vessels.

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Bile acids—Steroid acids such as cholic acid that occur in bile, an alkaline fluid secreted by the liver and passed into a part of the small intestine where it aids in absorption of fats.

Bile alcohol—A steroid acid with an alcohol group attached.

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light, resulting in blurry vision. Surgery may be performed to remove the cataract.

Dementia—A condition of deteriorated mental ability characterized by a marked decline of intellect and often by emotional apathy.

Hypomyelination—The death of myelin on a nerve or nerves.

Ischemic attack—A period of decreased or no blood flow.

Leukoencephalopathy—Any of various diseases, including leukodystrophies, affecting the brain's white matter.

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

Subcortical infarcts—Obstruction of nerve centers below the cerebral cortex of the brain.

usually migraine headaches, followed in about ten years by ischemic attacks and small strokes then by mood disturbances and dementia. Epilepsy sometimes occurs.

- CTX may present initial symptoms of cataracts, mild intellectual disability, and fatty tumors (called xanthomas) in tendons, especially the Achilles tendon or heel cord. Later symptoms include seizures, emotional or psychiatric disturbances, and impaired motion or muscle movement.
- Ovarioleukodystrophy syndrome usually has onset symptoms of walking difficulties and/or intellectual disability.
- Van der Knapp syndrome can have onset at or shortly after birth with the symptom of an extremely enlarged head. Onset usually occurs between ages four and five with initial symptoms of cerebella ataxia followed by spasticity. Later symptoms include mental slowing and

learning problems and sometimes epileptic seizures and severe walking impairment.

Diagnosis

Leukodystrophies are occasionally misdiagnosed as muscular dystrophy, since they all are neurological disorders involving white matter. Genetic testing is usually necessary for all leukodystrophies. A nerve conduction velocity (NCV) test is sometimes used to evaluate nerve damage in people with metachromatic leukodystrophy. The NCV test sends small electrical shocks through one end of a nerve. The time it takes to travel to the other end of the nerve is measured to help determine the severity of nerve damage. Diagnosis of CTX is made by measuring the levels of bile alcohol in the blood or urine or of cholestanol in the blood. Cholestanol is similar chemically to cholesterol but can be distinguished from it by special chemical tests. MLD and Van der Knapp syndrome diagnosis are usually made by a brain imaging scan called magnetic resonance imaging. A series of biochemical tests is sometimes used to diagnose MLD.

Treatment and management

With the exception of CTX, none of the leukodystrophies covered here are treatable. In some of the disorders, specific symptoms can be treated. For example, some infections associated with MLD, such as pneumonia, can be treated with antibiotics. In ovarioleukodystrophy syndrome, ovarian insufficiency can be treated with hormone replacement therapy. However, there are no treatments available for most of the conditions associated with leukodystrophies, such as intellectual disability; dementia; deterioration of speech, vision, and mobility; and degeneration of myelin (white matter). In CTX, administration of certain bile acids, especially chenodeoxycholic acid, can prevent further progression of the disorder and in some cases may bring improvement.

Prognosis

The prognosis varies between leukodystrophy types, but overall most people with leukodystrophy can expect a shortened lifespan. Infants with Alexander's disease generally do not live past the age of five or six. Infants with MLD usually do not live past age 10. In children and adults, Alexander's disease and MLD progress more slowly but life expectancy is still shortened, roughly 10 years post onset. Life expectancy with CACH is also shortened, with few people living beyond age 40. CADA-SIL progresses slowly, but death occurs on average about 21–22 years after onset of symptoms. Life expectancy is closer to normal with CTX provided it is diagnosed and treated early. Ovarioleukodystrophy is a relatively newly

QUESTIONS TO ASK YOUR DOCTOR

- What type of leukodystrophy does my child have?
- What are the treatment options for my child?
- What are the chances that any of my future children will have a leukodystrophy, and is genetic testing available to us?
- What is the prognosis for my child?
- How can this be managed to improve the quality of life of my child?

identified disorder and there is not enough information available to make a prognosis of life expectancy other than to say it is probably reduced. The average life expectancy is also unknown for Van der Knapp syndrome; several patients have died in their 20s, but others are still alive in their 40s.

A number of government agencies and private foundations are currently funding research into many of the leukodystrophies, including identifying the cause of individual disorders, developing therapies to prevent disease progression, and preventing onset of disease. However, according to the Myelin Project, a private research foundation, little research is being done on therapies to repair damage already done by the disorders or to restore functions lost because of the disorders.

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National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

United Leukodystrophy Foundation, 224 N. Second St., Suite 2,
DeKalb, IL 60115, (815) 748-3211 or (800) 728-5483,
(815) 895-2432, office@ulf.org, http://www.ulf.org

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Le Merrer syndrome see **3-M syndrome**

Li-Fraumeni syndrome

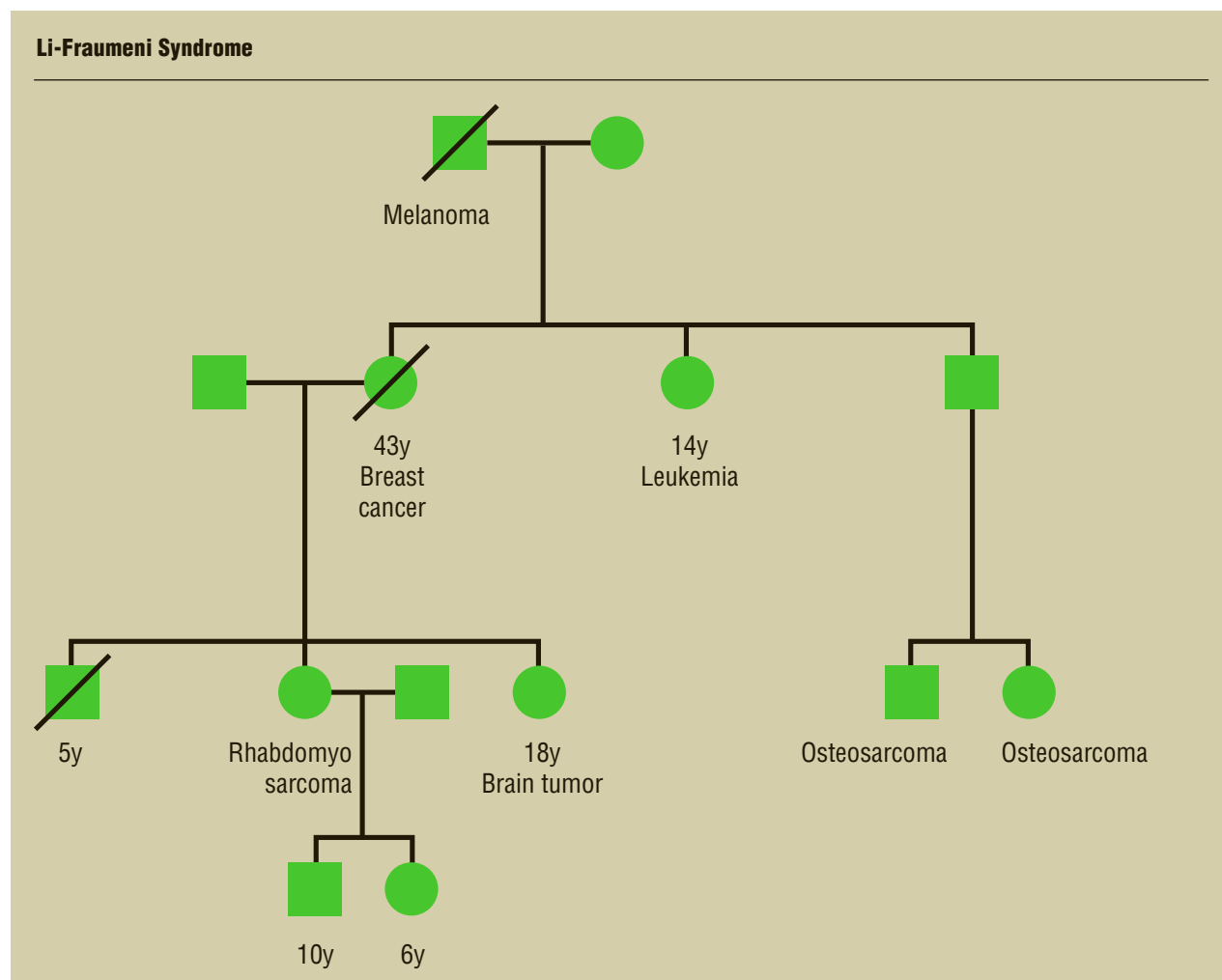
Definition

Li-Fraumeni syndrome (LFS) is a hereditary condition in which individuals have an increased risk of developing certain kinds of tumors. The characteristic tumors of LFS are adrenocortical carcinoma, breast cancer, brain cancer, leukemia, and sarcoma. Li-Fraumeni syndrome

was previously known as the sarcoma, breast, leukemia, and adrenal gland (SBLA) syndrome.

Description

Li-Fraumeni syndrome is an inherited condition that is associated with a significantly increased risk of developing certain kinds of cancer. It is classified as a hereditary cancer syndrome and was first described in 1969 by two American physicians, Frederick Pei Li (1940–) and Joseph F. Fraumeni, Jr. (1933–). Hereditary cancer syndromes typically result in multiple family members developing cancer, in family members developing the same kind(s) of cancer, in family members developing cancer at a young age, and in family members developing more than one primary cancer. In contrast, most people who develop cancer are diagnosed later in life, often in their 60s and 70s, and do not have multiple close family members, such as a



Li-Fraumeni syndrome: pedigree analysis chart (Gale)

parent and/or siblings, who have developed the same kind of cancer.

Five cancers are characteristic of LFS. These five cancers are adrenocortical carcinoma, breast cancer, brain cancer, leukemia, and sarcoma. Such other types of cancer as melanoma, colon cancer, and stomach cancer have been seen in families with LFS, but it is not certain whether these tumors are truly a part of LFS.

Adrenocortical carcinoma is a rare cancer affecting a specific part of the adrenal gland called the adrenal cortex. There are two adrenal glands, and each one sits on the upper part of a kidney. Adrenal glands produce hormones, and if a cancer is present, more hormones may be produced, resulting in symptoms. In LFS, adrenocortical carcinomas typically develop in childhood.

Brain cancer refers to a tumor developing in the brain. There are different kinds of tumors that may develop in the brain; the type depends upon the part of the brain involved. The brain tumors that occur in LFS tend to develop in young adulthood, although they may develop at any age.

Breast cancer is a cancer affecting the breast. In LFS, women are often diagnosed with breast cancer in their 20s, 30s, and 40s. Although breast cancer in men is rare, it does occur both within families with LFS and in the general population.

Leukemia refers to cancer of the blood. There is more than one type of leukemia; the type depends upon the kind of blood cell involved and whether the cancer is fast (acute) or slow (chronic) growing. Overall, acute lymphocytic leukemia (ALL) is the most common leukemia in children, and acute myelogenous leukemia (AML) is common in young adults. Chronic myelogenous leukemia (CML) is a common leukemia in older individuals. Li-Fraumeni syndrome is typically associated with acute leukemias and is most often diagnosed in children, adolescents, and young adults.

Sarcoma refers to a soft-tissue tumor, meaning that the tumor has developed in bone, muscle, or connective tissue. Osteosarcoma refers to a sarcoma that has developed in the bone. Rhabdomyosarcoma is a sarcoma that has developed in the muscle. Both of these sarcomas are associated with LFS and typically are diagnosed in children and in adults before the age of 35 years. A third type of sarcoma, Ewing’s sarcoma, is another type of sarcoma arising in bone, but it is not associated with LFS.

An individual inheriting the familial LFS gene alteration has a significantly increased risk of developing one of the five characteristic cancers in his/her lifetime. This risk is about 85%–90% by age 60, meaning that 85–90 out of 100 individuals inheriting a LFS gene

Age of onset for cancers associated with Li-Fraumeni syndrome	
Age of onset	Type of cancer
Infancy	Development of adrenocortical carcinoma
Under 5 years of age	Development of soft-tissue sarcomas
Childhood and young adulthood	Acute leukemias and brain tumors
Adolescence	Osteosarcomas
Twenties to thirties	Premenopausal breast cancer is common

(Gale)

alteration will develop one of the five characteristic cancers by the time he/she reaches 60 years of age. Much of this risk occurs in childhood through middle adulthood, with the majority of individuals developing cancer by the time they reach 30 years of age.

Genetic profile

Li-Fraumeni syndrome follows an autosomal dominant inheritance pattern, meaning that every individual diagnosed with LFS has a 50% chance of passing on the condition to each of his/her children. Nearly every individual inheriting the LFS gene alteration will develop at least one of the characteristic tumors. However, not every family member inheriting the LFS gene alteration will develop the same kind of tumor. Additionally, some family members may develop more than one tumor, whereas other family members may develop one tumor. For example, a family history may include a father who was diagnosed with a brain tumor at age 50, a daughter who was diagnosed with an adrenocortical carcinoma at age three and breast cancer at age 43 years, and a granddaughter who was diagnosed with sarcoma at age seven.

The majority of families with LFS have an alteration in the *TP53* gene located on the short arm of chromosome 17 at location 17p13.1. This gene codes for a protein that functions as a tumor suppressor. Mutations in the *TP53* gene that alter the tumor suppressor protein thus allow cells with damaged DNA to continue to reproduce, thus increasing the individual’s risk of developing tumors. Some cases of LFS, however, develop in individuals without a family history of the syndrome. Researchers estimate that between 7% and 20% of mutations in the *TP53* gene are *de novo* mutations.

Another gene that has recently been associated with Li-Fraumeni syndrome is the *CHEK2* gene on the long arm of chromosome 22 at 22q12.1. This gene codes for a protein that is also involved in DNA repair and the programmed death of damaged cells. As of 2015, several families with cancers characteristic of LFS have been identified with mutations in the *CHEK2* gene.

Researchers are not yet certain, however, whether mutations in this gene actually cause LFS or whether they simply increase the risk of developing the cancers typical of Li-Fraumeni syndrome.

Demographics

Li-Fraumeni syndrome is a rare condition. One American registry indicates that about 400 people from 64 families in the United States have LFS. About 400 families worldwide have been reported in the medical literature as of 2015; however, not all families with LFS have been reported in the medical literature. Males and females are equally affected. There was no evidence as of 2015 that certain races or ethnic groups are at greater risk of LFS than others.

Signs and symptoms

General symptoms of cancer include unexplained weight loss, weakness, fatigue, and pain. It should be noted that the same kind of cancer may cause different symptoms in different people. Individuals with LFS may develop other kinds of cancer; consequently, any new and/or unusual symptom should be evaluated by a physician.

Symptoms specific to each tumor are as follows: Adrenocortical carcinomas may cause abdominal pain. In some cases, the tumor causes extra hormones to be produced and, if so, the individual may experience high blood pressure, diabetes, deepening of the voice, swelling of the sexual organs and/or breasts, or growth of hair on the face. Brain cancer may result in a number of symptoms including vomiting, seizures, headaches, behavioral changes or problems, changes in eating or sleeping patterns, fatigue, or clumsiness. Breast cancer typically results in a lump in the breast. Occasionally, the nipple may invert, or the skin over the lump may dimple. In rare cases, the breast may suddenly become red and swollen. Breast cancer can be identified before symptoms develop by the use of mammography. Leukemia may result in unusual bruising, a pale appearance, and/or recurrent infections. Little red or purple spots called petechiae may develop on the skin. Sarcomas result in different symptoms depending upon the type of sarcoma. Osteosarcomas often lead to swelling and pain, symptoms that may be confused with an injury. Rhabdomyosarcomas cause a lump to develop and produce swelling.

Diagnosis

Evaluation of a family history for LFS requires a detailed three-generation family tree as well as medical records and/or death certificates to confirm or clarify the tissues involved as well as the age of the individual at

KEY TERMS

Chemotherapy—Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of the cancerous cells or by killing the cancer cells.

De novo mutation—A genetic mutation that is not inherited from either parent. The Latin phrase means “new.”

Mammography—X-rays of the breasts; used to screen for breast cancer.

Metastasis (plural, metastases)—The spreading of cancer from the original site to other locations in the body.

Primary tumor—The organ or tissue where the tumor began.

Protocol—A set of guidelines for medical tests or treatments.

Radiation therapy—Treatment using high-energy radiation from x-ray machines, cobalt, radium, or other sources.

Stage—The extent of the tumor. Tests are done to determine whether the tumor is localized to the organ or whether it has spread to the lymph nodes and/or other organs. Treatment is determined by the stage of the cancer.

Tumor—An abnormal growth of cells. Tumors may be benign (noncancerous) or malignant (cancerous).

the time of his/her diagnosis. Diagnosis of LFS depends upon the types of tumors family members have developed and the ages at which the tumors were diagnosed. A set of criteria for diagnosing LFS has been established.

A family may not meet the criteria for diagnosis of LFS but may have features that suggest LFS. Families such as these may be said to be “Li-Fraumeni-like” (LFL). Two sets of criteria have been developed for LFL, which, like the diagnostic criteria, are based upon the high incidence of tumors in these families and the early ages of diagnosis.

Caution needs to be used when evaluating a family history of early-onset breast cancer, that is, diagnosis in the 20s and 30s, since several other genes besides *TP53* are known to result in women’s having an increased risk of developing breast cancer at young ages. The clinical features of these other genes must be taken into account and evaluated while evaluating a family for LFS.

Genetic testing for *TP53* gene mutations is available and provides an additional method for making a diagnosis. It may be offered to an individual who has developed one of the tumors characteristic of LFS and who has a family history that meets the diagnostic criteria or strongly suggests LFS in order to confirm the diagnosis of LFS in the family. This is referred to as diagnostic testing. If a mutation is identified, the positive test result provides proof of the diagnosis. If no mutation is identified, this negative test result does not necessarily eliminate the diagnosis of LFS. Genetic testing may not identify a mutation for two reasons. First, laboratory techniques are not perfect, and not every mutation in the *TP53* gene has been or can be identified; about 70%–80% of mutations are identifiable. Second, it is possible that mutations in other genes, including *CHEK2*, contribute to a person's risk of LFS.

Genetic testing for LFS may be offered for a second reason. Genetic testing may be offered to an individual who has no personal history of cancer but whose family history meets the diagnostic criteria for LFS or is strongly suggestive of LFS. It is usually offered in order to determine this individual's risk of developing cancer and to help with decisions regarding medical screening. Genetic testing in this case is referred to as predictive or presymptomatic genetic testing. Predictive genetic testing should not be done unless a *TP53* genetic alteration has already been identified in an affected family member.

Genetic testing for diagnostic and predictive purposes is associated with significant risks and limitations, and uncertain benefits, and is best done with a geneticist (a doctor specializing in genetics) and/or genetic counselor knowledgeable about LFS and the implications of genetic testing. Predictive genetic testing for LFS does not provide a clear benefit for all family members at risk of inheriting a familial *TP53* gene alteration, since medical screening and prevention methods are not available for the tumors associated with LFS.

Prenatal diagnosis of LFS is available only if a *TP53* genetic alteration has already been identified in the family. Prenatal diagnosis of LFS is considered to be predictive genetic testing, and therefore the issues surrounding predictive genetic testing exist in this situation. An additional issue is how the test result will be used with regard to continuation of the pregnancy. Individuals considering prenatal diagnosis of LFS should confirm its availability prior to conception.

Treatment and management

There is no cure or method for preventing LFS. Treatment depends upon the tumor(s) that an individual develops. An individual does not require treatment until

QUESTIONS TO ASK YOUR DOCTOR

- What is the most serious health risk faced by a child diagnosed with Li-Fraumeni syndrome?
- Are there medications or medical procedures that can be used to cure my child's Li-Fraumeni syndrome or to reduce its severity?
- Are there books, pamphlets, brochures, or other material in which my child can eventually read about this condition?
- What is the best way to monitor the progress of my child's Li-Fraumeni syndrome over the years?

a tumor develops, and then the treatment will be specific to the type of tumor that has developed. An individual without symptoms should undergo regular medical checkups.

In general, tumors are treated by surgery, chemotherapy, and/or radiation therapy. Adrenocortical carcinomas and breast cancers, depending upon the stage of the tumor, use one or more of these treatments. Brain cancer is treated by surgery and/or radiation. In some cases, chemotherapy is also used. Leukemia is primarily treated by chemotherapy. In some cases, bone marrow transplantation is used. Osteosarcoma is treated by surgery. Rhabdomyosarcoma is treated by surgery, chemotherapy, and radiation therapy.

It is very important that an individual's physician be aware of the family history and the cancer risk. It has been suggested that children of a parent with LFS have a complete physical examination, urinalysis, complete blood count (CBC), and abdominal ultrasound examination each year. For adults at risk of having inherited a familial *TP53* gene alteration, it has been suggested that they undergo a complete physical examination with skin, nervous system, and rectal examinations once a year, and that women undergo a clinical breast examination every six months and mammography once a year. Women at risk should also begin having mammograms at an earlier age, usually around age 25.

According to the Li-Fraumeni Syndrome Association, however, it is difficult to develop a surveillance protocol that is applicable to all persons in a family with a history of LFS. This complexity is the result of the fact that people with LFS are at risk of several different types of hereditary tumors that develop at different points in the person's lifetime. An additional complication is psychological; as reported by a group of Yale cancer specialists

in 2015, some patients with LFS are made extremely anxious by intensive surveillance and may find repeated screening an emotional burden.

One recent protocol that has been recommended is a combination of blood tests, colonoscopy, mammography, ultrasound, breast MRI, brain MRI, and whole-body MRI. The Association points out that while this series of tests appeared to improve survival in the group of patients who received the screening, the tests are time-consuming and expensive, and the long-term benefits of this approach are unclear as of 2015. The Association recommends that patients with LFS discuss screening and surveillance with their doctors on an individual basis.

There is controversy concerning the use of mammography in women with LFS because of some suggestion that *TP53* gene alterations are sensitive to radiation. In general, an individual may decrease his/her chance of developing cancer by exercising on a regular basis, eating a healthy diet, limiting sun exposure, limiting alcohol intake, and not smoking. Lastly, an individual with or at risk of LFS should not delay seeing his or her physician if he or she notices a new or unusual symptom.

Prognosis

An individual who has LFS has a very high chance of developing a cancerous tumor by the time he/she is 60 years old. In contrast, individuals in the general population have about a 2% risk of developing cancer by the same age. The cancers associated with LFS each have a different prognosis, so an individual's prognosis is highly dependent upon the type of cancer he or she has developed. In some cases, prognosis is associated with how early the cancer has been found. For example, breast cancer found early has a better prognosis than breast cancer found later. In general, the cancers typically seen in LFS are curable if caught early. For this reason, regular medical screening is important. Prognosis may also be affected by the individual's overall health; consequently, being healthy and engaging in healthy behaviors may increase the chances of a good outcome.

Resources

BOOKS

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PERIODICALS

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WEBSITES

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"Li-Fraumeni syndrome." MedlinePlus. <https://medlineplus.gov/genetics/condition/li-fraumeni-syndrome/> (accessed July 8, 2021).

ORGANIZATIONS

Li-Fraumeni Syndrome Association, PO Box 6458, Holliston, MA 01746, (855) 239-LFSA, <http://www.lfsassociation.org>

National Cancer Institute, Office of Communications, MSC 9760, 9609 Medical Center Dr., Bethesda, MD 20892, (240) 276-6600, <http://cancer.gov>

National Human Genome Research Institute (NHGRI), Bldg. 31, Room 4B09, 31 Center Dr., MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, (301) 402-2218, <http://www.genome.gov>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06813, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Limb-girdle muscular dystrophy

Definition

Limb-girdle muscular dystrophy (LGMD) encompasses a diverse group of hereditary degenerative muscle disorders characterized by weakness and deterioration of the proximal skeletal muscles. Some doctors prefer to speak of these disorders in the plural—limb-girdle muscular dystrophies—because the various types differ widely in terms of frequency, severity, and associated genes.

Description

The term "limb-girdle muscular dystrophy" is used to describe a group of muscular dystrophies that cause a muscle deterioration that primarily affects the voluntary muscles around the limb girdle. The muscles of the limb girdle include those around the shoulders and hips. As the disease develops, the distal muscles of the limbs can become affected. Most individuals' muscles of the heart are not affected, but exceptions can occur. There are at least 24 different LGMDs (some researchers count as many as 30) that had been identified as of 2015, each having a different constellation of symptoms. Each of the muscular dystrophies results in an absent, deficient, or abnormal protein that is required for normal structure and function of the muscles. It can be difficult to differentiate

Symptoms of the limb-girdle muscular dystrophies

Type	Age of onset	Early symptoms	Late symptoms
*Sarcoglycanopathy (complete deficiency)	3–15 years (8.5 average)	Proximal weakness; Difficulty walk/run; Enlarged calf muscle	Contractures; Curvature in the spine; Wheelchair bound; Possible: Cardiac conduction defect; Dilated cardiomyopathy
**Sarcoglycanopathy (partial deficiency)	Adolescence/Young adulthood	Muscle cramps; Intolerance to exercise	
Calpainopathy	2–40 years (8–15 average)	Proximal weakness; Jutting backwards of shoulder blades (scapular winging); Decreased size of calf muscles; Contractures; Curvature in the spine	Wheelchair bound
Dysferlinopathy	17–23 years	Some patients have distal weakness and some have proximal weakness; Inability to tip-toe; Difficulties walk/run	
Telethoninopathy	Early teens		Wheelchair bound
LGMD2H	8–27 years		Wheelchair bound
LGMD2I	1.5–27 years		Wheelchair bound
LGMD1A	18–35 years	Proximal leg and arm weakness; Tight Achilles tendon; Problems with articulation of speech; Nasal sounding speech	Distal weakness
LGMD1B	4–38 years (50% onset childhood)	Proximal lower limb weakness	Contractures; Irregular heart beat; Sudden death due to cardiac problems (if untreated)
LGMD1D	<25 years	Proximal muscle weakness; Cardiac conduction defect; Dilated cardiomyopathy	All patients remain able to walk
LGMD1E	9–49 years (30 average)	Proximal lower and upper limb muscle weakness	Contractures; Difficulties swallowing
Caveolinopathy	Approx. 5 years	Mild to moderate proximal weakness; Muscle cramping; Enlargement of the calf muscles; Some have no symptoms	
Bethlem myopathy	<2 years	Floppy muscles in infancy; Proximal muscle weakness; Contractures	2/3 of patients are wheelchair bound by age 50

*Includes alpha, beta, gamma and delta sarcoglycanopathies that result in complete absence of a sarcoglycan protein

**Includes alpha, beta, gamma and delta sarcoglycanopathies that result in decreased amounts of a sarcoglycan protein

(Gale)

LGMD from other muscular dystrophies and muscle disorders that can also result in weakness in the limb girdle.

Genetic profile

Each type of limb-girdle muscular dystrophy is caused by changes in a different type of gene that produces a protein normally involved in the functioning of the skeletal muscles. Each gene is found at a specific location on a chromosome. Every person inherits two copies of a gene, one from their mother and one from their father. Each type of gene produces a specific type of protein. A change (mutation) in a gene can cause it to produce an abnormal protein, to produce an increased or decreased amount of normal protein, or to stop producing protein altogether. Abnormal or decreased amounts of skeletal muscle proteins can affect the development or functioning of the muscle cells, causing the symptoms of LGMD. Most forms of LGMD are autosomal recessive, although some rare forms are autosomal dominant. As of 2015, 16 forms of LGMD had been identified as autosomal recessive, and 8 forms as autosomal dominant.

The autosomal dominant forms are identified by the symbol LGMD1 followed by the letters A through H for the 8 subtypes. Similarly, the autosomal recessive forms are identified by the symbol LGMD2 followed by the letters A through Q.

An autosomal recessive form of LGMD is caused by a change in both genes of a pair. One of the changed genes is inherited from the egg cell of the mother, and one is inherited from the sperm cell of the father. Parents who have a child with an autosomal recessive form of LGMD are called carriers, since they each possess one changed *LGMD* gene and one unchanged *LGMD* gene. Carriers do not have any symptoms, as they have only one unchanged gene, which produces enough normal protein to prevent the symptoms of LGMD. Each child born to parents who are both carriers for the same type of LGMD has a 25% chance of having LGMD, a 50% chance of being a carrier, and a 25% chance of being neither a carrier nor affected with LGMD. Parents who are each a carrier for a different type of LGMD are not at increased risk for having children affected with LGMD.

The autosomal dominant forms of LGMD are caused by a change in only one gene of a pair. This changed gene is inherited from either the mother or the father. If the changed gene is inherited, each child born to a carrier of LGMD has a 50% chance of inheriting the condition. Sometimes the change occurs spontaneously when the egg and sperm come together to form the first cell of the baby. In this case, other relatives, such as siblings, are probably not at increased risk for inheriting LGMD. People with an autosomal dominant form of LGMD have a 50% chance of passing the condition on to their children. Some people who possess an autosomal dominant LGMD gene change do not have any symptoms.

Demographics

The incidence of the LGMDs is difficult to estimate, as the various subtypes can have a wide variety of symptoms. The rate of incidence of LGMD is 1 in 14,500–123,000 people and is found equally in men and women. LGMD is also difficult to differentiate from other muscular disorders. Some forms of LGMD are found more commonly in people of a certain ethnic background; for example, one rare form of autosomal recessive LGMD has been found only in people of Turkish ancestry and another only in people of Finnish ancestry.

Signs and symptoms

Each type of LGMD has a different range of symptoms. The symptoms can even vary among individuals with the same type of LGMD. The age of onset of symptoms can range from infancy to adulthood. In general, the

autosomal dominant subtypes of LGMD have a later onset in life than the autosomal recessive forms. The most common symptom of LGMD is muscle weakness and deterioration that involves the muscles around the hips and shoulders. The disorder progresses at a different rate in each person. Although individuals with an onset of the disorder in adulthood may have a slower progression and milder symptoms, the exact progression and extent of muscle deterioration cannot be predicted.

The first noticeable symptom of LGMD is often a waddling gait due to weakness of the hip and leg muscles. Difficulties in rising from a chair or toilet seat and difficulties in climbing stairs are common. Eventually, walking may become impossible and lead to the need of a wheelchair or scooter for locomotion. Enlargement or a decrease in size of the calf muscles can also be seen. Some individuals with LGMD also experience contractures and muscle cramps. The limited mobility associated with LGMD can result in muscle soreness and joint pain.

Lifting heavy objects, holding the arms outstretched, and reaching over the head can become impossible for people affected with LGMD because of weaknesses in the shoulder muscles. Some individuals with LGMD may eventually have difficulties swallowing and feeding themselves. Sometimes the back muscles can become weakened and result in scoliosis (curvature of the spine).

LGMD can occasionally result in a weakening of the heart muscles (cardiomyopathy) and/or the respiratory muscles. Some people may develop a conduction defect, an abnormality in the electrical system of the heart that regulates the heartbeat. A weakening of the muscles

Genetic causes of the limb-girdle muscular dystrophies

Type	Mode of inheritance	Gene involved	Chromosomal location
*Alpha-sarcoglycanopathy	Recessive	LGMD2D (SGCA)	17q12–q21.3
*Beta-sarcoglycanopathy	Recessive	LGMD2E (SGCB)	4q12
*Gamma-sarcoglycanopathy	Recessive	LGMD2C (SGCG)	13q12
*Delta-sarcoglycanopathy	Recessive	LGMD2F (SGCD)	5q33
Calpainopathy	Recessive	LGMD2A (CAPN3)	15q15.1–q21.1
Dysferlinopathy/Miyoshi distal myopathy	Recessive	LGMD2B (DYSF)	2q13.3–p13.1
Telethoninopathy	Recessive	LGMD2G (TCAP)	17q12
LGMD2H	Recessive	LGMD2H (TRIM32)	9q31–34.1
LGMD2I	Recessive	LGMD2I (FKRP)	19q13.3
LGMD1A	Dominant	LGMD1A (TTID)	5q31
LGMD1B	Dominant	LGMD1B (LMNA)	1q21.2
Caveolinopathy	Dominant	LGMD1C (CAV3)	3p25
LGMD1D	Dominant	LGMD1D	7q
LGMD1E	Dominant	unknown	unknown
Bethlem myopathy	Dominant	COL6A1	21q22.3
	Dominant	COL6A2	21q22.3
	Dominant	COL6A3	2q37

* Each type of sarcoglycanopathy can result from a gene change that results in complete absence of sarcoglycan protein or decreased amounts of sarcoglycan protein.

(Gale)

Frequency of limb-girdle muscular dystrophy

Type	Frequency	Most common in:
Alpha-sarcoglycanopathy		None
Beta-sarcoglycanopathy	Majority with severe disease	Amish
Gamma-sarcoglycanopathy	10% of those with mild disease	North Africans; Gypsies
Delta-sarcoglycanopathy		Brazilian
Calpainopathy	Approximately 10%–30%	Amish; La Reunion Isle.; Basque (Spain); Turkish
Dysferlinopathy	Approximately 10%	Libyan Jews
Telethoninopathy	Rare	Italian
LGMD2H	Unknown	Unknown
LGMD2I	Unknown	Unknown
LGMD1A	Rare	Unknown
LGMD1B	Rare	Unknown
Caveolinopathy	Rare	Unknown
LGMD1D	Rare	Unknown
LGMD1E	Rare	Unknown
Bethlem myopathy	Rare	Unknown

(Gale)

necessary for respiration can cause breathing difficulties. LGMD does not, however, affect the brain and the ability to reason and think. Individuals with LGMD maintain normal bladder and bowel control and sexual functioning.

Diagnosis

No single test can diagnose LGMD. A diagnosis is based on clinical symptoms, physical examinations, and a variety of tests. The physician will first take a medical history to establish the type of symptoms experienced and the pattern of muscle weakness. Questions will usually be asked about the family history to see whether other relatives have similar symptoms.

It is necessary for the doctor to establish whether the weakness is due to problems with the muscles or due to a problem with the nerves that control the muscles. Sometimes this distinction can be accomplished through a physical examination. Electromyography testing is often performed to establish whether the weakness is in the nerves or the muscles. During electromyography, a needle electrode is inserted into the muscle and measurements are taken of the electrical activity of the muscle in response to stimulation by the nerves.

A blood test that measures the amount of creatine kinase is often performed. Creatine kinase is an enzyme that is produced by damaged muscles. High levels of creatine kinase suggest that the muscle is being destroyed, but high levels by themselves cannot indicate the cause of the damage. The most common causes of increased creatine kinase levels are muscular dystrophy and muscle inflammation.

A muscle biopsy will often be performed if LGMD is suspected. During the muscle biopsy, a small amount of

muscle is surgically removed. The muscle sample is examined to check for changes that are characteristic of muscular dystrophies. The amount and type of muscle proteins present in the sample can sometimes help to confirm a diagnosis of LGMD and can sometimes indicate the type of LGMD.

Ultimately, a diagnosis can be difficult to make, as there are many types of LGMD and a wide range of symptoms. It can also be difficult to differentiate LGMD from other muscular dystrophies that have similar symptoms, such as Becker and Duchenne muscular dystrophies. Anyone suspected of having LGMD should consider undergoing testing for other types of muscular dystrophies.

DNA testing for some forms of LGMD is now available through clinical and commercial laboratories. DNA testing is complicated by the many genes—at least 22 known as of 2015—and the types of gene mutations (changes) that can cause LGMD. To help with the cost and complexity of genetic testing for LGMD, a consortium of seven different muscular dystrophy foundations and healthcare systems is offering free genetic testing for these disorders (<http://lgmd-diagnosis.org/home>). Physicians who use the lgmd-diagnosis.org website can connect automatically to an online tool called the Automated LGMD Diagnostic Assistant (ALDA), developed by the Jain Foundation. ALDA is a subtyping tool that allows the physician to identify the most likely subtypes of LGMD affecting a given patient, thus saving the time and money that would be required to sequence all the genes that have been linked to LGMD. In October 2014, the American Academy of Neurology and the Practice Issues Review Panel of the American Association of

KEY TERMS

Amniocentesis—A procedure performed between 16 and 18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into the uterus to draw out a small sample of the amniotic fluid from around the fetus; either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Amniotic sac—Contains the fetus that is surrounded by amniotic fluid.

Autosomal dominant—A pattern of genetic inheritance in which only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are needed to display the trait or disease.

Cardiac conduction defect—An abnormality of the electrical system of the heart that regulates the heartbeat.

Carrier—A person who possesses a gene for a trait without showing signs of the disorder; the person may pass the mutated gene on to offspring.

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA; humans have 46 chromosomes arranged into 23 pairs.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Dilated cardiomyopathy—A diseased and weakened heart muscle that is unable to pump blood efficiently.

Distal muscles—Muscles that are farthest away from the center of the body.

DNA testing—Analysis of DNA (the genetic component of cells) in order to determine mutations in genes that may indicate a specific disorder.

Gene—A building block of inheritance that contains the instructions for the production of a particular protein and is made up of a molecular sequence found on a section of DNA; each gene is found on a precise location on a chromosome.

Limb girdles—The areas of the body around the shoulders and hips.

Prenatal testing—Testing for a disease, such as a genetic condition, in an unborn baby.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures, and controlling the basic functions of the human body.

Proximal muscles—The muscles closest to the center of the body.

Scapular winging—The jutting-back of the shoulder blades that can be caused by muscle weakness.

Skeletal muscle—A muscle under voluntary control that attaches to bone and controls movement.

Neuromuscular and Electrodiagnostic Medicine issued updated guidelines about the importance of genetic testing in diagnosing the various subtypes of LGMD and guidance for physicians about which of the many genetic tests they should select.

DNA testing may be performed on a sample of blood cells or a sample of muscle cells. If an autosomal dominant gene mutation is detected in someone with LGMD, then both of the individual's parents can be tested to see whether the gene mutation was inherited. If the gene mutation was inherited, siblings can be tested to see whether they have inherited the mutated gene. If autosomal recessive gene mutations are detected, relatives, such as siblings, can be tested to see if they are carriers.

Prenatal testing for LGMD is available only if DNA testing has detected an autosomal dominant *LGMD* gene mutation in one parent or an autosomal recessive gene

mutation in both parents. Cells for prenatal testing are obtained through amniocentesis or chorionic villus sampling. These cells are analyzed for the *LGMD* gene mutation or mutations that were found in one or both parents.

Treatment and management

Physical therapy and exercises can often help keep the muscles and joints mobile and prevent contractures. Muscle and joint pain can be treated through exercise, warm baths, and pain medications. Surgical treatment of such complications as contractures or a curved spine may be necessary. Breathing exercises can sometimes help if breathing becomes difficult. If breathing independently becomes impossible, a portable mechanical ventilator can be used. A wheelchair or scooter can help when a person can no longer walk. Patients with autosomal dominant forms of LGMD should be carefully

QUESTIONS TO ASK YOUR DOCTOR

- How is limb-girdle muscular dystrophy different from other forms of muscular dystrophy?
- Please explain the process of gene therapy for this disorder and review the current state of research in this area.
- How can our family get in touch with organizations that provide information and support for families with some form of muscular dystrophy?
- How can you determine the prognosis for my child with limb-girdle muscular dystrophy?

monitored by a cardiologist for heart disorders. Medications are often prescribed for cardiomyopathies and heart conduction defects. A device such as a pacemaker that creates normal contractions of the heart muscle may be necessary for some people with heart muscle abnormalities.

Gene therapy may one day cure or improve LGMD. Gene therapy introduces unchanged copies of a *LGMD* gene into the muscle cells. The goal of therapy is for the normal *LGMD* gene to produce normal protein that will allow the muscle cells to function normally. Gene therapy clinical trials are still in their infancy. As of 2015, the two most notable trials of gene therapy for LGMD were one conducted in a laboratory in Paris and funded by the French Muscular Dystrophy Association and one conducted in the Center for Gene Therapy in the Nationwide Children's Hospital in Columbus, Ohio. It will take quite a few years, however, for gene therapy to become a viable way to treat LGMD.

Prognosis

The prognosis of LGMD varies tremendously. Most people with LGMD do not have severe symptoms, and most experience a normal life expectancy. Cardiac and respiratory difficulties may, however, shorten the patient's lifespan; patients who become wheelchair-bound in their early teens usually die of respiratory failure by their late teens.

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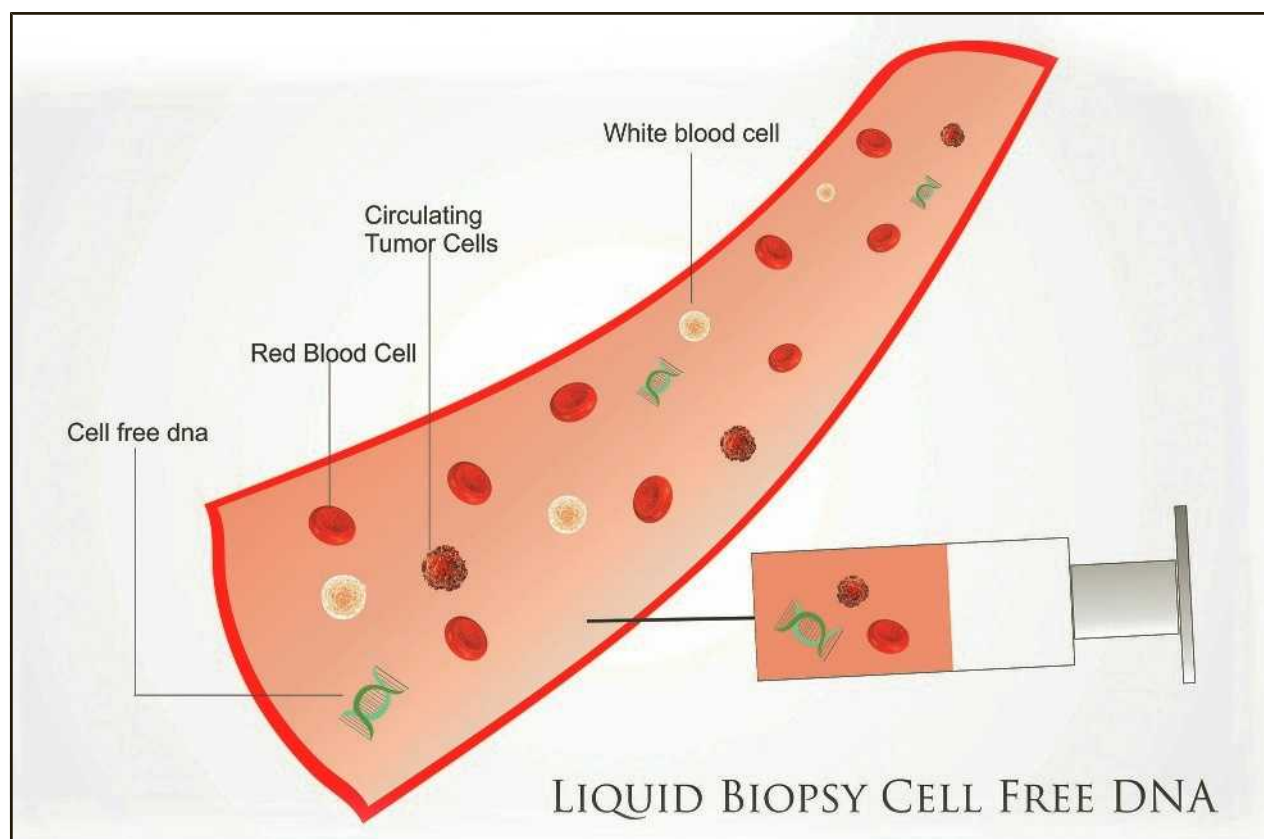
Center for Gene Therapy, Nationwide Children's Hospital, 700 Children's Dr., Columbus, OH 43205, (614) 722-2000 or (800) 792-8401, <http://www.nationwidechildrens.org/center-for-gene-therapy>
 Jain Foundation, 9725 Third Ave. NE, Suite 204, Seattle, WA 98115, (425) 882-1492, patients@jain-foundation.org, <http://www.jain-foundation.org>
 Muscular Dystrophy Association, 222 S. Riverside Plaza, Suite 1500, Chicago, IL 60606, (800) 572-1717, mda@mdausa.org, <http://www.mda.org>
 Muscular Dystrophy Canada, 2345 Yonge St., Suite 900, Toronto ON Canada M4P 2E5, (866) 687-2538, (416) 488-7523, info@muscle.ca, <http://www.muscle.ca>
 Muscular Dystrophy UK, 61A Great Suffolk St., London, UK SE1 0BU, 020 7803 4800, info@muscardystrophyuk.org, <http://www.muscardystrophyuk.org>
 National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Suzanne M. Carter, MS, CGC
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Liquid biopsy

Definition

Liquid biopsy is a procedure in which a sample of non-solid human tissue is collected for analysis of DNA and other biomarkers present in body fluids. It is also called fluid biopsy or fluid phase biopsy. As of 2021, liquid biopsy most often involves blood samples, although cerebrospinal fluid has also been used to measure biomarkers of Alzheimer's disease. In addition, a recently introduced liquid biopsy test for prostate cancer uses urine samples.



Liquid biopsy. (Shutterstock/Abhinav Chaudhary)

Description

How the test is done

When blood is used for a liquid biopsy, the test is ordered by the patient's physician, most often a hematologist or oncologist. The blood is drawn from a vein in the patient's arm in the same way it is collected for other types of blood tests. In most cases, no special preparation is required, although the doctor may instruct the patient to temporarily discontinue certain prescription medications before the blood draw.

After the blood is collected, it is sent to a laboratory for analysis. There are two methods used for analyzing liquid biopsies as of 2021: polymerase chain reaction (PCR) and next-generation sequencing (NGS). In PCR, DNA fragments present in the blood are replicated (copied) thousands of times until there are enough copies for accurate identification and measurement. NGS is a platform that allows for the simultaneous sequencing of a number of regions of interest in the DNA fragments found in blood. PCR assays have the advantage of faster turnaround times and lower expense, while NGS is better able to detect previously unsuspected mutations in a patient's DNA. NGS has the disadvantages of higher

cost, longer turnaround times, and technical difficulty. In general, it can take anywhere from several days to more than a week for the results of a liquid biopsy to be reported to the patient's physician.

Biomarkers used in liquid biopsies

There are several different types of biomarkers that may be analyzed in blood taken for a liquid biopsy:

- **Cell-free DNA (cfDNA) and cell-free fetal DNA (cffDNA).** CfDNA was the first type of circulating DNA identified in human blood in 1948, but it attracted little interest at the time. It was not until 1977 that researchers noticed that the level of cfDNA is significantly higher in cancer patients than in healthy controls. Cell-free fetal DNA is released from the placenta into the bloodstream of a pregnant woman; it can be used after the tenth week of pregnancy to evaluate the presence of a chromosomal abnormality in the developing fetus.
- **Circulating tumor DNA (ctDNA).** This biomarker is released into the blood by tumor cells. It can be used to determine whether the tumor contains a genetic mutation indicating resistance to targeted therapy.

KEY TERMS

Analyte—The medical term for a substance or sample that is of interest in a laboratory test.

Assay—A laboratory test to identify and measure the amount of a specific substance.

Biomarker—A distinctive biological indicator of a process, event, disease, or other condition.

Companion diagnostic test—A test that provides information about the safety and efficacy of a corresponding medication. Some liquid biopsies are companion diagnostic tests.

Exosomes—Very small (between 30 and 150 nanometers in diameter) vesicles secreted by various types of cells that contain proteins, nucleic acids, or other biomolecules. Exosomes are of particular interest in liquid biopsy, because they can be found in blood, urine, and cerebrospinal fluid and thus may serve as biomarkers.

Hematology—The branch of medicine that deals with the diagnosis and treatment of diseases of the blood and bone marrow.

Next-generation sequencing (NGS)—A platform that allows for the simultaneous sequencing of a number of regions of interest in a patient's DNA.

Oncology—The branch of medicine concerned with the study, diagnosis, treatment, and prevention of cancer.

Platelets—Small, irregularly shaped particles in the blood that clump together to plug broken blood vessels during the process of blood clotting.

Polymerase chain reaction (PCR)—A method used to make millions to billions of complete or partial copies of a specific DNA sample in order to obtain a sufficient quantity to study in detail.

Precision medicine—An approach to health care that bases the prevention and treatment of disease on each individual's unique genetic makeup and lifestyle habits. It is sometimes called personalized medicine.

Targeted therapy—A type of drug or other substance that identifies and attacks specific types of cancer cells with less damage to normal cells. Most targeted therapy drugs are either monoclonal antibodies or small-molecule drugs.

Tumor-educated platelets (TEPs)—Platelets that have had their RNA profiles changed through association with cancerous tumors.

Vesicle—A membrane-bound structure within a cell in which enzymes and other materials are transported or stored.

- **Circulating tumor cells (CTCs).** These are cells shed into the bloodstream by the tumor. A circulating tumor cell count (CTC) is a type of liquid biopsy in which the number of circulating tumor cells in a given quantity of blood is measured and used to evaluate the patient's chances of successful treatment.
- **Exosomes (also called extracellular vesicles or EVs).** Exosomes, which are the single most common analyte in a liquid biopsy sample, contain a wide variety of different molecules, including nucleic acids, proteins, or lipids.
- **Tumor-educated platelets (TEPs).** Platelets are small, irregularly shaped particles in the blood that clump together to plug broken blood vessels during the process of blood clotting. Tumor-educated platelets, or TEPs, are platelets found in the blood of cancer patients that have distinct RNA profiles acquired from tumor cells.
- **MicroRNAs (miRNAs).** These are short single-stranded noncoding RNAs that control gene expression; they offer promise as biomarkers of the growth and progression of cancerous tumors. The last three biomarkers on this list are considered experimental in the development of liquid biopsy tests as of 2021.

Regulation and approval

The Food and Drug Administration (FDA) is the federal agency that oversees and regulates liquid biopsies as well as other technologies used in cancer treatment. Regulatory oversight of liquid biopsies is carried out in the Oncology Center of Excellence on the main FDA campus, which combines the review of oncology products from three different FDA centers: the Center for Drug Evaluation and Research; the Center for Biologics Evaluation and Research; and the Center for Devices and Radiological Health.

The FDA approved its first DNA-based liquid biopsy in June 2016, a diagnostic test called the cobas® EGFR Mutation Test v2. This is a PCR-based test that detects and sequences the epidermal growth factor receptor (*EGFR*) gene in patients with metastatic non-small-cell lung cancer. In the same year, the FDA approved the Epi proColon test, a blood test used to screen adults over 50 for colorectal cancer; it is also a PCR-based test.

In August 2020, the FDA approved two liquid biopsy tests based on NGS technology, which permits analysis of changes in multiple genes rather than just a

single gene. The first test, the Guardant360 CDx assay, identifies changes in 55 different genes to determine whether a patient with non-small-cell lung cancer (NSCLC) might benefit from a specific anticancer drug called osimertinib. The second test, the FoundationOne Liquid CDx, looks for mutations in 324 different genes. The FDA approved it as a companion diagnostic test for drugs used to treat advanced metastatic prostate cancer with mutations in the *BRCA1* and *BRCA2* genes, and NSCLC with *EGFR* mutations.

The FDA expanded the approved uses of the FoundationONE test in October and November 2020 to include other targeted drugs and genetic mutations related to advanced cancers of the breast and ovary, NSCLC, and metastatic prostate cancer.

Purpose

Liquid biopsy is increasingly important in personalized or precision medicine because of its growing role in identifying genetic mutations in malignant tumors. It is used for the following purposes as of mid-2021:

- To detect cancer at an early stage.
- To plan cancer treatment. Liquid biopsies that detect mutations in certain genes are useful in evaluating whether the patient will respond to targeted therapy.
- To evaluate how well therapy is progressing.
- To detect cancer spread or recurrence.
- To determine the presence of molecular changes in a cancerous tumor that may affect the tumor's response to treatment.
- To determine the patient's prognosis (likelihood of recovery). Circulating tumor cell counts are often used for this purpose, as prostate, breast, and colon cancers all have cutoff points above which the CTC count no longer has a favorable prognosis. The most commonly used CTC test since the early 2000s is CellSearch®, which uses specially coated beads to separate CTCs from other blood cells. CellSearch® was approved by the FDA for monitoring metastatic breast cancer; in 2007 for monitoring metastatic colorectal cancer; and in 2008 for monitoring prostate cancer.

Advantages and limitations

Liquid biopsy has the obvious advantage of being less invasive than a traditional tissue biopsy as well as being better tolerated by the patient; it also has a much lower risk of severe pain, infection, or uncontrolled bleeding. It can be repeated as often as needed to monitor a tumor or the progress of the patient's treatment. A liquid biopsy may detect genetic mutations in certain cancers—particularly lung cancer and melanoma—that do not appear in the specific samples removed for a

QUESTIONS TO ASK YOUR DOCTOR

- Have you ever ordered a liquid biopsy for one of your patients?
- If so, was it a circulating tumor cell test or a circulating tumor DNA test?
- Do you think that ongoing progress in sequencing technology and analysis of the various components in blood will make liquid biopsy a standard clinical tool?
- What do you consider the greatest obstacle to the increased use of liquid biopsy?

standard tissue biopsy. A liquid biopsy also can be useful when the patient's tumor is difficult to reach, as in certain types of head and neck or lung cancer.

As of 2021, however, a liquid biopsy is more often regarded as a complement to tissue a biopsy rather than as a replacement for it; it is not yet considered a standard clinical tool. A tissue biopsy is still usually needed to establish the initial diagnosis of cancer. Not all cancers shed DNA into the bloodstream, which means that a liquid biopsy is not helpful in monitoring those cancers that do not. Some types of liquid biopsy are very expensive or require specialized measurement techniques not readily available in most laboratories. Some biomarkers used in investigational liquid biopsies have not yet been standardized, meaning that they lack validated assays, are difficult or time-consuming to detect, or are not specific to a given cancer type.

Research

Three types of analytes in human blood are being studied for their potential in liquid biopsy tests: miRNAs, exosomes, and tumor-educated platelets (TEPs). There are 16 clinical trials of liquid biopsy tests based on exosomes registered with the NIH as of mid-2021, 14 trials of miRNA liquid biopsies, and two trials for TEP-based liquid biopsies. Researchers expect that these and other clinical trials will lead to newer types of liquid biopsy that can detect and monitor a wider range of cancers, provide more accurate prognoses for the patients, and improve the success rates of targeted therapies.

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American Cancer Society (ACS), 250 Williams Street NW, Atlanta, GA 30303, (800) 227-2345, <https://www.cancer.org/>

American Society of Clinical Oncology (ASCO), 2318 Mill Road, Suite 800, Alexandria, VA 22314, (888) 282-2552, (703) 299-0158, (703) 299-0255, <https://www.asco.org/>

American Society of Hematology (ASH), 2021 L Street NW, Suite 900, Washington, DC 20036, (866) 828-1231, (202) 776-0544, (202) 776-0545, <https://www.hematology.org/contact-us>, <https://www.hematology.org/>

College of American Pathologists (CAP), 325 Waukegan Road, Northfield, IL 60093-2750, (800) 323-4040, (847) 832-7000, (847) 832-8000, <https://www.cap.org/contact-and-support/contact-us>, <https://www.cap.org/>

National Cancer Institute (NCI), 9609 Medical Center Drive, Rockville, MD 20850, (800) 422-6237, (301) 435-3848, NCInfo@nih.gov, <https://www.cancer.gov/>

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) 463-6332, <https://www.fda.gov/>

Rebecca J. Frey, PhD

Lissencephaly

Definition

Lissencephaly, a term that means "smooth brain," is a rare congenital malformation of the brain that results in profound intellectual impairment and severe seizures.

Lissencephaly is caused by an arrest in development of the fetal brain during early pregnancy. The cerebral cortex, the top layer of the brain controlling higher thought processes, does not develop the normal sulci, the indentations or valleys in the cortex, and gyri, the ridges or convolutions seen on the surface of the cortex. Instead, the cortex in a person with lissencephaly is thickened and smooth with disorganized neurons that have not migrated to their proper places. The typical cortex has six layers of neurons, but brains with lissencephaly usually have only four.

Description

The condition was first reported in 1914 by pathologists Culp and Erhardt, who described a human brain with a smooth surface, lacking the normal gyri. They called it lissencephaly.

Lissencephaly is one of more than 20 conditions called neural migration disorders that occur because the developing neurons do not proceed correctly to their

Types of lissencephaly

Disorder	Inheritance	Gene location	Proportion of patients	Gene name	Protein product	Clinical test
MDS(Miller-Dieker syndrome)	AD	17p13.3	100%	LIS1	Platelet activating factor acetylhydrolase 45K	Yes
ILS1 (Isolated lissencephaly sequence 1)	AD	17p13.3	>40%	LIS1	Platelet activating factor acetylhydrolase 45K	Yes
X-linked lissencephaly and subcortical band heterotopia	X-linked	Xq22.3–q23	Unknown	XLIS	Unknown	No
Cobblestone lissencephaly (lissencephaly type 2)	AR	Unknown	Unknown	Unknown	Unknown	No

(Gale)

normal place in the brain's cortex during fetal development. In fact, the brain of a person with lissencephaly, with its smooth and immature cortex, resembles a typical human fetal brain at about 10 to 14 weeks of development.

Children with lissencephaly are almost always severely to profoundly intellectually impaired, and the vast majority develop seizures that are difficult to treat. Life expectancy is reduced, and survivors need constant care.

Lissencephaly can occur as an isolated birth defect or can be one of many abnormalities occurring together in a specific inherited syndrome. There are at least 10 inherited syndromes that include lissencephaly and many more that include variants of this brain malformation. Lissencephaly can also occur by itself without other characteristics.

Some cases of lissencephaly are caused by new changes in the genetic material of that particular baby—these cases are caused by sporadic, or random, gene mutations (also called *de novo*). This means that the genetic change is not present in the parents or anyone else in the family. Some cases of lissencephaly are caused by rearrangements of chromosome material that can be inherited from a healthy parent. Other types of lissencephaly are inherited in an autosomal recessive pattern. This means that a couple who has a child with an autosomal recessive lissencephaly syndrome has a 25% chance in any future pregnancy to have another affected child. There are also types of lissencephaly caused by changes in a gene or genes on the X chromosome. X-linked lissencephaly affects mainly males, who have only one X chromosome. Females who carry an X-linked gene change on one of their two X chromosomes often have mild brain changes.

Other known causes of lissencephaly include viral infections of the fetus or insufficient blood supply to the brain during the first trimester of pregnancy.

The medical community has categorized lissencephaly in several ways. There are over 20 different types

of lissencephaly and it is a component of many different syndromes. The simplest way to distinguish between types of lissencephaly is based on the phenotype or physical features. Using this approach, lissencephaly may be divided into three main types:

Classical or type 1 lissencephaly

In this type of lissencephaly the surface of the brain is completely smooth except for a few shallow valleys (sulci). The cortex is thicker than normal and there are clumps of neurons found in areas outside the cortex (heterotopia). The corpus callosum, the band of tissue between the hemispheres of the brain, is often small and is sometimes absent. The posterior ventricles, the fluid-filled spaces in the center of the brain, are often larger than normal.

Type 1 lissencephaly can be seen in a number of genetic syndromes and can also occur by itself in a condition called isolated lissencephaly sequence (ILS). The vast majority of cases of ILS is a result of mutations or deletions (missing sections) in one of two different genes involved in brain development.

An example of a genetic syndrome involving type 1 lissencephaly is Miller-Dieker syndrome (MDS). This disorder is caused by a deletion of part of the short arm of chromosome 17 (17p13) that includes the *LIS1* gene. In addition to lissencephaly, children with MDS have distinctive facial features including a high forehead, short upturned nose, and thin lips. They also have narrowing at the temples and a small jaw, although these traits can also be seen in ILS and other lissencephaly syndromes. Children with MDS occasionally have other birth abnormalities of the heart, kidneys, or palate. Calcium deposits in the midline of the brain are common in MDS, but not in ILS or other syndromes.

Cobblestone dysplasia or type 2 lissencephaly

Type 2 lissencephaly is also called cobblestone dysplasia because of the pebbled appearance to the surface of the cerebral cortex. Brains with cobblestone

dysplasia often show abnormalities of the white matter, enlarged ventricles, underdeveloped brain stem and cerebellum, and absence of the corpus callosum.

There are four known syndromes that include cobblestone dysplasia: cobblestone lissencephaly without other birth defects (CLO), Fukuyama congenital muscular dystrophy (FCMD), muscle-eye-brain disease (MEB), and Walker-Warburg syndrome (WWS). These disorders are quite rare, and all are inherited in an autosomal recessive pattern. Diagnosis depends on MRI studies and clinical evaluations. There are no specific genetic tests available for clinical use for these conditions.

Other types of lissencephaly

There are other rare syndromes involving lissencephaly and variants of lissencephaly; these syndromes and variants may involve the completely smooth brain seen in classic lissencephaly, the pebbled appearance seen in cobblestone dysplasia, or may involve varying degrees of abnormalities of the cerebral cortex. Examples of other types of lissencephaly include X-linked lissencephaly and subcortical band heterotopia. X-linked lissencephaly is characterized by varying degrees of abnormal folds and grooves of the cerebral cortex. The smoother the brain surface, the more severe the symptoms seen in that individual. Other symptoms include abnormal genitalia that can include an unusually small penis (micropenis), undescended testes (cryptorchidism), or external genitalia that do not look clearly male or clearly female (ambiguous genitalia).

Genetic profile

Lissencephaly has been associated with mutations on several genes. The gene causing the majority of cases of ILS is called the *PAFAH1B1* (or *LIS1*) and is located on the short arm of chromosome 17. Between 40% and 64% of persons with ILS have a deletion of a portion of the *PAFAH1B1* gene, and about 24% have a mutation that disrupts the normal function of the gene. Most deletions and mutations in the *PAFAH1B1* gene are sporadic and are not present in other family members. Another 12% of persons with ILS have a mutation in a gene called *DCX* (or *XLIS*), located on the long arm of the X chromosome. Mutations in *XLIS* cause X-linked lissencephaly in males and may or may not cause symptoms in the mothers who carry the mutation.

Classical or type 1 lissencephaly is caused by mutations in the *PAFAH1B1* (*LIS1*), *DCX*, and *TUBA1A* genes. These genes are responsible for the production of the double-cortin, acetyl hydrolase 1B (*PAFAH1B*), and alpha-tubulin (α -tubulin) proteins. These proteins are important in the development of the fetal brain. When

KEY TERMS

Agyria—The absence of gyri, or convolutions, in the cerebral cortex.

Cerebellum—A portion of the brain consisting of two cerebellar hemispheres connected by a narrow vermis. The cerebellum is involved in control of skeletal muscles and plays an important role in the coordination of voluntary muscle movement. It interrelates with other areas of the brain to facilitate a variety of movements, including maintaining proper posture and balance, walking, running, and fine motor skills such as writing, dressing, and eating.

Cerebral cortex—The outer surface of the cerebrum made up of gray matter and involved in higher thought processes.

Congenital malformation—A birth defect or physical abnormality present at birth.

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

Heterotopia—Small nodules of gray matter that are present outside the cortex.

Lissencephaly—A condition in which the brain has a smooth appearance because the normal convolutions (gyri) failed to develop.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Microcephaly—An abnormally small head.

Pachygyria—The presence of a few broad gyri (folds) and shallow sulci (grooves) in the cerebral cortex.

Prenatal diagnosis—The determination of whether a fetus possesses a disease or disorder while it is still in the womb.

Subcortical band heterotopia—A mild form of lissencephaly type 1 in which abnormal bands of gray and white matter are present beneath the cortex near the ventricles.

Ventricle—The fluid-filled spaces in the center of the brain that hold cerebral spinal fluid.

these proteins do not form correctly or in correct numbers, it affects formation of neurons and neural migration, the process by which neuron move to the appropriate location within the brain. These abnormalities lead to lissencephaly.

Cobblestone dysplasia or type 2 lissencephaly is caused by mutations in the *FKTN*, *FKRP*, *LARGE*, *RELIN*, *POMGnT1*, *POMT1*, *POMT2*, and *TUBA1A* genes. These genes are responsible for the production of the FKRP, fukutin, ISPD, LARGE, POMT complex, reelin, and alpha-tubulin (α -tubulin) proteins. These proteins, like those associated with type 1 lissencephaly, are important in the development of the fetal brain and in neural migration and abnormalities in them lead to type 2 lissencephaly.

X-linked lissencephaly and subcortical band heterotopia are caused by mutations in genes located on the X chromosome. X-linked lissencephaly is inherited in an X-linked pattern meaning that the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes in each cell. Males have only one X chromosome, and therefore one altered copy of the gene in each cell is sufficient to cause the condition. In females, who have two copies of the X chromosome, one altered copy of the gene in each cell may lead to less severe brain malformations or may cause no symptoms at all. In X-linked inheritance, fathers cannot pass X-linked traits to their sons because sons receive their only X chromosome from their mothers. These mutations affect formation of the *ARX* gene and the ARX protein and cause abnormal neural migration in the developing fetus that lead to lissencephaly.

Subcortical band heterotopia is a rare form of lissencephaly that is inherited in an X-linked dominant pattern, meaning that only one copy of the gene must be present for an individual to have the condition. It affects females more than males. It is also caused by mutations in the *PAFAH1B1* (*LIS1*) gene located on chromosome 17. As in the other forms of lissencephaly, mutations in this gene lead to neural migration delays and cause the abnormal brain formation of lissencephaly.

Demographics

Lissencephaly affects fewer than 1 in 100,000 individuals and occurs in all parts of the world. The sporadic and autosomal recessive types of lissencephaly occur equally in males and females. X-linked syndromes that include lissencephaly occur mainly in boys, although carrier mothers sometimes have milder signs.

Signs and symptoms

Many babies with lissencephaly appear normal at birth, although some have immediate respiratory problems. After the first few months at home, parents typically notice feeding problems, inability to visually track objects, and lessened activity in their child. Breath-holding spells (apnea) and muscle weakness are also

common. Seizures frequently begin within the first year of life, are usually severe, and are difficult to treat with medication. Muscle weakness changes to spasticity (a condition of excessive muscle tension) over time. Repeated pneumonias from swallowing food down the airway and into the lungs are common.

Head size is usually within normal limits at birth; however, as the baby's body grows, head growth lags and a small head (microcephaly) results. Babies with isolated lissencephaly often have hollowing at the temples and small jaws, both thought to be a result of the abnormal brain shape. Genetic syndromes involving lissencephaly will include other symptoms and signs.

Diagnosis

The diagnosis of lissencephaly is initially based on tests using magnetic resonance imaging (MRI) and computed tomography (CT) scans. MRI findings in type 1 lissencephaly include a lack of, or very shallow, convolutions on the surface of an unusually thick cerebral cortex. Enlargement of the ventricles is sometimes present.

On average, persons with Miller-Dieker syndrome have more severe MRI findings than persons with ILS. It is sometimes possible to distinguish between chromosome 17-related lissencephaly (ILS and MDS) and X-linked ILS based on MRI findings. The smooth brain appearance is more striking in the back portion of the brain in persons with chromosome 17 *LIS1* deletions and mutations. In contrast, it is more conspicuous in the front part of the brain in persons with *XLIS* mutations. In addition, underdevelopment of part of the cerebellum is more commonly seen in persons with *XLIS* mutations.

Individuals with subcortical band heterotopia (SBH), a milder form of lissencephaly often seen in female carriers of *XLIS*, often have minor changes in the gyri, shallow sulci, and ribbons of white and gray matter beneath the cortex that show up on MRIs.

MRI findings in type 2 lissencephaly can include a cobblestone appearance of the cortex, enlarged ventricles, abnormalities of the white matter, and changes in the cerebellum, corpus callosum, and brain stem.

A CT scan can be done to look for calcium deposits in the midline of the brain. Calcium deposits are common in MDS but not found in other lissencephaly syndromes.

In addition to MRI and CT testing, a careful clinical evaluation and examination by a medical geneticist is necessary to confirm the diagnosis and evaluate the child for the presence of a syndrome. It is essential for a child to have a precise diagnosis in order for genetic counselors to be able to give the family complete and accurate information about the inheritance pattern and chances for the condition to recur in future children.

To confirm the diagnosis of MDS or ILS, chromosome testing and other specialized genetic tests are often helpful. A test called fluorescent in situ hybridization (FISH) is used to detect *LIS1* gene deletions. High-resolution chromosome testing can often determine whether a deletion is sporadic or due to an inherited chromosome rearrangement. If necessary, mutation analysis, looking for specific errors in the sequence of the *LIS1* or *XLIS* gene, can be performed.

Parents of a child with ILS who have a confirmed deletion or mutation in *LIS1*, and who have normal genetic studies themselves, have a less than 1% chance of having another child with ILS. Similarly, MDS with a confirmed sporadic deletion in *LIS1* has a low chance of recurring. MDS caused by a chromosome rearrangement carries a higher chance of happening again. Actual risks depend on the specific rearrangement.

XLIS mutations are often inherited from a carrier mother. If a woman has genetic testing and is confirmed to have an *XLIS* mutation, she will have a 25% chance with each pregnancy to have an affected male and a 25% chance to have a carrier female who may have SBH.

If a detectable mutation, deletion, or chromosome rearrangement has been confirmed in the affected family member, prenatal diagnosis is available during future pregnancies. Ultrasound of the fetal anatomy during pregnancy cannot diagnose lissencephaly. However, ultrasound performed by a specialist at 18 to 22 weeks of pregnancy can sometimes detect other birth abnormalities that occur in some of the syndromes involving lissencephaly.

Treatment and management

There is no treatment or cure for lissencephaly. Seizures occur in almost all children with lissencephaly and are often difficult to control, even with the strongest anti-seizure medications. A severe type of seizure called infantile spasms can occur and may need to be treated with injections of adrenocorticotrophic hormone (ACTH), although this treatment is not always effective.

Feeding difficulties can include choking, gagging, or regurgitating food or liquid. Aspiration—swallowing food down the trachea and into the lungs—is a serious problem that can lead to pneumonia. Liquids and thick foods can be thinned to make swallowing easier. There are medications available to help with reflux. Children who continue to have serious problems may need a permanent feeding tube placed into the stomach to ensure adequate nutrition.

Physical and occupational therapy can help prevent or reduce tightening of the joints and help to normalize

muscle tone. However, the improvements are often limited and temporary.

Prognosis

Persons with classical lissencephaly usually need life-long care for all basic needs. Many babies do not live past infancy, but the average age of survival depends on the particular syndrome involved, the type of lissencephaly, and the severity of the brain abnormalities in a given child. Babies with MDS usually die by two years of age, but the majority of persons with ILS live into childhood, although often not into adulthood. Many babies with cobblestone dysplasia die in infancy; however, some affected people have lived into their 20s. In contrast, persons with SBH have very variable signs and symptoms, may be asymptomatic, mildly affected, or severely intellectually disabled, and may have near-normal or normal lifespans.

Resources

BOOKS

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- Spranger, Jürgen, et al., eds. *Bone Dysplasias: An Atlas of Genetic Disorders of Skeletal Development*. 4th ed. New York: Oxford University Press, 2018.

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WEBSITES

- "Isolated Lissencephaly sequence." MedlinePlus. <https://medlineplus.gov/genetics/condition/isolated-lissencephaly-sequence/> (accessed June 13, 2021).
- "Lissencephaly." NORD. <https://rarediseases.org/rare-diseases/lissencephaly/> (accessed June 13, 2021).

ORGANIZATIONS

- American Epilepsy Society, 135 South LaSalle St., Suite 2850, Chicago, IL 60603, (312) 883-3800, <http://www.aesnet.org>
- Epilepsy Foundation of America, 8301 Professional Place East, Suite 200, Landover, MD 20785-2353, (800) 332-1000, <http://www.epilepsy.com>
- Lissencephaly Network, 716 Autumn Ridge Lane, Fort Wayne, IN 46804-6402, (219) 432-4310, (219) 432-4310, lissencephalyOne@aol.com, <http://www.lissencephaly.org>

Barbara J. Pettersen
and Deborah L. Nurmi, MS

Long bone deficiencies associated with cleft lip/palate see **Roberts SC phocomelia**

Long QT syndrome

Definition

Long QT syndrome (LQTS) is the overarching term used to describe a family of genetic or acquired disorders that are characterized by irregular heartbeats caused by problems in the heart's electrical activity (cardiac arrhythmias). The cardiac arrhythmias of long QT syndrome can lead to fainting (syncope), cardiac arrest, and sudden death. The syndrome is characterized by a longer-than-normal QT interval on an electrocardiogram.

Description

LQTS is one of the sudden arrhythmia death syndromes (SADS). It is a major cause of sudden, unexplained death in children and young adults, resulting in as many as 3,000–4,000 deaths per year in the United States. Its characteristic symptoms include seizures or fainting, often in response to stress, and long QT intervals found on an electrocardiogram.

LQTS was first described by C. Romano and co-workers in 1963 and by O. C. Ward in 1964 as a syndrome that was almost identical to Jervell and Lange-Nielsen syndrome but without congenital deafness. Therefore, the condition is known as Romano-Ward syndrome or Ward-Romano syndrome. Because other genetic disorders are now known to be associated with long QT syndrome, Romano-Ward syndrome is identified by the symbol LQT1 or as long QT syndrome type 1.

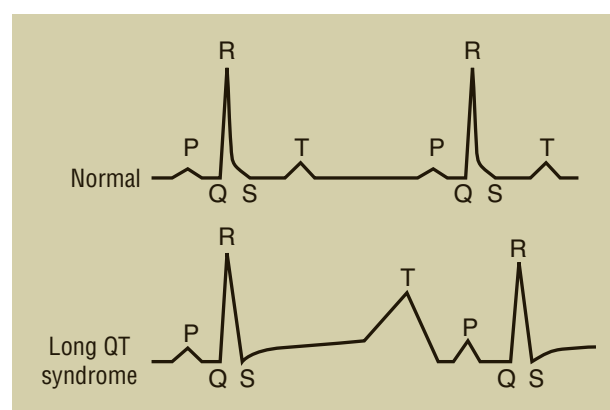
LQTS involves irregularities in the recharging of the heart's electrical system that occurs after each heartbeat or contraction. The QT interval is the period of relaxation or recovery that is required for the repolarization, or recharging, of the electrical system following each heart contraction. Depolarization, or electrical activity that causes heart contraction, and repolarization are orchestrated by the flow of potassium, sodium, and calcium through the heart cell's ion channels. As sodium channels in the heart open, positively charged sodium ions flow into the cells, making the inner surfaces of the cell membranes more positive than the outside and creating the action potential or electrical charge. During depolarization, the sodium channels shut, and after a delay, potassium channels open and allow positively charged potassium ions to move out of the cells, returning the cell membranes to their resting state in preparation for the next heart contraction.

Individuals with LQTS have an unusually long period of relaxation or recovery called the QT interval after each heart contraction. If the electrical impulse for the next contraction arrives before the end of the QT

recovery period, a specific arrhythmia arises in the ventricles (lower chambers) of the heart. This arrhythmia is called polymorphous ventricular tachycardia, meaning fast heart (above 100 beats per second), or *torsades de pointes*, which means turning or twisting of the points. A normal heartbeat begins in the right atrium of the heart and progresses down to the ventricles. In ventricular tachycardia or *torsades de pointes*, the heartbeat may originate in the ventricle. Usually this very fast and abnormal heartbeat reverts to normal. If it does not, it leads to ventricular fibrillation (VF), in which the heart beats too quickly, irregularly, and ineffectively. This arrhythmia can result in cardiac arrest and death. Variations in the QT interval from one heart cell to another also can cause arrhythmias and ventricular fibrillation in LQTS.

LQTS usually results from changes (mutations) in one of 13 or more genes. These genes encode proteins that form the ion channels in the heart. Depending on the other functions of the gene that is mutated, features beyond irregular heartbeats may occur in individuals affected by the different forms of LQTS. Although some mutations causing LQTS can arise spontaneously in an individual, they are most often passed on from parent to offspring. Thus LQTS usually runs in families.

Acquired LQTS is caused by factors other than genetic inheritance or mutation. Many different medications, including heart medicines, antibiotics, digestive medicines, psychiatric drugs, and antihistamines, as well as certain poisons, can result in LQTS. Some of these drugs block potassium ion channels in the heart. Diuretic medications can cause LQTS by lowering levels of potassium, magnesium, and calcium in the blood. Mineral



A comparison of the "QT" interval found in a normal patient versus one diagnosed with long QT syndrome obtained from an electrocardiogram. The typical QT interval is 400–440 milliseconds, but for patients with long QT syndrome the interval exceeds 460 milliseconds. This lengthened interval is obvious in the comparison above. (Gale)

imbalances, resulting from chronic vomiting, diarrhea, anorexia, malnutrition, or starvation, can also result in LQTS. Such additional medical issues as strokes, some neurological problems, or alcoholism also can cause LQTS. However, since only certain individuals develop LQTS under these circumstances, multiple genetic factors play a role in the acquired disorder.

Genetic profile

Although all of the genes that are known to be involved in LQTS encode proteins that form sections or subunits of ion channels through cellular membranes, the type of LQTS depends on the specific gene defect. Although new genetic mutations that cause LQTS are still being discovered, the majority of inherited LQTS cases result from mutations in *KVLQT1* or *KCNQ1*, causing LQT1, or mutations in *hERG* or *KCNH2*, causing LQT2.

Most types of LQTS are autosomal dominant genetic disorders: the genes that cause LQTS are carried on one of the 22 pairs of numbered autosomal chromosomes, rather than on the X or Y sex chromosomes. Furthermore, in autosomal dominant conditions, only one copy of the mutant, or nonworking, gene is necessary for the development of LQTS. An individual who inherits a normal gene copy from one parent and an abnormal gene copy from the other parent is likely to have LQTS. The children of an individual with one normal gene copy and one mutated copy have a 50% chance of inheriting LQTS.

Some types of LQTS are inherited in an autosomal recessive pattern. In an autosomal recessive pattern, two copies of the mutant, or nonworking, gene are needed to develop the symptoms of LQTS. In these cases, both parents each carry one copy of a mutant gene. Individuals with only one copy of a nonworking gene for a recessive condition are known as carriers and have no problems related to the condition. In fact, each person carries between 5 and 10 nonworking genes for harmful, recessive conditions. However, when two people with the same nonworking recessive gene have children together, there is a 25% chance with each pregnancy for the child to inherit two nonworking copies, one from each parent. That child then has no working copies of the gene and has the signs and symptoms associated with a recessive condition.

Long QT syndrome 1 and long QT syndrome 5

Long QT syndrome 1 (LQT1) is the most common form of LQTS, accounting for about 45% of cases. It is caused by any of a number of gene mutations in the *KVLQT1* (*KvLQT1*) gene located on the short arm of chromosome 11 (11p15.5). *KVLQT1* is also known as *KCNQ1*. The *KVLQT1* gene codes a critical part of a

voltage-gated potassium ion channel that helps the heartbeat. Even if the *KVLQT1* creates an abnormal potassium ion channel part, it can still join with the other parts of the channel. A potassium ion channel that is constructed with an abnormal part or subunit does not work as well as a channel formed of all normal parts. Most mutations in *KVLQT1* causing LQT1 are passed down in an autosomal dominant pattern through the family; however, some mutations in this gene may be passed down in an autosomal recessive pattern. In these cases, LQTS is present only in individuals with two abnormal *KVLQT1* genes, one inherited from each parent. The pattern of inheritance depends on which type of LQTS-causing mutation is present in the family because some mutations cause a potassium ion channel part that works better than other mutations. Mutation analysis of the *KVLQT1* gene and/or a detailed medical family history can determine the inheritance pattern of LQT1 in a specific family.

The *KCNE1* (*MinK* or *IsK*) gene on chromosome 21 codes for another critical part of the voltage-gated potassium ion channel that combines with the part encoded by *KVLQT1*. Together, they form the ion channel that is responsible for the heart's potassium current. The channel encoded in *KCNE1* and *KVLQT1* is a slow ion channel that starts working when the heart is in depolarization. Depolarization of the heart causes the channel to open and potassium ions to move freely out of the cells during repolarization. Mutations in *KCNE1* also can cause a defective potassium channel protein, resulting in a LQT1 form of LQTS; however, LQTS resulting from mutations in *KCNE1* may also be referred to as long QT syndrome 5 (LQT5). Mutations in potassium channel genes reduce the number of functional potassium channels in the heart and lengthen the QT interval by delaying depolarization.

Jervell and Lange-Nielsen syndrome

Jervell and Lange-Nielsen syndrome (JLNS) is a specific autosomal recessive form of LQTS. In JLNS, an individual has inherited two copies of an abnormal *KVLQT1* or *KCNE1* gene: one inherited from the mother and the other from the father. The syndrome is characterized by congenital deafness, as well as a prolonged QT interval.

Long QT syndrome 2 and long QT syndrome 6

Long QT syndrome 2 (LQT2) is the second most common form of LQTS, accounting for about 42% of cases. Mutations in the *hERG* gene (so named because it is the human equivalent of a fruit fly gene called ether-à-go-go) can result in LQT2. *hERG*, located on chromosome 7 (7q35-q36), encodes a protein part of another potassium

ion channel found in the heart. Mutations in *hERG* result in loss of the potassium current called IKr.

Long QT syndrome 6 (LQT6) is caused by mutations in the *KCNE2* gene. The *KCNE2* or *MiRP1* (for *MinK*-related) gene is located on chromosome 21 (21q22.1). The gene encodes a protein part that combines with the protein encoded by *hERG* to form a potassium ion channel used in the heart. Mutations in potassium channel genes reduce the number of functional potassium channels in the heart and lengthen the QT interval by delaying depolarization.

Long QT syndrome 3

Mutations in the *SCN5A* gene can result in a less common form of LQTS known as long QT syndrome 3 (LQT3). About 7% of cases of long QT syndrome are diagnosed as LQT3. *SCN5A*, on the short arm of chromosome 3 (3p21), encodes a part of a cardiac sodium ion channel. Some mutations in this gene prevent the channel from being turned off or inactivated. Thus, although the channel opens normally and sodium ions flow into the cells with each contraction, the channel does not close properly. Sodium ions continue to leak into the cells, which prolongs the action potential.

Brugada syndrome

Brugada syndrome is caused by a mutation in *SCN5A*, located on the short arm of chromosome 3 (3p21). The type of mutation that causes Brugada decreases the flow of sodium ions into the cells and shortens the time of action potential. The symptoms of Brugada syndrome, which include ventricular arrhythmia, cardiac arrest, and sudden death, are caused by the shortened action potential.

Long QT syndrome 4

Long QT syndrome 4 (LQT4) is a very rare condition; it is most often referred to as sick sinus syndrome with bradycardia. LQT4 is associated with mutation in the ankyrin-B gene called *ANK2*, which is located on the long arm of chromosome 4 (4q25-q27). *ANK2* plays a vital role in the organization of a sodium pump that exchanges sodium and calcium in and out of the heart. A mutation in the *ANK2* gene reduces the ability to get necessary proteins and calcium to the heart cells. Individuals with LQT4 have the typical cardiac dysfunction seen in LQTS. However, a long QT interval is not always seen in individuals with LQT4, so it is considered a condition distinct from classical long QT syndromes.

Long QT syndrome 7

Long QT syndrome 7 (LQT7) is also known as Andersen cardiodysrhythmic periodic paralysis, Andersen

syndrome, periodic paralysis, potassium-sensitive cardiodysrhythmic type, and Andersen-Tawil syndrome. LQT7 is associated with mutations in the *KCNJ2* gene located on the long arm of chromosome 17 (17q23.1-q24.2). Mutations in *KCNJ2* decrease the ability of a potassium channel in the heart to react to a specific important protein, called phosphatidylinositol 4,5-bisphosphate (PIP2), and move potassium in and out of the body's muscles. The movement of potassium in and out of the body's muscles allows movement of the arms, legs, and other muscles.

Long QT syndrome 8 with syndactyly

Long QT syndrome 8 with syndactyly is also known as LQT8 or Timothy syndrome (TS). Long QT syndrome 8 with syndactyly is caused by new mutations in the *CACNA1C* gene located on the short arm of chromosome 12 (12p13.3). Mutations in *CACNA1C* keep calcium ion channels open and pull in calcium ions. By constantly pulling in calcium ions, repolarization is delayed and the chance of an irregular heartbeat (arrhythmia) is increased.

Long QT syndrome 9

Long QT syndrome 9, or LQT9, was identified in 2006 and traced to a mutation in the *CAV3* gene on the short arm of chromosome 3 at 3p25. This gene codes for caveolin-3, a protein that is the main component of caveolae, small pouches in the membranes of muscle cells. It is thought that mutations in the *CAV3* gene disrupt ion transport through sodium channels in the caveolae in heart muscle, thus leading to the abnormal heart rhythm found in long QT syndrome. LQT9 has been particularly implicated in SIDS deaths.

Other forms of LQTS

A small number of individuals with LQTS have mutations in more than one of the known genes and may have symptoms of multiple LQTS types. Other families with inherited LQTS lack mutations in any of these known genes, suggesting the existence of other genes that can cause LQTS. Furthermore, individuals with identical LQTS genes may differ significantly in the severity of their symptoms, again suggesting the existence of other genes that can cause or modify LQTS. Between 2000 and 2005, several large studies characterized the presence of gene variants or alleles in genes, including *KCNA5*, *KCNQ1*, *KCNH2*, *KCNE1*, and *KCNE2*, that help control the length of the QT interval.

Between 2005 and 2015, mutations in such other genes as *CAV3*, *SCN4B*, *AKAP9*, *SNTA1*, and *KCNJ5* were identified as contributing to various subtypes of long QT syndrome. Some of these mutations were identified in only one patient or one family. In 2007, mutations

in the *SCN4B* gene on the long arm of chromosome 11 (11q23.3) were identified as the cause of LQT10, a rare form of LQTS found in only three people in one family as of 2015. LQT11 was also identified in 2007 and traced to a mutation in the *AKAP9* gene on the long arm of chromosome 7 at 7q21.2. This mutation has been identified in only two people—sisters in the same Caucasian family. LQT12, caused by a mutation in the *SNTA1* gene on chromosome 20 at 20q11.21, had been identified in only one patient as of 2015. The *SNTA1* mutation interacts with the *SCN5A* gene to increase the flow of sodium ions. LQT13 was identified in 2010 in a Chinese family and was traced to a mutation in the *KCNJ5* gene on the long arm of chromosome 11 at 11q23.3.

Demographics

Large-scale studies of LQTS, such as the International Registry for LQTS established in 1979, have revealed that the disorder is much more prevalent than was originally thought. Inherited LQTS is estimated to occur in 1 out of every 5,000–10,000 individuals and occurs in all racial and ethnic groups worldwide. Some researchers think that LQTS is underdiagnosed. LQTS may result in fetal death. It (especially LQT9) accounts for some cases of SIDS and has been implicated in many instances of sudden death and unexplained drowning among individuals who were previously without symptoms.

As an autosomal non-sex-linked genetic disorder, LQTS should affect males and females in equal numbers. However, it appears to be more prevalent among women. Nearly 70% of the time, a female is the first member of a family recognized as having LQTS. Females are two to three times more likely than males to exhibit symptoms of LQTS. In general, however, males manifest symptoms of LQTS at an earlier age than females. At puberty, the QT interval shortens in males, whereas in females it stays the same or shortens only slightly. Therefore, unaffected women have slightly longer QT intervals than unaffected men. Men with LQT1 or LQT2 have shorter QT intervals than either women or children with these two forms of the disorder. Women also are more likely than men to develop drug-induced or acquired LQTS. These gender-related differences may be due to the effects of the female hormone estrogen on the regulation of cardiac ion channels, particularly potassium channels.

Signs and symptoms

Tragically for many individuals with LQTS, sudden death by cardiac arrest is the first symptom. For this reason, LQTS sometimes is referred to as a “silent” killer. Approximately one-third of deaths from LQTS are not preceded by any symptoms of the disease. At least one-

third of the individuals carrying a gene variant that causes LQTS do not exhibit any symptoms. SIDS claims the lives of 1 or 2 out of every 1,000 infants. In 1998, the results of the Multicenter Italian Study of Neonatal Electrocardiography and a SIDS study found that a large number of SIDS victims had prolonged QT intervals.

Common symptoms of LQTS include dizziness, sudden loss of consciousness or fainting spells (syncope), or convulsive seizures. These occur because the heart is unable to pump sufficient blood to the brain. Following a loss of consciousness or syncope, the *torsades de pointes* rhythm (fast heartbeat of the lower heart chambers) usually reverts spontaneously to a normal rhythm within one minute or less, and the individual regains consciousness. These symptoms may first appear during infancy or early childhood, although sometimes no symptoms are evident until adulthood. Some individuals may experience syncopal episodes from childhood on, whereas others may experience one or two episodes as children, with no recurrence throughout adulthood. On average, males with LQTS first exhibit symptoms at about age eight and females at about age 14. These symptoms usually occur upon awakening, during strenuous physical activity, during a rapid change in posture, or during moments of excitement or stress.

Affected newborn infants and children under the age of three may exhibit slower than normal resting heart rates. Individuals with LQTS may experience irregular heartbeats accompanied by chest pain.

Symptoms of LQTS can vary depending on the specific gene mutation. Certain mutations in the *KVLQT1* gene that cause LQT1 may result in arrhythmias when an individual is under stress. Exercise is a major trigger for cardiac events in LQT1. Swimming can trigger syncopic episodes and appears to be a gene-specific trigger in individuals with *KVLQT1* mutations. Sudden loud noises, such as telephones or alarm clocks, are more likely to trigger arrhythmias and syncopic episodes in individuals with LQT2. Cardiac events, including syncope, aborted cardiac arrest, and sudden death, are more common among individuals with LQT1 or LQT2 than among those with LQT3. However, cardiac events are more likely to be lethal in individuals with LQT3. Certain variants of the *SCN5A* gene that cause LQT3 result in abnormal heart rhythms during sleep.

Individuals with LQT4 have the typical cardiac dysfunction seen in LQTS: slow heartbeat (sinus node bradycardia) leading to the abnormal function of the body's natural pacemaker (sinus node dysfunction), severely abnormal heartbeat of the lower heart chambers (ventricular fibrillation), rapid heartbeat (ventricular tachycardia), episodes of severely abnormal heartbeat in the heart's

KEY TERMS

Action potential—The wave-like change in the electrical properties of a cell membrane, resulting from the difference in electrical charge between the inside and outside of the membrane. The action potential acts as a signal for certain activities and processes in the body.

Arrhythmia—Abnormal heart rhythm; examples are a slow, fast, or irregular heart rate.

Beta-adrenergic blocker—A drug that works by controlling the nerve impulses along specific nerve pathways.

Caveolae (singular, caveola)—Tiny, flask-shaped pockets in the plasma membranes of human and animal cells.

Depolarization—The dissipation of an electrical charge through a membrane. In the heart, depolarization causes the heart muscle to contract.

Electrocardiogram (ECG, EKG)—A test used to measure electrical impulses coming from the heart in order to gain information about its structure or function.

Fibrillation—A rapid, irregular heartbeat.

Ion channel—Cell membrane proteins that control the movement of ions into and out of the cell.

QT interval—The section on an electrocardiogram between the start of the QRS complex and the end of the T wave, representing the firing or depolarization of the ventricles and the period of recovery prior to repolarization, or recharging, for the next contraction.

Repolarization—Period when the heart cells are at rest, preparing for the next wave of electrical current (depolarization).

Syncope—A brief loss of consciousness caused by insufficient blood flow to the brain.

Tachycardia—An excessively rapid heartbeat; a heart rate above 100 beats per minute.

Torsades de pointes (TdP)—Term that means turning of the points in French; a type of fast heartbeat or tachycardia of the ventricles that is characteristic of long QT syndrome.

upper chambers (atrial fibrillation) in adulthood (though not childhood), and risk of sudden death. However, a long QT interval is not always seen in individuals with LQT4, so it is considered a condition distinct from classical long QT syndromes. Individuals with some of the

variants of the *KCNE2* gene that cause LQT6 may be adversely affected by exercise and some medications.

Individuals with LQT7 are affected by episodes in which they cannot move (potassium-sensitive periodic paralysis), heart problems, and unusual face and body features. The symptoms of LQT7 can include short stature, wide-spaced eyes (hypertelorism), low-set ears, small chin (hypoplastic mandible), palate abnormalities, curved fingers and toes (clinodactyly), fused fingers and toes (syndactyly), curved back (scoliosis), periodic paralysis, long QT interval, abnormal heartbeat in the upper and lower chambers of the heart, rapid heartbeat, and sudden death.

Long QT syndrome with syndactyly is characterized by symptoms in multiple parts of the body that include lethal heart arrhythmias, webbing of fingers and toes (syndactyly), heart defects present at birth, immune deficiency, severe low blood sugar that comes and goes, developmental delays, and autism.

Diagnosis

A diagnosis of LQTS most often comes from an electrocardiogram (ECG or EKG). An ECG records the electrical activity of the heart using electrical leads placed at specific sites on the body. The electrical activity due to the depolarization and repolarization of the heart is recorded by each lead and added together. The recordings, on paper or on a monitor, show a series of peaks, valleys, and plateaus.

The QRS complex is a sharp peak and dip on the ECG that occurs as the electrical impulses fire the cells of the ventricles, causing contraction and depolarization of the action potential. The *torsades de pointes* (turning of the points) refers to these spikes in the QRS complex. Sometimes it is possible to diagnose *torsades de pointes* from an ECG. The T wave on the ECG occurs as the cells recover and prepare to fire again with the next heartbeat. Thus, the T wave represents the repolarization of the ventricles. The QT interval on the ECG is the period from the start of the depolarization of the ventricles (Q), as the electrical current traverses the ventricles from the inside to the outside, through the repolarization of the ventricles (T), as the current passes from the outside to the inside. The QT interval represents the firing and recovery cycle of the ventricles. In LQTS, the QT interval on the ECG may be a few one-hundredths of a second longer than normal. A QT interval that is longer than 440 milliseconds is considered to be prolonged. There also may be abnormalities in the T wave of the ECG.

ECGs may vary depending on the specific mutation that is the cause of the LQTS. Furthermore, up to 12% of individuals with LQTS may show normal-appearing or

borderline-normal QT intervals. An individual's ECGs can vary from reading to reading, and additional ECGs or ECGs performed during exercise may reveal an abnormal QT interval. ECGs of parents or siblings may contribute to a diagnosis, since one parent, and possibly siblings, may carry a gene variation that causes LQTS and therefore may exhibit a prolonged QT interval on an ECG.

Children with LQTS may exhibit a low heart rate; specifically, a resting heart rate that is below the second percentile for their age. A fast heart rate of 140–200 beats per minute may indicate tachycardia resulting from LQTS. Convulsive seizures due to LQTS sometimes are misdiagnosed as epilepsy, particularly in children. Some individuals with LQTS may have low levels of potassium in their blood.

Some individuals with LQTS may be identified by the combination of the standard diagnostic measurement with ECG and physical examination. Long QT syndrome with syndactyly, LQT7, and Jervell and Lange-Nielsen syndrome have such features as a hearing impairment, fused fingers, or facial features that may lead to a diagnosis.

Currently, there is no single specific diagnostic test that can identify all cases of LQTS. The difficulty in developing a comprehensive test is due to the fact that more than 200 specific changes in many different genes have been found to be responsible for LQTS. Additionally, approximately half the individuals diagnosed with LQTS do not carry any of the known genetic variations. However, when family members are known to carry a specific LQTS gene mutation, genetic testing may be used to diagnose LQTS in other family members. As of 2015, molecular genetic testing was available for all types of long QT syndrome except types 4, 7, and 8.

Treatment and management

Beta-adrenergic blockers, or beta-blockers, are the most common treatment for the ventricular arrhythmia resulting from LQTS. Propranolol is the most frequently prescribed drug. It lowers the heart rate and the strength of the heart muscle contractions, thereby reducing the oxygen requirement of the heart. Propranolol also regulates abnormal heart rates and reduces blood pressure. Other beta-blockers prescribed for patients with LQTS include atenolol, metoprolol, and nadolol.

Approximately 90% of individuals with LQTS can be treated successfully with these drugs. Since the prophylactic effects disappear within one or two days of stopping the beta-blocker, treatment with these drugs usually lasts for life. Since the first symptom of LQTS may be sudden death, younger individuals with prolonged QT intervals or with family histories of LQTS are commonly treated with beta-blockers, even in the absence of symptoms.

QUESTIONS TO ASK YOUR DOCTOR

- What does the acronym QT mean in the term “long QT syndrome”?
- What are the primary medical problems to be concerned about for a child diagnosed with long QT syndrome?
- What medications are recommended for use with a child with long QT syndrome?
- What is the prognosis for a person with long QT syndrome?

Beta-blockers are considered to be safe medications. Any side effects from propranolol are usually mild and disappear once the body has adjusted to the drug. However, propranolol and other beta-blockers can interact dangerously with many other medications.

As knowledge of the causes of LQTS increases, other drugs may prove to be more effective for treating some forms of LQTS. For example, mexiletine, a sodium-channel blocker, is used to shorten the QT interval in individuals with LQT3 that results from mutations in the *SCN5A* gene.

Elevating the levels of blood potassium may relieve symptoms of LQTS in individuals with mutations in potassium channel genes. For example, increased blood potassium raises the outward potassium current in the *hERG*-encoded channel. Thus, treatment with potassium can compensate to some extent for the shortage of functional potassium ion channels in individuals with LQT2, thereby shortening the QT interval.

Left cardiac sympathetic denervation, the surgical cutting of a group of nerves connecting the brain and the heart, may reduce cardiac arrhythmias in individuals with LQTS. Pacemakers or automatic implanted cardioverter defibrillators (AICDs) are also used to regulate the heart-beat or to detect and correct abnormal heart rhythms. Sometimes, a pacemaker or AICD is used in combination with beta-blockers.

Since the likelihood of developing symptoms of LQTS after about age 45 is quite low, individuals who are at least middle-aged when first diagnosed may not be treated. However, all individuals that have been diagnosed with LQTS must avoid reductions in blood potassium levels, such as those that occur with the use of diuretic drugs. Additionally, individuals with LQTS must avoid a very long list of drugs and medications that can

increase the QT interval or otherwise exacerbate the syndrome.

Infants in LQTS families should be screened with ECGs and monitored closely due to the 41-fold increase in the risk of SIDS.

Individuals with LQTS usually are advised to refrain from competitive sports and to have someone around them during moderate exercise. Family members may be advised to learn cardiopulmonary resuscitation (CPR) in case of cardiac arrest.

Individuals with LQTS require special attention and careful management before, during, and after surgery. Recommendations include monitoring baseline QT interval, using adequate amounts of beta-blocker medications, maintaining a quiet and calm environment, preparing a defibrillator to be available for immediate use, using premedications as needed, ensuring the patient is adequately anesthetized before laryngoscopy and tracheal intubation to avoid sympathetic stimulation, and using of topical anesthesia before intubation. During the operation, recommendations include monitoring the QT interval, keeping a quiet and calm environment, and avoiding patient hypothermia. Specific agents are recommended to be used for general anesthesia, including propofol for induction or as continuous infusion throughout, isoflurane as volatile agent of choice, vecuronium for muscle relaxation (dose appropriately to avoid pharmacologic reversal), and fentanyl for analgesia. After surgery, careful monitoring of the patient and his or her QT interval is recommended until the patient has recovered from anesthesia and the monitored QT interval has returned to baseline. It is also recommended to ensure adequate pain control after surgery.

Prognosis

The prognosis usually is quite good for LQTS patients who receive treatment; only 4%–5% of cardiac events were fatal as of 2015. Symptoms may disappear completely and, often, at least some of the ECG abnormalities revert to normal. In contrast, the death rate for LQTS can be very high among untreated individuals.

Women with LQTS usually do not experience an increase in cardiac events during pregnancy or delivery. However, they may experience an increase in serious episodes of irregular heartbeat in the months following delivery. This is especially true for women who have experienced syncopic episodes prior to pregnancy. This increase in symptoms may be due to the physical and emotional stress of the postpartum period. Women who receive beta-blocker therapy during pregnancy and following delivery experience far fewer cardiac events. Beta-blockers do not appear to adversely affect a pregnancy, nor do they appear to harm the fetus.

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- American College of Cardiology (ACC), Heart House, 2400 N St. NW, Washington, DC 20037, (202) 375-6000 or (800) 253-4636, (202) 375-7000, resource@acc.org, <http://www.acc.org>
- American SIDS Institute, 528 Raven Way, Naples, FL 34110, (239) 431-5425, (239) 431-5536, <http://sids.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06813, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>
- SADS Foundation, 508 E. South Temple, Suite 202, Salt Lake City, UT 84102, (800) STOP-SAD or (801) 531-0937, <http://www.sads.org>

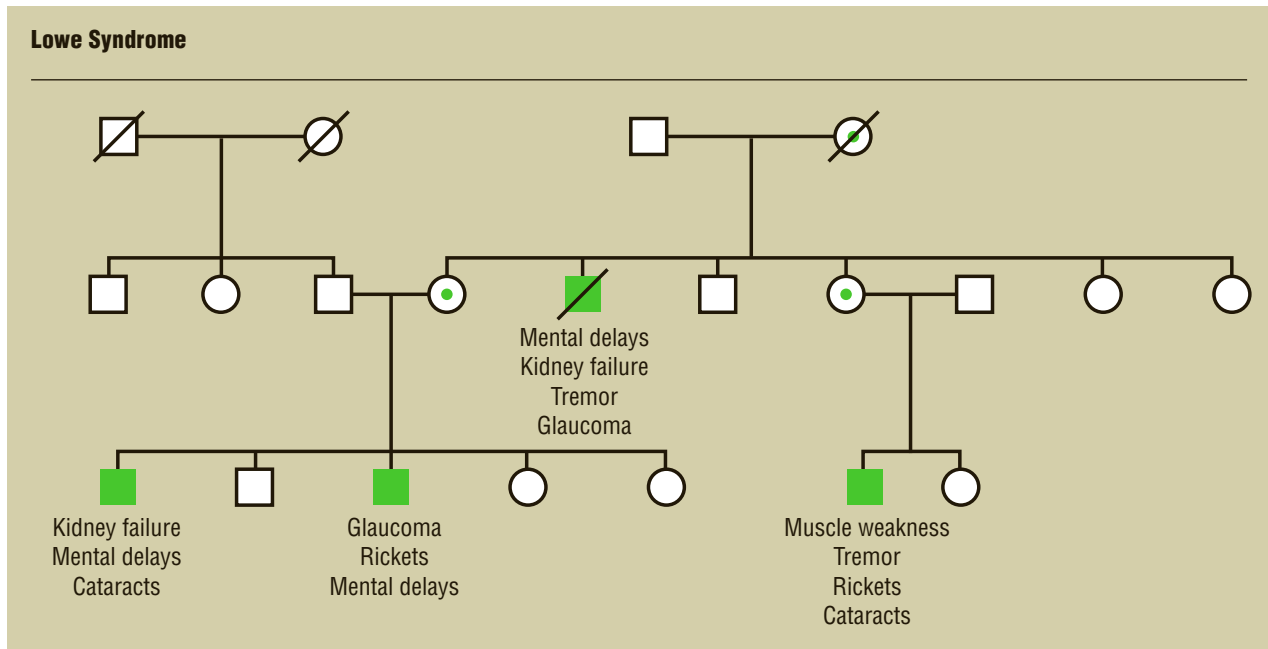
Dawn Jacob Laney, MS,
Margaret Alic, PhD
and Rebecca J. Frey, PhD

Lou Gehrig disease see **Amyotrophic lateral sclerosis**

Lowe oculocerebrorenal syndrome

Definition

Lowe oculocerebrorenal syndrome is a rare genetic condition that affects males. It is caused by an enzyme deficiency, and affects many body systems including the eyes, the kidneys, and the brain.



Lowe syndrome: pedigree analysis chart (Gale)

Description

Lowe oculocerebrorenal syndrome was first described by Dr. Charles Lowe in 1952. The syndrome is caused by a change (mutation) in the *OCRL1* gene. This gene is responsible for the production of the enzyme phosphatidylinositol 4,5-bisphosphate 5-phosphatase. A mutation in the *OCRL1* gene leads to a decrease in enzyme activity. This decrease in the activity of phosphatidylinositol 4,5-bisphosphate 5-phosphatase is responsible for the physical and mental problems associated with Lowe oculocerebrorenal syndrome. The reason a deficiency of this enzyme causes Lowe oculocerebrorenal syndrome is still unknown. Phosphatidylinositol 4,5-bisphosphate 5-phosphate phosphatase is thought to be limited to a specific part of the cell called the Golgi apparatus. The relationship between the function of the Golgi apparatus, the enzyme deficiency, and the features of Lowe oculocerebrorenal syndrome is unclear.

The name Lowe oculocerebrorenal syndrome describes the body systems most commonly affected by this genetic disease. The term “oculo” refers to the eye problems commonly seen in individuals with the disease. Cataracts (cloudiness of the lens of the eye) are a classic feature and are usually present at birth (congenital). Other eye problems are also common. The term “cerebro” refers to the brain dysfunction commonly seen in the disease. The majority of affected males have intellectual disabilities and behavior disturbances. The term “renal” refers to the associated kidney problems, which can interfere

with normal bone development and eventually lead to kidney failure.

Genetic profile

Changes (mutations) in the *OCRL1* gene decrease the activity of the enzyme phosphatidylinositol 4,5-bisphosphate 5-phosphatase. There have been many different mutations identified in the *OCRL1* gene. These mutations may be different between families. The *OCRL1* gene is located on the X chromosome. Since the *OCRL1* gene is located on the X chromosome, Lowe oculocerebrorenal syndrome is considered to be X-linked. This means that it only affects males.

A person’s sex is determined by his or her chromosomes. Males have one X chromosome and one Y chromosome, while females have two X chromosomes. Males who possess a mutation in their *OCRL1* gene will develop Lowe oculocerebrorenal syndrome. Females who possess a mutation in their *OCRL1* gene will not; they are considered to be carriers. This is because females have another X chromosome without the mutation that allows normal function, and prevents them from getting this disease. If a woman is a carrier, she has a 50% risk during pregnancy of passing on her X chromosome with the mutation. Therefore, with every male pregnancy, she has a 50% risk of having an affected son, and with every female pregnancy, she has a 50% risk of having a daughter who is a carrier.

Demographics

Lowe oculocerebrorenal syndrome affects approximately 1 in 100,000 live births. It occurs evenly among ethnic groups. Almost always, only male children are affected. Women carriers usually do not have physical or mental problems related to the disease.

Signs and symptoms

The signs and symptoms of Lowe oculocerebrorenal syndrome are variable. Some individuals with Lowe oculocerebrorenal syndrome have many severe symptoms, while other affected individuals have fewer, more mild symptoms.

Eye problems are a common feature of Lowe oculocerebrorenal syndrome. Congenital cataracts are a classic feature of the disorder. These cataracts may be one of the first symptoms noticed during infancy. Approximately 50% of males with Lowe oculocerebrorenal syndrome will develop increased pressure behind the eye (glaucoma). This pressure can damage the eye. Other eye problems include strabismus (crossed or divergent eyes), nystagmus (uncontrollable rhythmic eye movements), and microphthalmia (small eyes).

The nervous system (brain and nerves) is also typically affected by Lowe oculocerebrorenal syndrome. Intellectual disability is a common feature of Lowe oculocerebrorenal syndrome. It can vary between mild and severe. Some males with Lowe oculocerebrorenal syndrome have normal intelligence. Seizures and behavior disturbances can also be seen in individuals with Lowe oculocerebrorenal syndrome. Behavior disturbances can include temper tantrums, aggression, obsessions, and repetitive hand movements. One of the first signs of brain dysfunction caused by Lowe oculocerebrorenal syndrome is muscle weakness (hypotonia) during infancy.

Kidney problems are another common finding in individuals with Lowe oculocerebrorenal syndrome. The kidneys normally filter chemicals and acids from the body. The kidneys allow the body to keep needed substances and to remove unneeded substances through the urine. Individuals with Lowe oculocerebrorenal syndrome cannot do this properly, allowing needed substances (calcium, phosphate, etc.) to be excreted in the urine. This kidney disturbance can ultimately lead to kidney failure.

Individuals with Lowe oculocerebrorenal syndrome frequently have slow growth and a short stature. Problems with bones can also develop due to the loss of

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light, resulting in blurry vision. Surgery may be performed to remove the cataract.

Cerebro—Related to the head or brain.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance, a needle is inserted through either the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Congenital—Refers to a disorder that is present at birth.

Germ line mosaicism—A rare event that occurs when one parent carries an altered gene mutation that affects his or her germ line cells (either the egg or sperm cells) but is not found in the somatic (body) cells.

Glaucoma—An increase in the fluid eye pressure, eventually leading to damage of the optic nerve and ongoing visual loss.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Nystagmus—Involuntary, rhythmic movement of the eye.

Oculo—Related to the eye.

Renal—Related to the kidneys.

Rickets—A childhood disease caused by vitamin D deficiency, resulting in soft and malformed bones.

Strabismus—An improper muscle balance of the ocular muscles, resulting in crossed or divergent eyes.

certain substances through the kidneys. Rickets and easily breakable bones are common features. Joints may become inflamed in individuals with Lowe oculocerebrorenal syndrome.

Diagnosis

The diagnosis of Lowe oculocerebrorenal syndrome is based initially on the presence of the symptoms of the disorder. Lowe oculocerebrorenal syndrome is definitively diagnosed by measuring the activity of the enzyme phosphatidylinositol 4,5-bisphosphate 5-phosphatase. When the activity of this enzyme is very low, it is diagnostic of Lowe oculocerebrorenal syndrome. In order to perform this test, a small piece of skin must be removed from the patient's body (skin biopsy). The enzyme is then measured from cells in this skin sample. In some cases it is also possible to look for a mutation in the *OCRL1* gene. The presence of mutation confirms the diagnosis of Lowe oculocerebrorenal syndrome in males.

Determining if a woman is a carrier of Lowe oculocerebrorenal syndrome can be done several different ways. Females who carry a mutation in their *OCRL1* gene commonly have changes in the lens of the eye. These changes can only be detected by an ophthalmologist with a special eye examination. These changes do not cause vision problems. The eye difference seen in carriers of Lowe oculocerebrorenal syndrome is best observed once females reach adulthood. Recent reports suggest that a detailed eye exam can detect 90% of carriers. In addition to eye examinations, carrier detection can be performed with DNA testing. If the *OCRL1* mutation has been identified in an affected male in the family, the females in the family can undergo DNA testing.

Prenatal diagnosis is possible by measuring the activity of phosphatidylinositol 4,5-bisphosphate 5-phosphatase in fetal tissue drawn by amniocentesis or chorionic villus sampling. In cases where the mutation is known, DNA testing can be used in prenatal diagnosis. Fetuses should be tested if the mother is a carrier of Lowe oculocerebrorenal syndrome. A woman is at risk of being a carrier if she has a son with Lowe oculocerebrorenal syndrome or someone in her family with Lowe oculocerebrorenal syndrome. Any woman at risk of being a carrier can undergo testing to determine if she is at risk to have a son with Lowe oculocerebrorenal syndrome.

Treatment and management

There is currently no cure for Lowe oculocerebrorenal syndrome. Individuals with Lowe oculocerebrorenal syndrome benefit from therapies and regular medical care. Physical therapy, occupational therapy, and speech therapy may be recommended due to developmental delays. Regular eye exams by an ophthalmologist are also recommended. Patients with Lowe oculocerebrorenal syndrome should be seen by a nephrologist (kidney doctor). Dialysis may ultimately be recommended for kidney failure.

Prognosis

The lifespan of males with Lowe oculocerebrorenal syndrome is limited by their multiple medical problems. Death by middle age is common. However, medical advances are improving the quality of life for individuals with this genetic condition.

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Lowe Syndrome Association, PO Box 864346, Plano, TX 75086-4346, (972) 733-1338, <http://www.lowesyndrome.org>

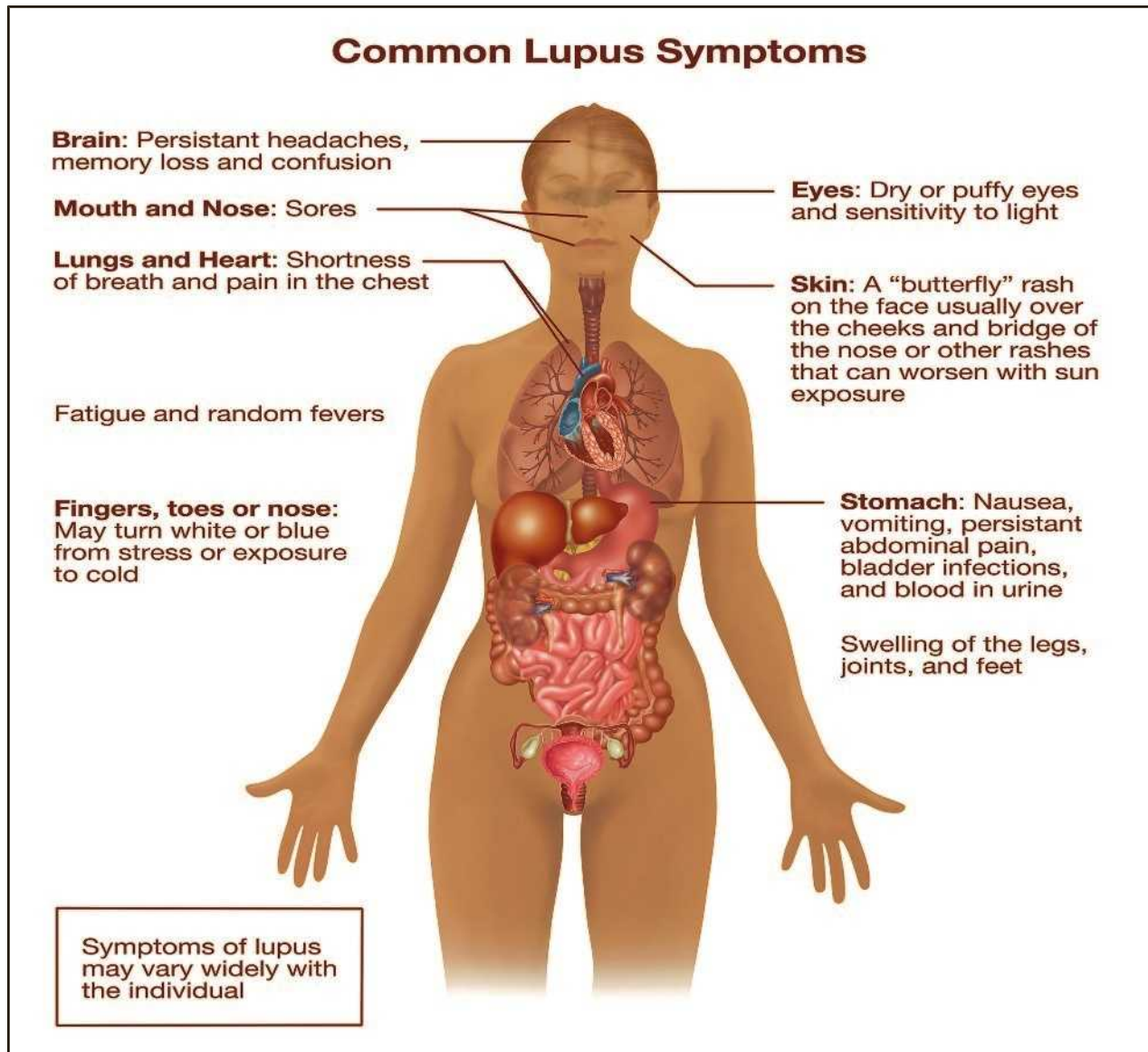
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Holly Ann Ishmael, MS

Lupus

Definition

Lupus refers to a large group of complex autoimmune disorders in which the immune system attacks and damages or destroys the body's own cells and tissues. The most common type of lupus is systemic lupus erythematosus (SLE), which can affect many different parts of the body. The Lupus Foundation estimates that as many as 1.5 million Americans have lupus, and most are women of childbearing age. Variations in a number of



Lupus is an autoimmune disease that can affect various parts of the body. (Gwen Shockey/Science Source)

different genes have been implicated in a susceptibility to SLE. As a result, SLE is a particularly complex and varied disorder. It has both hereditary and environmental risk factors. For example, according to author Daniel J. Wallace, environmental risk factors that may trigger lupus include exposure to tobacco smoke; some viruses, especially Epstein-Barr; and exposure to substances such as crystalline silica. In addition, there is probable environmental association to heavy metals and pesticides.

Description

The immune system normally protects the body from foreign organisms and other substances. By contrast, lupus is a disorder in which immune system components

attack the healthy cells and tissues. Lupus is a complex disorder that can damage skin, joints, blood vessels, and internal organs, including the kidneys, heart, lungs, and brain.

SLE is a chronic disorder that causes inflammation of the connective tissues, such as cartilage and the lining of blood vessels. Kidney disease occurs in about one-third of patients with SLE. SLE can cause various heart problems, such as pericarditis (inflammation of the membrane enclosing the heart) or heart valve abnormalities. People with SLE are also prone to heart disease from atherosclerosis (the buildup of fat and plaque in the blood vessels). Inflammation from SLE can damage the nervous system, causing a variety of problems, including

peripheral neuropathy (weakness and pain in the limbs), seizures, stroke, and cognitive impairment that affects memory, learning, and reasoning. Anxiety and depression are common with SLE. As a result of these multiple health risks, patients with SLE or other forms of lupus need to see their primary care physicians on a regular basis to manage their symptoms.

Other types of lupus include the following:

- discoid lupus erythematosus that causes a chronic rash
- subacute cutaneous lupus erythematosus that results in sores after exposure to sunlight
- medication-induced lupus, which many drugs may trigger, such as hormones, antibiotics, anticonvulsants, lithium, and other drug categories
- neonatal lupus, a rare form affecting newborns

Causes

The cause of lupus is not known, but the disorder appears to stem from a combination of genetic factors that contribute to a susceptibility to the disorder as well as to environmental factors or triggers. Sex hormones appear to

play a role in triggering lupus. Environmental factors can include diet, stress, chemical exposure, sunlight, and viral infections. About 10% of SLE cases appear to be triggered by drug exposure, and more than 80 different drugs that can trigger SLE have been identified.

A characteristic of SLE is that cells that have self-destructed (undergone apoptosis)—either because they are damaged or have reached the end of their functional lifespan—are not properly eliminated from the body. It has been suggested that these dead cells may release substances that trigger improper immune system reactions.

Another possible cause is a specific type of immune cell. In a study reported by the National Institutes of Health (NIH) in 2020, researchers identified two types of dysregulated neutrophils that appeared to be implicated in lupus. Neutrophils are white blood cells active in the immune system. Researchers have found two types of low density granulocytes (LDGs) present in some neutrophils that may be implicated in the disease process, including one set that lacks a substance known as C10 and another more mature set that includes CD10. The researchers found that the higher levels of CD10-



A person's hands displaying signs of lupus. (*Biophoto Associates/Science Source*)

positive LDGs from the more mature subpopulation of neutrophils isolated from the blood of lupus patients correlated with more severe organ damage and reduced kidney function. This finding may help scientists develop clinical biomarkers so they can more aggressively treat lupus patients with higher numbers of these mature LDGs. The hope is that a path will also be found enabling researchers to decrease the abnormal actions of these problematic neutrophils.

Genetic profile

Lupus, especially SLE, and other autoimmune disorders appear to run in families. Normal variations, known as polymorphisms, in at least 17 different genes are known to increase the risk of SLE. Thus, the genetic contributions to the development of SLE and perhaps other types of lupus are complex. In most cases, people with SLE do not inherit a gene that causes the disorder; rather, they inherit variations in genes that increase the risk of developing the disorder under the influence of other factors or triggers. Most genes that have been associated with SLE are involved in the functioning of the immune system, and SLE-associated variations in these genes may affect the control and specific targeting of the immune response.

Rarely, SLE is caused by autosomal recessive mutations in the *TREX1* gene. *Autosomal recessive* means that an individual must inherit two mutated copies of the *TREX1* gene, one from each parent, to develop SLE. The parents, each carrying one copy of the mutant gene, do not have signs and symptoms of SLE. Mutations in *TREX1* can also cause a rare form of SLE called chilblain lupus that primarily affects the skin. *TREX1* encodes a protein called an exonuclease that breaks down DNA so that it can be repaired. *TREX1* mutations also cause disorders other than lupus.

Demographics

Although lupus can affect anyone, women are more often affected, representing about 90% of all lupus cases. Nonwhite women, especially African American, Hispanic, Asian, and Native American women, have a greater risk for lupus than white women. For example, African American women are three times more likely to develop lupus compared to white women. Non-white women usually develop lupus at a younger age and develop more severe medical problems, such as kidney issues, than white women. Although SLE is more common among younger women, 20% of cases occur in people over age 50. Symptoms of SLE vary greatly and can resemble signs and symptoms of other disorders, so SLE may be underdiagnosed. Nevertheless, the prevalence of

SLE increased ten-fold in the industrialized West from 1970 to 2020, for reasons that are unclear.

Some researchers have found that lupus has been greatly underestimated as a cause of death, which in turn underestimates the burden of the disease on individuals as well as society at large. For example, in a study in Sweden in 2017, Titilola Falasinnu and colleagues compared data from more than 8,000 people with lupus and found that of 1,802 deaths among patients with SLE, more than half (59%) had no report of SLE listed in their death records. Individuals ages 85 years and older were least likely to have SLE listed as a cause of death. The researchers noted that in three of five patients who died with SLE, there was no report of the SLE diagnosis. The researchers said others have seen similar findings, and this factor accounts for the underreporting of rare diseases such as SLE. The researchers found that the primary cause of death among those who died with SLE was cardiovascular disease (ICVS); however, for most people with lupus, the cause of their CVD is the SLE itself.

Signs and symptoms

Signs and symptoms of lupus vary greatly. Symptoms are often intermittent, with flare-ups that range from mild to severe, or the development of new symptoms. Common symptoms include the following:

- joint swelling or pain
- muscle pain
- fever
- red rashes, especially on the face
- hair loss
- swollen glands
- chest pain when breathing deeply
- pale or purple fingers or toes
- sensitivity to sunlight
- swelling in the legs or around the eyes
- mouth or nose sores
- fatigue

Other symptoms can include the following:

- low red blood cell count (anemia)
- headaches
- dizziness
- sadness
- confusion
- seizures

Additional symptoms of SLE can vary greatly because so many different organs may be affected. Initial symptoms may include fatigue, malaise, fever, loss of appetite, and weight loss. Joint pain affects most people

with SLE, usually in the same joints on both sides of the body. Muscle pain and weakness also affect many patients. Skin rashes are common, especially a flat red rash, called a butterfly rash, across the bridge of the nose and cheeks. Other skin problems include calcium deposits under the skin (calcinosis), tiny red spots called petechiae from bleeding under the skin due to a lack of platelets for clotting, and damaged blood vessels under the skin (vasculitis).

Diagnosis

Lupus can be difficult to diagnose; it often takes months or years to reach a diagnosis. A medical history, complete physical exam, blood tests, and biopsy of the skin and/or kidney for examination under a microscope may all contribute to the diagnosis.

A blood test called an antinuclear antibody panel is an important component of diagnosis. It tests for the presence of antinuclear antibodies (ANA), which are immune-system antibodies that attack the body's own tissues in autoimmune disorders, especially SLE. Although healthy people may have low levels of ANA, high levels are suggestive of SLE or another autoimmune disorder. High amounts of ANA in the blood are particularly suggestive of SLE if antibodies against double-stranded DNA are also present. Some researchers also suggest considering other biomarkers for SLE; for example, Benoit Brillard and colleagues in France found in their study of 109 patients with SLE and 47 healthy controls, the levels of interleukin-1 (IL-1) were significantly higher in the patients with SLE compared to the controls. These levels were also higher in patients with SLE with active symptoms compared to those whose symptoms were not active.

Treatment and management

The goals of lupus management are to prevent flare-ups, treat flare-ups when they occur, and reduce the risks for organ damage and other complications of SLE. Treatment may include various medications for reducing pain and swelling, preventing or reducing flare-ups, suppressing the immune system, reducing or preventing damage to joints, and balancing hormones. Drugs to reduce cholesterol levels and blood pressure or prevent or treat infection may also be necessary.

Drugs

Anti-inflammatory medications are the most common lupus drugs, and for many people they are the only treatment required. Anti-inflammatories reduce inflammation and pain and can quickly relieve fever or arthritis. These drugs include aspirin, acetaminophen (Tylenol), or

KEY TERMS

Allele—One of two or more different genes encoding specific and inheritable characteristics that occupy corresponding locations on a pair of chromosomes.

Antibody—A protein produced by the mature B cells of the immune system that attach to invading microorganisms and target them for destruction by other immune system cells.

Antinuclear antibodies (ANAs)—Abnormal antibodies against cell nuclei. They are found in the blood of people with autoimmune diseases such as lupus.

Autoantibody—An antibody against the body's own proteins that the immune system produces.

Autoimmune disorder—A disorder that occurs when the body's tissues are attacked by its own immune system, as in RA.

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are needed to display the trait or disease.

Monoclonal antibody (mAB)—A protein, produced in large quantities in a laboratory, designed to attack a specific target in the body.

Nonsteroidal anti-inflammatory drug (NSAID)—A pain reliever, such as ibuprofen or naproxen.

Polymorphism—A change in the base pair sequence of DNA that may or may not be associated with a disease.

Systemic lupus erythematosus (SLE)—A chronic, inflammatory autoimmune disorder that is the most common type of lupus.

nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen, indomethacin, nabumetone, or celecoxib. Corticosteroids (glucocorticoids, cortisone, and steroids) are drugs that function like the hormone cortisol in the body to decrease inflammation, regulate blood pressure, and suppress the immune system. Prednisone is the most common corticosteroid prescribed for lupus. Prednisolone or methylprednisolone may be prescribed for patients with liver problems. Steroids are usually taken as pills, but they can also be injected into muscles, joints, or skin lesions or administered intravenously over a period of several hours (pulse steroids) so that the effects last for weeks to control a flare-up. Topical steroid creams or gels are used for skin symptoms. Steroids are usually taken only during lupus flares, in gradually reduced dosages, or intermittently, because of

QUESTIONS TO ASK YOUR DOCTOR

- Why do you think I might have lupus?
- How is lupus diagnosed?
- Can I have genetic testing for lupus-associated genes?
- Could I pass lupus on to my children?
- What treatments do you recommend?

long-term complications from their use, including increased risk of infection. Antimalarial drugs such as hydroxychloroquine (Plaquenil) are given to treat cutaneous and musculoskeletal issues. If antimalarials as well as drugs such as methotrexate have no effect, then belimumab (Benlysta), a monoclonal antibody that was developed in the laboratory, may be used to suppress the immune system. A drug in the immune modulator category, voclosporin (Lupkynis), as well as belimumab, is approved to treat lupus nephritis, or kidney disease caused by lupus.

Antimalarial drugs may be used in combination with other drugs such as steroids to reduce their required doses. Antimalarials are most often used for skin rashes, mouth ulcers, and joint pain. Antimalarials decrease auto-antibody production and help protect against ultraviolet radiation from sunlight. Hydroxychloroquine (Plaquenil) or chloroquine (Aralen) are most often prescribed for lupus skin rashes and joint pain.

Immunosuppressives or immune modulators are used to control inflammation from an overactive immune system, especially when steroids cannot control symptoms. These drugs can significantly increase the risk of infection. Immunosuppressives used for lupus include azathioprine and the anticancer drugs cyclophosphamide and methotrexate.

Anticoagulants help prevent blood clots, which can be a life-threatening symptom of lupus. Anticoagulants include low-dose aspirin, heparin, and warfarin. Anticoagulant therapy may be continued for life. Variations in two genes may affect responses to warfarin, and people with particular variations in these genes may need lower doses.

Belimumab (Benlysta) is a monoclonal antibody (mAB) that prevents the activation of immune-system B cells by interfering with a protein called BLyS that is required for B-cell activity. It was the first drug developed and approved specifically for treating lupus.

Prognosis

Because lupus, especially SLE, comprises such a varied group of disorders, prognosis is difficult. Infection is one of the leading causes of death in people with lupus. SLE usually occurs in episodes of flares or exacerbations and remissions (when symptoms lessen or disappear). In general, however, SLE worsens over time, and organ damage may become life-threatening.

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ORGANIZATIONS

- Lupus Foundation of America, 2121 K St. NW, Suite 200, Washington, DC 20037, (202) 349-1155 or (800)

558-0121, (202) 349-1156, info@lupus.org, http://www.lupus.org

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Information Clearinghouse., Information Clearinghouse, National Institutes of Health, Building 31, Room 4C02, 31 Center Dr., MSC 2350, Bethesda, MD 20892-2350, (301) 496-8190, (301) 718-2814, NIAMSinfo@mail.nih.gov, https://www.niams.nih.gov

Margaret Alic, PhD
Revised by Christine Adamec

Lynch cancer family syndrome see **Hereditary colorectal cancer**

Lynch syndrome

Definition

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is a family cancer syndrome caused by a germline mutation and characterized by a sharply increased risk of developing cancer of the colon and rectum. Cancers of the colon and rectum are termed colorectal cancer and are potentially life-threatening tumors that develop in the large intestine. Most cases of colorectal cancer (about 95%) are sporadic, however, rather than hereditary; Lynch syndrome accounts for only 3%–5% of cases. The syndrome is named for Henry Lynch, the American physician who first described it in 1966 and originally termed it “cancer family syndrome.”

Description

Lynch syndrome is the name given to one of several inherited cancer susceptibility syndromes that sharply increase the risk of developing cancer of the large intestine (colon) and the rectum (the last several inches of the colon). About two-thirds of cases of colorectal cancer attributable to the syndrome begin in the proximal colon (the ascending or beginning portion of the colon located in the right side of the abdomen) as opposed to the distal colon closer to the rectum.

Generally, colon cancers start out as small benign polyps, which over time become cancerous. The most commonly occurring type of polyp with the potential to become cancerous is called an adenoma. Because patients with Lynch syndrome do develop adenomatous polyps, the term “nonpolyposis” in its alternate name is somewhat misleading. In fact, the rapid progression from benign polyps to cancerous tumors, which is known as



3D colonoscopy image showing the location of a cancerous growth (center right) in the colon of a 59-year-old patient. (Zephyr/Science Source)

accelerated carcinogenesis, is one of the key features of Lynch syndrome.

With Lynch syndrome, there is an increased rate of progression from benign polyps to cancer because the rate of genetic mutation in the affected cells is two to three times higher than in normal cells. For example, other types of colon cancer may develop over the course of eight to ten years, while in persons with Lynch syndrome, the progression from benign polyps to cancerous ones may occur within two to three years.

Persons with Lynch syndrome are also at increased risk of developing other cancers, especially of the female reproductive tract (endometrial and ovarian cancers) as well as stomach, small bowel, hepatobiliary tract (the liver, gall bladder, and bile ducts), pancreas, urinary tract, and brain cancers. The lifetime estimated risks (the risk of developing a disease during the course of a lifetime) for these cancers in persons with Lynch syndrome are as follows: endometrial (40% by age 70); ovarian (9%–12%); gastric (2%–13%); urinary tract (1%–12%); small bowel (4%–7%); brain (1%–4%); and hepatobiliary (2%). Because of this increased risk of developing cancers outside the large intestine, some experts divide Lynch syndrome into two types: Lynch syndrome I, characterized by hereditary colon cancer; and Lynch syndrome II, associated with other cancers of the reproductive system and gastrointestinal tract.

Genetic profile

Lynch syndrome results from an inherited germline mutation (the presence of an altered gene in the egg or

sperm that can be passed from one generation to the next) in genes that normally protect against the development of cancer by working to repair the body's DNA. There are at least seven genes whose mutations may result in Lynch syndrome: *MLH1* on the short arm of chromosome 3 at 3p21.3, *MSH2* on the short arm of chromosome 2 at 2p21, *MSH6* on the short arm of chromosome 2 at 2p16, *PMS2* on the short arm of chromosome 7 at 7p22, *PMS1* on the long arm of chromosome 2 at 2q32.2, *MSH3* on the long arm of chromosome 5 at 5q14.1, and the *EPCAM* gene, which lies next to the *MSH2* gene on chromosome 2.

The first six genes are genes that recognize and correct errors that occur during DNA replication that have been found to cause Lynch syndrome. Called *mismatch repair genes* or *MMR* genes, these genes are involved in maintaining the integrity of DNA. They check for, correct, and repair mistakes made when DNA is replicated in preparation for cell division. A mutation in any one of these genes prevents the repair of DNA replication errors. When DNA replication mistakes are not corrected, abnormal cells are produced. As these abnormal cells continue to divide, the risk of the kind of uncontrolled cell growth that can cause cancer increases. Mutations in the seventh gene, the *EPCAM* gene, cause the *MSH2* gene to be inactivated or "turned off," thus preventing the *MSH2* gene from performing DNA mismatch repair.

Mutations in the *MLH1* and *MSH2* genes are responsible for the vast majority (90%) of mutations in families with Lynch syndrome. Mutations in *MSH6* account for about 7%–10% of families with Lynch syndrome, and mutations in *PMS2* affect less than 5% of families with the syndrome. Cases resulting from mutations in the *PMS1* and *MSH3* genes are very rare.

Lynch syndrome is most often transmitted in an autosomal dominant manner, which means that it takes just one abnormal gene from one parent for the offspring to inherit the disease; or in this case, the syndrome. An affected parent has a 50% chance of passing a mutated gene to the offspring, so each child of the affected parent has a 50% chance of inheriting the mutation. Individuals with Lynch syndrome are born with a normally functioning gene on one chromosome and a mutated gene on the other chromosome.

Although most people with a gene mutation associated with Lynch syndrome have a family history of cancer, not all have a parent with cancer. This is the case because of incomplete penetrance, which means that not all mutation carriers will express the symptoms of the disease; or in this case, increased risk of developing cancer. In addition to variable or incomplete penetrance, other factors influence the development of and susceptibility

KEY TERMS

Colectomy—Surgical removal of the colon.

DNA mismatch repair—A system for recognizing and replacing wrongly paired (mismatched) nucleotide bases during DNA replication. The system can also repair some forms of DNA damage.

Germline mutation—A mutation that occurs within a germ cell (cell that gives rise to a sperm or ovum) and can be passed on to offspring.

Microsatellite instability (MSI)—An abnormally high rate of change in repeated short sequences of DNA (microsatellites) that indicates impairment of DNA mismatch repair.

Penetrance—In genetics, the proportion of persons carrying a specific genotype (genetic makeup) who express the associated phenotype (external appearance or characteristics).

Polyp—An abnormal tissue growth arising from a mucous membrane. The formation of an unusually large number of polyps is called polyposis.

Prophylactic—Referring to a medical or surgical intervention intended to prevent rather than treat disease.

Protocol—A set of guidelines for medical tests or treatments.

Sporadic cancer—A cancer that occurs at random in the population with no known cause.

Tumor—An abnormal growth of cells. Tumors may be benign (noncancerous) or malignant (cancerous).

to a disease, so while mutations in the mismatch repair genes linked to Lynch syndrome predispose individuals to cancer, it is important to observe that not all people who carry these mismatch repair gene mutations will develop cancer.

Demographics

The American Cancer Society (ACS) estimates that 93,090 new cases of colon cancer and 39,610 new cases of rectal cancer will be diagnosed in the United States in 2015, with 49,700 deaths resulting from these cancers. Lynch syndrome accounts for between 3% and 5% of these cases, or about 7,500 new cases in an average year. People with Lynch syndrome have an 80% chance of developing colorectal cancer and are at increased risk of cancers of the stomach, small intestine, kidney, pancreas,

brain, bile duct, and urinary tract. Women with Lynch syndrome are at increased risk of endometrial and ovarian cancer. Although Lynch syndrome occurs in all racial and ethnic groups worldwide, Asians with Lynch syndrome are at increased risk of stomach cancer.

Families affected by Lynch syndrome have more cases of colon cancer than would generally be expected. Furthermore, these colon cancers as well as benign polyps (noncancerous clumps of cells or gland-like growths) in the colon usually occur at younger ages than they do in the general population. For example, in the general population, the median age (half are older and half are younger) at which colorectal cancer is diagnosed is 71; about two-thirds of colorectal cancers are diagnosed in people over age 65. In contrast, colorectal cancer associated with Lynch syndrome often occurs in younger adults and is frequently diagnosed in persons in their 40s; the median age at diagnosis is 44.

Signs and symptoms

Because the Lynch syndrome gene mutations are germline mutations, they are present in every cell in the body, cancers outside the colon may develop. Among women with Lynch syndrome who develop both colon cancer and endometrial cancer, about one-half are first diagnosed with endometrial cancer, often in their mid-40s. In some families affected by Lynch syndrome, endometrial cancer occurs more frequently than colon cancer.

There are no symptoms associated with carrying the Lynch syndrome gene mutations. Similarly, it is possible to have colorectal cancer without any symptoms. Frequently, symptoms of colorectal cancer do not appear until the disease has advanced. Furthermore, the symptoms associated with colorectal cancer may also be caused by other conditions. These symptoms include:

- abdominal distress (gas, bloating, and cramps)
- rectal bleeding or blood in stool
- changes in bowel movements, such as diarrhea or constipation, or change in consistency of stools
- unexplained weight loss and/or decreased appetite
- unexplained iron-deficiency anemia (low red blood cell count)
- weakness and fatigue

Diagnosis

The diagnosis of Lynch syndrome may be made on the basis of personal and family history but is confirmed using genetic and other laboratory testing.

QUESTIONS TO ASK YOUR DOCTOR

- Am I at risk of having Lynch syndrome with only one known relative who developed colon cancer?
- Are other members of my family at risk?
- Should I consider genetic testing for the syndrome?
- When should I have my first colonoscopy, and how often should I have one?
- What other types of screening tests will you recommend?

Examination

The first step in identifying people at risk of Lynch syndrome is for the healthcare practitioner to obtain a personal and extended family history. Individuals with a family history that includes multiple relatives with colorectal cancer, other syndrome-associated cancers, or occurrence of colorectal cancer before age 60 are generally advised to undergo genetic screening and evaluation for Lynch syndrome and to consult with a genetics counselor or medical geneticist. The results of these genetic test results can guide screening recommendations for affected individuals and their families.

Tests

Genetic testing for Lynch syndrome involves examining an individual's DNA, which is extracted from the individual's blood, to detect mutations in mismatch repair genes. Because *MLH1* or *MSH2* account for the vast majority of detectable mutations, many genetic tests examine these two genes first. However, the introduction of next-generation sequencing meant that it was possible as of 2015 to test an individual for all known Lynch syndrome genes at much lower cost than a series of single-gene tests.

When a mutation is identified, it is vitally important to perform predictive genetic testing of other family members who are at increased risk (e.g., parents, offspring, siblings) because these relatives have a 50% chance of carrying the mutation. Individuals who are found to have the mutation are advised to have earlier and more frequent intensive cancer screening.

A negative test result means that no genetic mutations were detected in the individual tested. When other family members have already tested positive for a

mutation, a negative result means the individual did not inherit the mutation. However, when the individual with a negative test result is the first family member who is tested, this finding does not necessarily mean that there is no basis for a family's higher-than-expected occurrences of cancers. The negative test result may indicate that available tests cannot pinpoint the genetic cause of a family's cancers because some of the genes responsible for the syndrome may not have been identified as of 2015.

It is also possible for genetic testing to produce an indeterminate test result, which means that a genetic variant (change) was detected but the variant detected was not one known to be associated with Lynch syndrome. In this case, it is often advisable to test other family members to determine whether the variant detected is associated with a family's higher-than-expected occurrences of cancer. In some cases, a screening test for Lynch syndrome in patients with colorectal or endometrial cancer can be performed on a sample of tumor tissue taken from the patient. The tissue sample may be tested for microsatellite instability (MSI), which means that short repeated sequences of DNA known as microsatellites are examined for indications that DNA mismatch repair is not taking place in the tumor sample. The number of microsatellites in the tumor sample is compared with the number in a sample of normal tissue from the same patient. If the number of repeats differs in the two samples, MSI is present.

The tumor tissue sample may also be tested by immunohistochemistry (IHC), a process that can be used to evaluate the proteins produced by the mismatch repair genes. If a specific protein is missing, it indicates that the gene that codes for that protein has a mutation. A combination of MSI and IHC testing is considered the most accurate way to identify cancer patients who are carriers of Lynch syndrome, and has been recommended as a screening procedure by the American Society of Clinical Oncology and the European Society for Medical Oncology.

Procedures

Enhanced cancer surveillance for individuals who test positive for Lynch syndrome (and those considered at greater risk despite negative or indeterminate test results) may consist of more frequent examinations of the colon, and prompt removal of polyps when they are present. Examination of the colon, called a colonoscopy, enables a physician to view the entire length of the large intestine using a colonoscope (a long flexible tube with a video camera on one end), which is inserted into the rectum and advanced through the intestine. During a colonoscopy, the physician may remove polyps and take a tissue sample,

which is sent to a laboratory for testing. The test is performed using a technique called immunohistochemistry, a process that involves treating a biopsy sample with antibodies that recognize cell proteins typical of certain kinds of cancers. The sample also is treated with chemicals that cause the cells containing specific proteins to change color, which allows them to be seen under a microscope.

In addition to more frequent colonoscopies, people with Lynch syndrome may be advised to have more frequent fecal occult blood tests that detect even small amounts of blood in the stool, which may indicate the presence of polyps or a tumor. When blood is detected in a stool sample, a colonoscopy is performed to pinpoint its source.

Women with Lynch syndrome may also be screened for endometrial cancer annually beginning at about age 30–35 or 5–10 years before the earliest cancer diagnosis in the family. Women who have already had children may consider having a preventive hysterectomy (surgical removal of the uterus) and bilateral salpingo-oophorectomy (removal of the fallopian tubes and ovaries) to reduce the risk of developing endometrial and ovarian cancers.

Although the frequency of screening tests may vary somewhat depending on an individual's personal and family medical history, the Amsterdam surveillance protocol recommends that persons with mutations in the *MLH1*, *MSH2*, or *MSH6* genes have colonoscopies every one to two years beginning at age 20–25; urine tests every one to two years beginning at age 30–35; and gastroscopy (visual examination of the stomach by means of a flexible viewing instrument inserted in the mouth and through the esophagus) every one to two years beginning at age 30–35. Women should have an ultrasound of the endometrium and a blood test for CA-125, a cancer marker detected in the blood, every one to two years beginning at age 30–35.

Treatment and management

Detecting and promptly removing precancerous polyps is an important way to prevent colorectal cancer from developing. This preventive measure is especially important in people diagnosed with Lynch syndrome.

When cancerous tumors are detected, portions of the colon or the entire colon may be removed to prevent the spread of the cancer. Because removing the colon is the only certain way to prevent colon cancer, some patients with Lynch syndrome choose to have a total colectomy (surgical removal of the colon) before cancer occurs. This practice, known as prophylactic surgery, is highly controversial.

Prognosis

Early identification of people with Lynch syndrome and timely screening can help to detect precancerous polyps so they may be removed. Similarly, regular screening can facilitate early detection of cancers and allow treatment to begin when it is most likely to be effective. Colorectal cancer is among the most curable cancers when it is detected and treated in its earliest stages. Further, people with Lynch syndrome who do develop colorectal cancer fare better than other patients with colorectal cancer; overall, those with the syndrome have higher rates of survival.

Resources

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/symptoms-causes/syc-20374714 (accessed June 13, 2021).

ORGANIZATIONS

American Cancer Society, 250 Williams St. NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org>

American Society of Colon & Rectal Surgeons, 85 W. Algonquin Rd., Suite 550, Arlington Heights, IL 60005, (847) 290-9184, (847) 290-9203, ascrs@fascrs.org, <http://www.fascrs.org>

C3: Colorectal Cancer Coalition, 1414 Prince St., Suite 204, Alexandria, VA 22314, (703) 548-1225 or (877) 427-2111, <http://fightcolorectalcancer.org>

Colon Cancer Alliance, 1025 Vermont Ave. NW, Suite 1066, Washington, DC 20005, (877) 422-2030, <http://www.ccalliance.org>

Lynch Syndrome International (LSI), PO Box 19, Madison, CT 06443, (203) 779-5034, <http://www.lynchcancers.com>

National Cancer Institute, MSC 9760, 9609 Medical Center Dr., Bethesda, MD 20892-9760, (800) 422-6237, <http://www.cancer.gov>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Barbara Wexler, MPH
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Lynch syndrome see **Muir-Torre syndrome**

Lysosomal trafficking regulator see **Chediak-Higashi syndrome**



Macular degeneration—age-related

Definition

Age-related macular degeneration (AMD) is one of the most common causes of vision loss among adults over age 55 living in developed countries. It is caused by the breakdown of the macula, the central part of the retina located in the back of the eye. The macula allows people to see objects directly in front of them (called central vision), as well as to see fine visual details. People with AMD usually have blurred central vision and difficulty seeing details and colors, and they may notice a distortion of straight lines.

Description

Both the function of the macula and the diagnosis of AMD are best understood by considering normal eye function. The eye is made up of many layers of different types of cells that all work together to send images from the environment to the brain, similar to the way a camera records images. When light enters the eye, it passes through the lens and lands on the retina, a very thin tissue that lines the inside of the eye. The retina is made up of 10 different layers of specialized cells, which allow it to function similarly to film in a camera, by recording images. The macula is a small, yellow-pigmented area located in the center of the back of the eye on the retina. It contains blood vessels and nerve fibers. It also contains many specialized cells, called photoreceptors, that sense light coming into the eye, convert light into electrical messages, and send those messages to the brain through the optic nerve. They allow the brain to perceive the environment.

The retina contains two types of photoreceptor cells: rods and cones. The rods are located primarily outside of the macula, and they allow for peripheral (side) and night vision. Most of the photoreceptor cells inside the macula

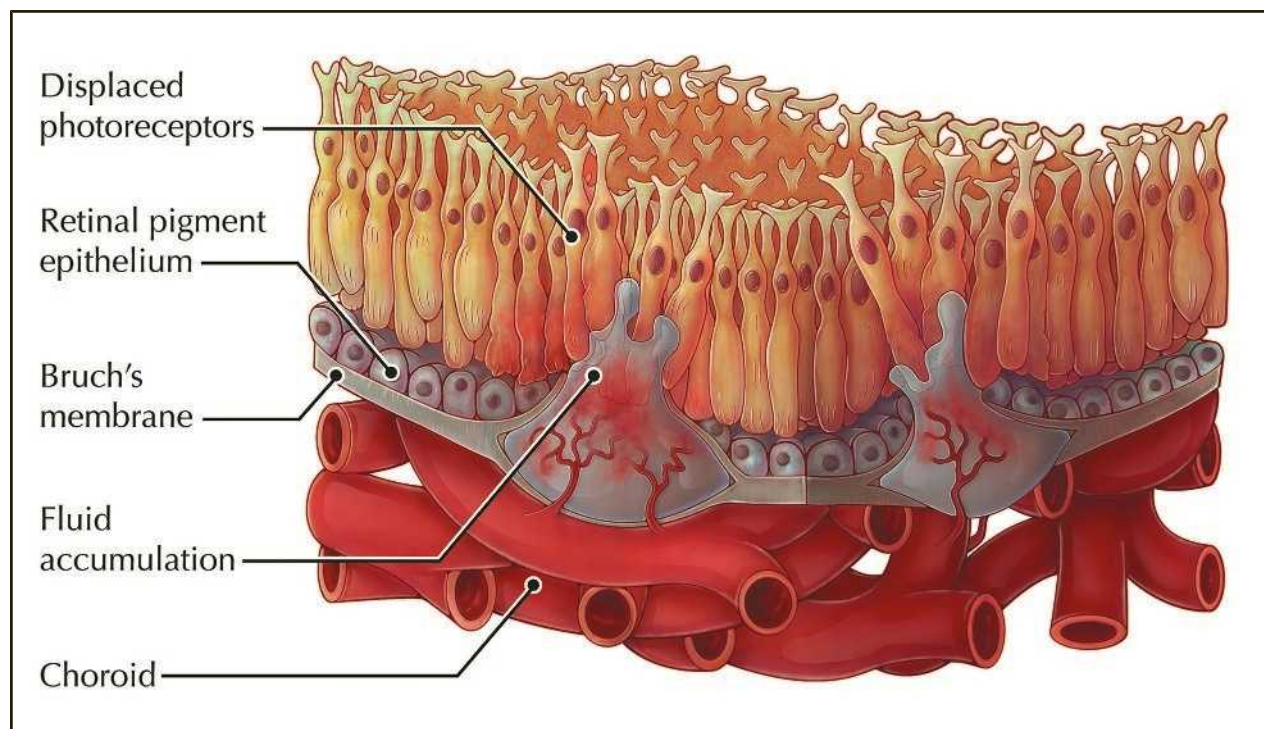
are the cone cells, which are responsible for perceiving color and viewing objects directly in front of the eye (central vision). If the macula is diseased, as in AMD, then color and central vision are altered. There are two different types of AMD: dry AMD and wet AMD.

Dry AMD

Approximately 90% of individuals with AMD have the dry form. This condition is sometimes referred to as nonexudative, atrophic, or drusenoid macular degeneration. In dry AMD, some of the layers of retinal cells (called retinal pigment epithelium, or RPE cells) near the macula begin to degenerate. The RPE is the insulating layer between the retinal and choroid layer, which contains blood vessels. It acts as a protective shield against damaging chemicals and as a filter for the nutrients that reach the retina from the choroid blood vessels. The RPE cells normally help remove waste products from the rods and cones. When the RPE cells are no longer able to provide this function, fatty deposits called drusen begin to accumulate, enlarge, and increase in number underneath the macula. The drusen formation can disrupt the cones and rods in the macula, causing them to degenerate or atrophy (die). This usually leads to central and color vision defects for people with dry AMD. However, some people with drusen deposits have minimal or no vision loss and require regular eye examinations to check for AMD. Dry AMD is sometimes called nonexudative, because even though fatty drusen deposits form in the eye, people do not have leakage of blood or other fluid (often called exudate) in the eye. Symptoms remain stable or worsen slowly from early stages to intermediate or advanced stages of dry AMD. Advanced stages of AMD may result in vision loss. Approximately 10% of people with dry AMD eventually develop wet AMD, the advanced stage of AMD.

Wet AMD

Approximately 10% of patients with AMD have wet AMD that progressed from some stage of the dry form. This form of AMD is also called subretinal neovascularization,



Wet age-related macular degeneration. The macula is a region near the center of the retina with a high density of photoreceptors responsible for high acuity vision. In wet AMD, blood vessels from the choroid undergo angiogenesis, resulting in abnormal blood vessel growth. Excess blood and fluid proteins leak into the retina and irreversibly damage or displace photoreceptors, resulting in vision loss. (Evan Oto/Science Source)

choroidal neovascularization, exudative form, or disciform degeneration. Wet AMD is caused by leakage of fluid and the formation of abnormal blood vessels (called neovascularization) in the choroid layer of the eye. The choroid is located underneath the retina and the macula, and it normally supplies them with nutrients and oxygen. When new, delicate blood vessels form, blood and fluid can leak from them. The formation of abnormal blood vessels underneath the macula leaks enough fluid to raise the macula up and away from the back of the eye and damages it. This causes central vision loss and distortion as the macula is pushed away from nearby retinal cells. Eventually, a scar (called a disciform scar) can develop underneath the macula, resulting in severe and irreversible vision loss. Wet AMD does not have early or intermediate stages. It is considered advanced AMD and is more severe than dry AMD.

Genetic profile

AMD is a complex disorder, caused by a combination of genetic and environmental factors. Researchers have identified more than 50 sites of genetic susceptibility, particularly in the *CFH* and the *ARMS2* genes, although no genetic therapy is available as of 2021. AMD exhibits multifactorial inheritance, and many factors interact with one another and cause the condition.

The aging process is one of the strongest risk factors for developing AMD. There is also genetic heterogeneity among different families with AMD, meaning that different genes can lead to the same or similar disease among different families. Overall, it has been estimated that siblings of individuals with AMD have four times the risk of developing AMD, compared to others.

Some researchers have used deep learning (artificial intelligence) to predict the development of wet AMD. In a study by Jason Yim and colleagues, a model successfully predicted the conversion of eyes to AMD within six months. In another study, Meriam Islam and colleagues used a smart phone application to analyze vision results from 245 patients receiving treatment for AMD. In 79 percent of cases, the application produced an alarm that indicated a drop in visual acuity or a change in the central macular thickness of the eye and a need for injection therapy.

In 1998, a family in which a unique form of AMD was passed from one generation to the next was discovered. Although most families with AMD do not display an obvious inheritance pattern, this particular family's pedigree showed an autosomal dominant form of AMD. Autosomal dominant refers to a specific type of inheritance in which only one allele (one copy of a gene pair)

needs to have a mutation for the disease to develop. An affected person with an autosomal dominant condition thus has one allele with a mutation and one allele that functions properly. There is a 50% chance for this individual to pass on the allele with the mutation, and a 50% chance to pass on the normal allele to each offspring. Genetic testing revealed that the autosomal dominant gene was located on chromosome 1q25-q31, in a locus now known as the *ARMD1* gene locus. In 2004, possible AMD linkage evidence was discovered in four chromosomal regions: 1q31, 9p13, 10q26, and 17q25.

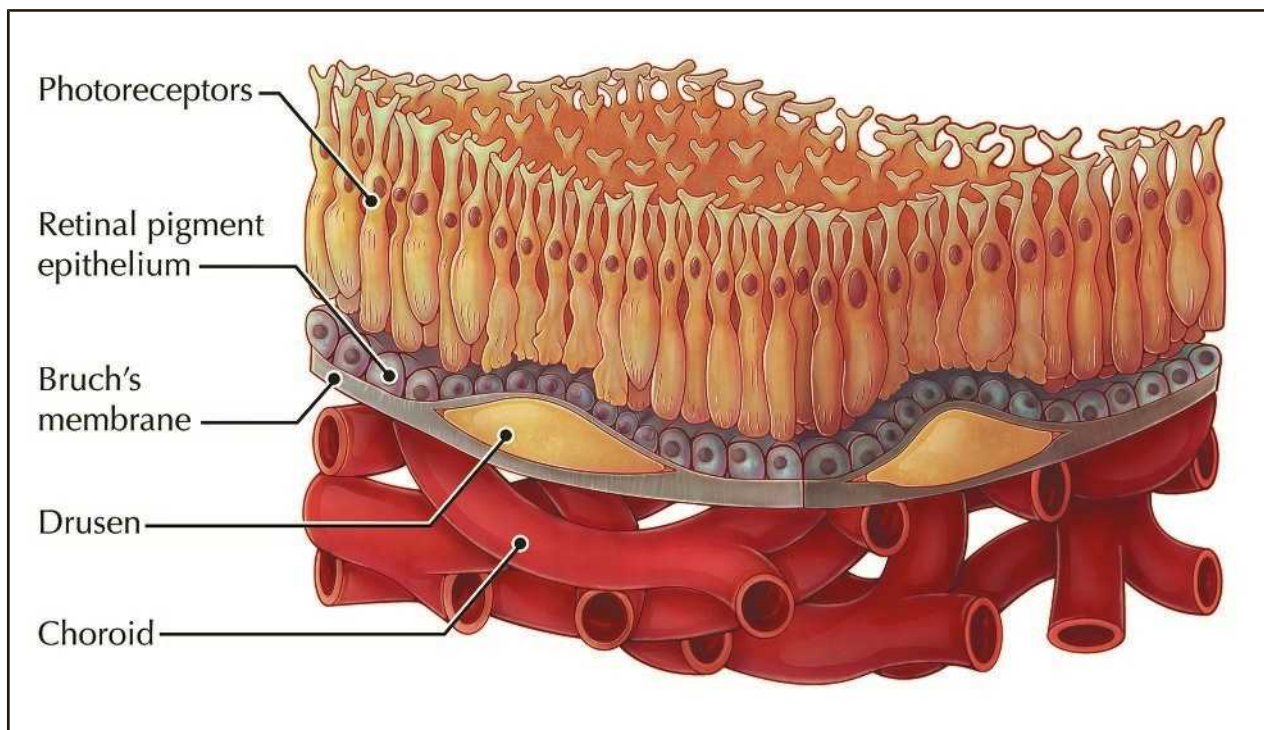
In March 2005, the National Eye Institute (NEI) described the discovery of a gene for AMD in Caucasians. AMD is significantly more common in Caucasians than in individuals of other races or ethnicities, affecting about 2.5% of white adults over age 50, compared to less than 1% each among African Americans or Hispanics. The difference increases further by age 80, when 14% of Caucasians are affected by AMD, compared to about 2% each for African Americans or Hispanics in this age group. In some individuals with AMD, eye inflammation may trigger a biological process leading to AMD. This variation is in a region of *CFH* that binds the C-reactive protein involved in inflammation. *CFH* functions as a brake on the immune system. The variation in *CFH* found in AMD causes the brake to be defective. The

CFH gene is located on chromosome 1q25-31 in the *ARMD1* locus that is repeatedly linked to AMD in family-based studies.

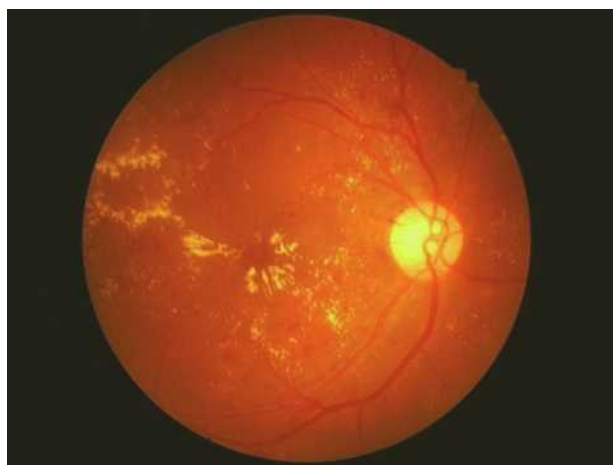
A second susceptibility locus for AMD located on chromosome 10q26 was also identified in 2005 and further confirmed in similar GWAS studies performed in 2006. The two genes that fall within the identified locus—*ARMS2* (LOC387715) and HtrA serine peptidase 1 (*HTRA1*)—are not as well studied as the *CFH* gene. The contribution of these two genes to AMD predisposition has not been established; however, *HTRA1* has been implicated in turnover of proteins involved in drusen formation.

The *CFH* and *ARMS2/HTRA1* gene variations account for the largest percentage of risk for AMD with a combined risk increase of 40%, but they are not an absolute determinant. Not all individuals with AMD have the *CFH* or *ARMS2/HTRA1* variants, and not all of those with the variants have AMD. In their research published in 2020, Xikun Han and colleagues discussed 21 novel genes that are present in the retinal tissue and may be involved in the causes of AMD.

Although one or two particular genes may be the main cause(s) of susceptibility for AMD, other genes or environmental factors may help alter the age of onset of



Dry age-related macular degeneration. In dry AMD, cellular debris called drusen accumulate between the retinal pigment epithelium and the choroid. As a result, photoreceptor cells in the retina can no longer receive nutrients or pass waste to the blood vessels in the choroid, resulting in damage. (Evan Oto/Science Source)



A retinal photograph showing macular degeneration.
(Memorisz/Shutterstock)

symptoms or eye defects. Studies have revealed numerous risk factors for AMD, including the following:

- obesity
- heart disease
- diabetes
- high blood pressure
- cataracts
- farsightedness
- light skin and eye color
- cigarette use
- high-fat/high-cholesterol diet
- ultraviolet (UV) exposure (sunlight)
- low levels of dietary antioxidant vitamins and minerals
- female gender

The exact amount of risk associated with many of these factors is still undetermined, though studies have consistently found a strong association between AMD and smoking. Risk factors in combination with a family history of AMD place an individual at highest risk.

Demographics

Among adults ages 55 and older, AMD is the leading cause of vision loss in developed countries. The risk of developing AMD increases with age and is most commonly seen in adults in their sixth and seventh decades. However, AMD has been reported in adults in their fourth decade. In developed countries, approximately one in 2,000 individuals is affected by AMD. By the age of 75, approximately 15% of people have early or mild forms of AMD, and approximately 7% have an advanced form of AMD. Although AMD occurs in both sexes, it is slightly more common in women.

The dry form of AMD is more common than the wet form. More than 85% of people with intermediate and advanced cases of AMD have the dry form. Within the category of advanced AMD, about two-thirds of AMD cases are the wet form. Almost all AMD-related vision loss results from advanced AMD; therefore, the wet, advanced form of AMD leads to significantly more vision loss than the dry form, which has varying stages of development. Individuals who have advanced AMD in one eye are at very high risk of developing it in the other eye.

Signs and symptoms

AMD causes no pain. In some cases, it advances so slowly that affected individuals might not notice much change in their vision. In other cases, the disease progresses quickly and may lead to a loss of vision in both eyes. One of the most common signs of early AMD is drusen, which is yellow deposits under the retina, most common in individuals over age 60. Drusen can be detected during a comprehensive dilated eye exam. Individuals with early AMD have several small drusen to a few medium-sized drusen. At that stage, there are no other symptoms and no vision loss. Individuals with intermediate AMD have many medium-sized drusen to one or more large drusen. The most common symptom at that stage is a blurred area in the central field of vision. Increased light may be necessary for reading and other tasks. Individuals with advanced AMD have drusen along with a degeneration of light-sensitive cells and supporting tissue in the central retinal area. A blurred spot in the central field of vision gets larger and darker over time. There is difficulty reading and recognizing objects from afar. As the AMD progresses, functional vision may be entirely lost in both eyes. AMD may also cause decreased color vision. Vision loss from dry AMD in only one eye may make it harder to notice changes in overall vision, as the other eye compensates.

While the majority of people with AMD maintain their peripheral vision, the severity of symptoms is dependent on the type of AMD. Wet AMD and advanced dry AMD are associated with the most symptoms. Wet AMD may cause straight lines to have a wavy appearance. The degree of change of visual acuity and other symptoms that can be seen by an eye exam increases over time. Individuals with dry AMD usually develop decreased visual acuity very slowly over a period of many years. Detectable changes are small from year to year, and central vision is partially retained. However, individuals with wet AMD usually have symptoms that precipitate quickly and have a greater risk of developing severe central vision loss in as little as a two-month period. Individuals with dry AMD may suddenly develop wet AMD without undergoing progressive stages of dry AMD.

KEY TERMS

Central vision—The ability to see objects located directly in front of the eye; necessary for reading and other activities that require people to focus on objects directly in front of them.

Choroid—A vascular membrane that covers the back of the eye between the retina and the sclera and serves to nourish the retina and absorb scattered light.

Drusen—Fatty deposits that can accumulate underneath the retina and macula and sometimes lead to AMD. Drusen formation can disrupt the photoreceptor cells, which causes central and color vision problems for people with dry AMD.

Exudate—Fluid that accumulates and penetrates the walls of vessels, leaking into the surrounding tissue.

Genetic heterogeneity—The occurrence of the same or similar disease, caused by different genes among different families.

Genome wide association study (GWAS)—A study that examines prevalent genetic variants among many individuals to determine whether the variants are associated with a particular genetic trait, disorder, or single-nucleotide polymorphism.

Macula—A small spot located in the back of the eye that provides central vision and allows people to see colors and fine visual details.

Multifactorial inheritance—A type of inheritance pattern in which many factors, both genetic and environmental, contribute to the cause.

Optic nerve—A bundle of nerve fibers that carries visual messages from the retina in the form of electrical signals to the brain.

Photoreceptors—Specialized cells (rod cells and cone cells) lining the innermost layer of the eye that convert light into electrical messages so that the brain can perceive the environment. Rod cells allow for peripheral and night vision, while cone cells are responsible for perceiving color and for central vision.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Single-nucleotide polymorphism—A single alteration of a nucleotide base (A, T, C, or G) within the DNA sequence of a population of individuals often linked to a genetic disorder or disease.

Diagnosis

A variety of tests are used to diagnose AMD. The visual acuity test measures the smallest letters an individual can read with one eye on a standardized chart at a distance of 20 feet (6 meters). The refraction test involves the same standardized eye chart but requires the patient to focus through a refraction lens to determine the amount of correction needed for optimum visual acuity. The pupillary reflex test examines the ability of the pupil to constrict or dilate in the presence or absence of bright light. The slit lamp examination is also known as biomicroscopy. A high-intensity light source is focused to shine as a slit on the anterior portion of the eye. The eyes are examined with a microscope designed for the eye, called a biomicroscope. The eyes may be temporarily stained with an orange-colored dye called fluorescein to help visualize their structures. Examination of the posterior portion of the eye involves dilating the pupils with specialized eye drops before examination. Retinal photography can then be performed. Fluorescein angiography, or retinal photography, uses fluorescein dye injected into a vein of the arm and a special camera to analyze and photograph the retina, choroid, and associated blood vessels. This examination can be used to visualize the changes in vasculature associated with wet AMD. Tonometry measures the pressure levels inside the eye. Color testing assesses the functioning of the cone cells in recognizing colors. Standardized pictures made up of dots of different colors are arranged in specific patterns and used to determine color recognition. The Amsler grid test uses a printed paper grid to test for decreased central vision, distorted vision, or blind spots.

Although it is known that multiple genes are implicated in AMD, the American Academy of Ophthalmology does not recommend genetic testing for genes associated with AMD. The reason is that even with known specific genetic variants, a person may or may not develop AMD. In addition, there is currently no information available on how to interpret test results as applies to an individual's likelihood of developing AMD. Individuals with AMD are encouraged to monitor changes in their own vision through the use of an Amsler grid.

Treatment and management

There is no universal cure for either type of AMD; however, individuals with wet AMD can prevent further progression of damage with laser photocoagulation therapy. Light rays are focused by a laser to burn off abnormal blood vessels forming beneath the macula, preventing further leakage of blood and fluid. Some normal tissue is also affected. Previously lost vision is not restored with this treatment. Only a small percentage of

wet AMD cases can be treated with laser surgery. It is most effective if the abnormal blood vessels have developed away from the fovea, the central part of the macula. Laser photocoagulation treatments do not prevent future abnormal blood vessels from forming, and they are not effective for dry AMD. In 2000, the FDA approved the use of a light-activated drug called Visudyne (verteporfin), which is injected into the bloodstream via a vein in the arm. It circulates through the body to the eyes, specifically attaching to the abnormal AMD blood vessels present under the macula. When light rays from a non-thermal laser hit these blood vessels, the Visudyne is activated to produce a chemical reaction that destroys the abnormal vessels, causing very little damage to nearby healthy tissues. If the abnormal blood vessels regrow, the procedure is repeated. While this therapy does not cure AMD, it is useful in managing specific problem areas and reducing further vision loss.

Once dry AMD reaches the advanced stage, no form of treatment can prevent vision loss. For this reason, whenever possible, preventive actions before reaching this stage are important. The National Eye Institute's Age-Related Eye Disease Study (AREDS) reported that taking a high-dose antioxidant and zinc supplement significantly reduces the risk of advanced AMD and vision loss. Supplementation is indicated in individuals with intermediate AMD in one or both eyes, or advanced AMD in one but not the other eye. The AREDS reported that supplementation did not keep individuals with early AMD from progressing to an intermediate stage.

Newer medications delay the progression of wet AMD. These medications are in the category of anti-vascular endothelial growth factor (anti-VEGF) drugs. VEGF is a chemical body protein that causes the growth of blood vessels. The three anti-VEGF medications that are used to treat wet AMD as of 2021 include bevacizumab (Avastin), ranibizumab (Lucentis), and aflibercept (Eylea). The ophthalmologist first cleans the eye to decrease the risk for infection and then inserts the drug directly into the eye with a very thin needle. This treatment slows down vision loss and sometimes may improve vision. In 2020, researchers at the National Institutes of Health (NIH) discovered that a protein that deposits mineralized calcium in the teeth may also be the cause of calcium deposits in the back of the eye in individuals with the dry form of AMD. It is hoped that this unique finding will lead to treatments for dry AMD. More recently, in 2021 researcher Mary Elizabeth Hartnett, MD discovered that an oxidized form of cholesterol may lead to AMD. This form of cholesterol is oxysterol 7-ketocholesterol (7KC), and it is also involved in heart disease and cancer. This substance, 7KC, causes scarring in the eyes. It is hoped that this discovery, too, will lead to

QUESTIONS TO ASK YOUR DOCTOR

- How often should I have my vision checked if I am at risk for AMD?
- Are there modifications to my daily routine that could reduce my risk for developing AMD?
- Where can I get an Amsler grid to monitor changes in my vision?
- What is the treatment for advanced AMD, and how successful is it?
- What are the risks associated with treatment, and how were these risks determined?

treatments for dry AMD, which thus far has not been responsive to treatments.

Prognosis

Most individuals with mild dry macular degeneration never develop disabling central vision loss. However, there is no current method of predicting which individuals will progress to an advanced stage of AMD. AMD can cause the loss of central vision only and cannot cause peripheral vision loss. Loss of central vision may interfere with many activities of daily life and significantly impact its quality. An individual with advanced AMD may become functionally blind, so that reading, driving, recognizing faces, and many other common activities become impossible. The prognosis depends on the stage of the disease and type. Mild forms of dry AMD have a better prognosis than advanced dry or wet AMD. As symptoms progress, individuals with AMD become more at risk for psychological distress due to decreasing quality of life and independence. The prognosis improves if low-vision devices and support groups are utilized to improve the quality of life.

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AMD Alliance International, Sixth Floor, City Gate East, Toll House Hill, Nottingham, United Kingdom 44 115-935-2100, info@amdalliance.org, <http://www.amdalliance.org>

American Macular Degeneration Foundation, P.O. Box 515, Northampton, MA 01061-0515, (413) 268-7660 or (888) 622-8527, <http://www.macular.org>

Foundation Fighting Blindness, 6925 Oakland Mills Road, Columbia, MD 21045, (800) 683-5555, <https://www.fightingblindness.org/>.

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Maffucci disease see **Chondrosarcoma**

Major histocompatibility complex

Definition

In humans, the proteins coded by the genes of the major histocompatibility complex (MHC) include human leukocyte antigens (HLA), as well as other proteins. HLA proteins are present on the surface of most of the body's cells and are important in helping the immune system distinguish "self" from "non-self."

HLA disease associations		
Disease	MHC allele	Approximate relative risk
Ankylosing spondylitis	B27	77–90
Celiac disease	DR3 1 DR7	5–10
Diabetes, Type 1	DR3	5
Diabetes, Type 1	DR4	5–7
Diabetes, Type 1	DR3 1 DR4	20–40
Graves disease	DR3	5
Hemochromatosis	A3	6–20
Lupus	DR3	1–3
Multiple sclerosis	DR2	2–4
Myasthenia gravis	B8	2.5–4
Psoriasis vulgaris	Cw6	8
Rheumatoid arthritis	DR4	3–6

The relative risks indicated in this table refer to the increased chance of a patient with an MCH allele to develop a disorder as compared to an individual without one. For example, a patient with DR4 is three to six times more likely to have rheumatoid arthritis and five to seven times more likely to develop type 1 diabetes than an individual without the DR4 allele.

Gale (Memorisz/Shutterstock)

Description

The function and importance of MHC is best understood in the context of a basic understanding of the function of the immune system. The immune system is responsible for distinguishing "self" from "non-self," primarily with the goal of eliminating foreign organisms and other invaders that can result in disease. There are several levels of defense characterized by the various stages and types of immune response.

Natural immunity

When a foreign organism enters the body, it is encountered by the components of the body's natural immunity. Natural immunity is the non-specific first line of defense carried out by phagocytes, natural killer cells (NK cells), and components of the complement system. Phagocytes are specialized white blood cells capable of engulfing and killing an organism. NK cells are also specialized white blood cells that respond to cancer cells and certain viral infections. The complement system is a group of proteins called the class III MHC that attack antigens. Antigens consist of any molecule capable of triggering an immune response. Although this list is not exhaustive, antigens can be derived from toxins, protein, carbohydrates, DNA, or other molecules from viruses, bacteria, cellular parasites, or cancer cells.

Acquired immunity

The natural immune response holds an infection at bay as the next line of defense mobilizes through acquired, or specific, immunity. This specialized type of immunity

KEY TERMS

Acquired immunity—Also called specific immunity, refers to immune reaction mediated by B-cells and/or T-cells. Includes humoral and cellular immunity.

Allele—One of two or more alternate forms of a gene.

Antibody—A protein produced by the mature B cells of the immune system that attach to invading microorganisms and target them for destruction by other immune system cells.

Antigen—A substance or organism that is foreign to the body and stimulates a response from the immune system.

Antigen presenting cell—Cells that are able to present foreign antigen in conjunction with MHC proteins to the immune system.

Autoimmune—Referring to an immune reaction erroneously directed toward “self” tissues.

B-cell—Specialized type of white blood cell that is capable of secreting infection-fighting antibodies.

Base pairs—Building blocks of DNA, the chemical that genes are made of.

Beta-2 microglobulin—A component protein of class I MHC.

Bone marrow—A spongy tissue located in the hollow centers of certain bones, such as the skull and hip bones. Bone marrow is the site of blood cell generation.

Cellular immunity—A type of acquired immunity mediated by killer T-cells; important in fighting “hidden” infections, such as those caused by cellular parasites and some viruses.

Class I MHC—Includes *HLA-A*, *HLA-B*, and *HLA-C*. Important in cellular immunity.

Class II MHC—*HLA-DP*, *HLA-DQ*, and *HLA-DR*. Important in humoral immunity.

Class III MHC—Includes the complement system.

Co-dominant—Describes the state when two alleles of the same gene are both expressed when inherited together.

Complement system—Class III MHC (major histocompatibility complex) proteins capable of destroying invading organisms directly via natural immunity, as well as indirectly through an interaction with other components of the immune system.

Cytokines—Proteins released by helper T-cells that stimulate and support immune responses mediated by B-cells and killer T-cells.

Graft-versus-host disease—In bone marrow transplantation, the complication that occurs when the donor’s cells attack the recipient’s tissues, in part due to non-identical donor-recipient HLA types.

Haplotype—A set of alleles that are inherited together as a unit on a single chromosome because of their close proximity.

Helper T-cell—Specialized white blood cell that assists in humoral and cellular immunity.

Human leukocyte antigens (HLA)—Proteins that help the immune system function, in part by helping it to distinguish “self” from “non-self.”

Humoral immunity—A type of acquired immunity mediated by B-cells and their secreted antibodies; important in fighting bacterial and some viral infections.

Major histocompatibility complex (MHC)—Includes HLA, as well as other components of the immune system. Helps the immune system function, in part by helping it to distinguish “self” from “non-self.”

Memory cells—B-cells whose antibodies recognized antigens from a previous infection; able to mount a quick, efficient response upon a second infection by the same organism.

Natural immunity—First line immune response that is non-specific. Includes action of phagocytes, natural killer cells, and complement cells.

Natural killer cells—Specialized white blood cells involved in natural immunity. Can kill some viruses and cancer cells.

Phagocyte—White blood cells capable of engulfing and destroying foreign antigen or organisms in the fluids of the body.

Plasma cells—Antibody-secreting B-cells.

Polymorphic—Describes a gene for which there exist multiple forms, or alleles.

Thymus gland—An endocrine gland located in the front of the neck that houses and transports T-cells, which help to fight infection.

is usually needed to eliminate an infection and is dependent on the role of the proteins of the major histocompatibility complex. There are two types of acquired immunity. Humoral immunity is important in

fighting infections outside the body’s cells, such as those caused by bacteria and certain viruses. Other types of viruses and parasites that invade the cells are better fought by cellular immunity. The major players in acquired

immunity are the antigen-presenting cells (APCs), B-cells and their secreted antibodies, and the T-cells.

Humoral immunity

In humoral immunity, antigen-presenting cells, including some B-cells, engulf and break down foreign organisms. Antigens from these foreign organisms are then brought to the outside surface of the antigen-presenting cells and presented in conjunction with class II MHC proteins. The helper T-cells recognize the antigen presented in this way and release cytokines, proteins that signal B-cells to take further action. B-cells are specialized white blood cells that mature in the bone marrow. Through the process of maturation, each B-cell develops the ability to recognize and respond to a specific antigen. Helper T-cells aid in stimulating the few B-cells that can recognize a particular foreign antigen. B-cells that are stimulated in this way develop into plasma cells, which secrete antibodies specific to the recognized antigen. Antibodies are proteins that are present in the circulation, as well as being bound to the surface of B-cells. They can destroy the foreign organism from which the antigen came. Destruction occurs either directly, or by “tagging” the organism, which is then more easily recognized and targeted by phagocytes and complement proteins. Some of the stimulated B-cells go on to become memory cells, which are able to mount an even faster response if the antigen is encountered a second time.

Cellular immunity

Another type of acquired immunity involves killer T-cells and is termed cellular immunity. T-cells go through a process of maturation in the organ called the thymus, in which T-cells that recognize “self” antigens are eliminated. Each remaining T-cell has the ability to recognize a single, specific, “non-self” antigen that the body may encounter. Although the names are similar, killer T-cells are unlike the non-specific NK cells in that they are specific in their action. Some viruses and parasites quickly invade the body’s cells, where they are “hidden” from antibodies. Small pieces of proteins from these invading viruses or parasites are presented on the surface of infected cells in conjunction with class I MHC proteins, which are present on the surface of nearly all of the body’s cells. Killer T-cells can recognize antigen bound to class I MHC in this way, and they are prompted to release chemicals that act directly to kill the infected cell. There is also a role for helper T-cells and antigen-presenting cells in cellular immunity. Helper T-cells release cytokines, as in the humoral response, and the cytokines stimulate killer T-cells to multiply. Antigen-presenting cells carry foreign antigen to places in the body where additional killer T-cells can be alerted and recruited.

The major histocompatibility complex clearly performs an important role in the functioning of the immune system. Related to this role in disease immunity, MHC is also important in organ and tissue transplantation, as well as playing a role in susceptibility to certain diseases. HLA typing can provide important information in parentage, forensic, and anthropologic studies.

Genetic profile

Present on chromosome 6, the major histocompatibility complex consists of more than 70 genes, classified into class I, II, and III *MHC*. There are multiple alleles, or forms, of each *HLA* gene. These alleles are expressed as proteins on the surface of various cells in a co-dominant manner. This diversity is important in maintaining an effective system of specific immunity. Altogether, the *MHC* genes span a region that is four million base pairs in length. Although this is a large region, 99% of the time these closely linked genes are transmitted to the next generation as a unit of MHC alleles on each chromosome 6. This unit is called a haplotype.

Class I

Class I *MHC* genes include *HLA-A*, *HLA-B*, and *HLA-C*. Class I *MHC* genes are expressed on the surface of almost all cells. They are important for displaying antigen from viruses or parasites to killer T-cells in cellular immunity. Class I *MHC* is particularly important in organ and tissue rejection following transplantation. In addition to the portion of class I *MHC* coded by the genes on chromosome 6, each class I MHC protein also contains a small, non-variable protein component called beta-2 microglobulin coded by a gene on chromosome 15. Class I *HLA* genes are highly polymorphic, meaning there are multiple forms, or alleles, of each gene. There are at least 57 *HLA-A* alleles, 111 *HLA-B* alleles, and 34 *HLA-C* alleles.

Class II

Class II *MHC* genes include *HLA-DP*, *HLA-DQ*, and *HLA-DR*. Class II *MHC* genes are particularly important in humoral immunity. They present foreign antigens to helper T-cells, which stimulate B-cells to elicit an antibody response. Class II *MHC* is only present on antigen-presenting cells, including phagocytes and B-cells. Like class I *MHC*, there are hundreds of alleles that make up the class II *HLA* gene pool.

Class III

Class III *MHC* genes include the complement system (i.e., C2, C4a, C4b, Bf). Complement proteins help to

activate and maintain the inflammatory process of an immune response.

Demographics

There is significant variability of the frequencies of HLA alleles among ethnic groups. This is reflected in anthropologic studies attempting to use HLA types to determine patterns of migration and evolutionary relationships in peoples of various ethnicities. Ethnic variation is also reflected in studies of HLA-associated diseases. Generally speaking, populations that have been subject to significant patterns of migration and assimilation with other populations tend to have a more diverse HLA gene pool. For example, it is unlikely that two unrelated individuals of African ancestry would have matched HLA types. Conversely, populations that have been isolated due to geography, cultural practices, and other historical influences may display a less diverse pool of HLA types, making it more likely for two unrelated individuals to be HLA-matched.

Testing

Organ and tissue transplantation

There is a role for HLA typing of individuals in various settings. Commonly, HLA typing is used to establish whether an organ or tissue donor is appropriately matched to the recipient for key HLA types, so as not to elicit a rejection reaction in which the recipient's immune system attacks the donor tissue. In the special case of bone marrow transplantation, the risk is for graft-versus-host disease (GVHD), as opposed to tissue rejection. Because the bone marrow contains the cells of the immune system, the recipient effectively receives the donor's immune system. If the donor immune system recognizes the recipient's tissues as foreign, it may begin to attack, causing the inflammation and other complications of GVHD. As advances occur in transplantation medicine, HLA typing for transplantation occurs with increasing frequency and in various settings.

Disease susceptibility

There is an established relationship between the inheritance of certain HLA types and susceptibility to specific diseases. Most commonly, these are diseases that are thought to be autoimmune in nature. Autoimmune diseases are those characterized by inflammatory reactions that occur as a result of the immune system mistakenly attacking "self" tissues. The basis of the HLA association is not well understood, although there are some hypotheses. Most autoimmune diseases are characterized by the expression of class II MHC on cells of the body that do not normally express these proteins. This

may confuse the killer T-cells, which respond inappropriately by attacking these cells. Molecular mimicry is another hypothesis. Certain HLA types may look like antigen from foreign organisms. If an individual is infected by such a foreign virus or bacteria, the immune system mounts a response against the invader. However, there may be a cross-reaction with cells displaying the HLA type that is mistaken for a foreign antigen. Whatever the underlying mechanism, certain HLA types are known factors that increase the relative risk for developing specific autoimmune diseases. For example, individuals who carry the HLA B-27 allele have a relative risk of 77–90 for developing ankylosing spondylitis—meaning such an individual has a 77–90-fold chance of developing this form of spinal and pelvic arthritis, as compared to someone in the general population.

In addition to autoimmune disease, HLA type less commonly plays a role in susceptibility to other diseases, including cancer, certain infectious diseases, and metabolic diseases. Conversely, some HLA types confer a protective advantage for certain types of infectious disease. In addition, there are rare immune deficiency diseases that result from inherited mutations of the genes of components of the major histocompatibility complex.

Parentage

Among other tests, HLA typing can sometimes be used to determine parentage, most commonly paternity, of a child. This type of testing is not generally done for medical reasons, but rather for social or legal reasons.

Forensics

HLA typing can provide valuable DNA-based evidence contributing to the determination of identity in criminal cases. This technology has been used in domestic criminal trials. Additionally, it is a technology that has been applied internationally in the human-rights arena. For example, HLA typing had an application in Argentina following a military dictatorship that ended in 1983. The period under the dictatorship was marked by the murder and disappearance of thousands who were known or suspected of opposing the regime's practices. Children of those who disappeared were often "adopted" by military officials and others. HLA typing was one tool used to determine non-parentage and return children to their biological families.

Anthropologic studies

HLA typing has proved to be an invaluable tool in the study of the evolutionary origins of human populations. This information, in turn, contributes to an understanding

of cultural and linguistic relationships and practices among and within various ethnic groups.

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ORGANIZATIONS

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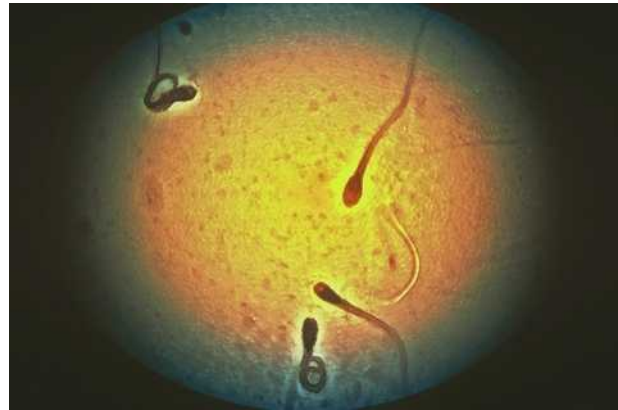
Male infertility

Definition

Male infertility is defined as the inability of a male to impregnate a female after at least one year of trying to conceive a child.

Description

There are many causes of male infertility. The most common causes are physical problems with the functioning of the testicles, such as undescended testicles. Hormone imbalances or blockages in the reproductive organs, such as in the ducts that carry the sperm (the vasa deferentia), are also common causes of male infertility. About 10%–15% of infertile men have a complete lack of sperm. About 40% of men with fertility problems have an enlarged vein in the testicle called a varicocele, which is the most common cause of low sperm production. Illnesses—such as a history of high fevers, mumps, or other infections—injuries, chronic health problems such as celiac disease, certain medications or surgeries, and lifestyle or environmental factors can also contribute to



Light micrograph of normal and atypical sperm. (GJLP, CNRI/Science Source)

male infertility. Other causes include problems with sexual intercourse or ejaculation and immune-system antibodies that mistakenly attack sperm. Finally, several genetic conditions result in male infertility. In about 50% of cases of male infertility, the cause cannot be determined.

Genetic causes of male infertility include:

- Y chromosome infertility—deletions in the Y chromosome that affect sperm production
- azoospermia—the complete absence of sperm
- teratozoospermia—abnormal sperm
- cystic fibrosis (CF)
- sensorineural deafness with male infertility
- X-linked congenital adrenal hypoplasia and Kallmann syndrome
- Klinefelter syndrome
- 48,XXYY syndrome
- Kartagener syndrome (primary ciliary dyskinesia with situs inversus totalis)

Genetic profile

Abnormal sperm production

Y chromosome infertility is a condition in which the male produces no sperm cells (azoospermia), fewer than the usual number of sperm (oligospermia), or sperm cells that are abnormally shaped or that do not swim properly. Most cases of Y chromosome infertility are caused by deletions in the A, B, or C regions of the azoospermia factor (AZF) region of the Y chromosome, which contains genes that provide instructions for producing proteins involved in sperm-cell development. Rarely, Y chromosome infertility is caused by mutations in the *USP9Y* gene located in AZF region A, which produces a protein called ubiquitin-specific protease 9. Some men with Y chromosome infertility that results in mild-to-moderate

oligospermia may eventually father a child naturally. Assisted reproductive technologies (ART) may help other affected men, since most men with Y chromosome infertility have some sperm cells in their testes that can be extracted for ART. The most severely affected men do not have any mature sperm cells in the testes. This form of Y chromosome infertility is called Sertoli-cell-only syndrome. Because men with AZF deletions are infertile, they do not normally pass on the genetic defect; thus, Y chromosome infertility is usually caused by new deletions in the Y chromosome in men without a family history of the disorder. However, when such men do reproduce, either naturally or by ART, they pass the defect on to all of their male offspring.

With azoospermia, no sperm are detectable in the seminal fluid. Non-obstructive azoospermia, in which the lack of sperm is not due to a physical obstruction, can be caused by mutations in the *SYKP3*, *KLHL10*, *AURKC*, or *SPATA16* genes, which are located in the AZF region of the Y chromosome and on autosomes (chromosomes other than the X and Y sex chromosomes). Mutations in the *TEX11* (*testis-expressed 11*) gene, on the long arm (q) of the X chromosome at Xq13.2, have been identified as also causing non-obstructive azoospermia. *TEX11* is required for sperm maturation.

Mutations in several different genes have been identified as causing teratozoospermia—a condition in which at least 85% of sperm are abnormal. The heads of normal sperm are oval-shaped with a cap called an acrosome containing enzymes that break down the outer membrane of the egg cell. Normal sperm also have one flagellum that enables them to swim to the egg. If all of the sperm have the same abnormal appearance, the condition is called monomorphic teratozoospermia. Mutations that cause monomorphic teratozoospermia are autosomal recessive, which means that two mutated genes are required for the production of the abnormal sperm, and these genes are not located on the X or Y sex chromosomes. Females are not affected by these mutations since they do not produce sperm. There are two types of monomorphic teratozoospermia: macrozoospermia and globozoospermia, which together account for less than 1% of cases of male infertility. In cases of monomorphic teratozoospermia, intracytoplasmic sperm injection (ICSI), a type of ART in which the sperm is injected directly into the egg in the laboratory prior to implantation in the woman's uterus, is generally unsuccessful because the sperm are abnormal.

In macrozoospermia, also called macrocephalic sperm head syndrome, the sperm heads are abnormally large and misshapen and, instead of one flagellum, the sperm have multiple (usually four) flagella. Most cases

KEY TERMS

Acrosome—The cap at the top of the sperm head that releases egg-penetrating enzymes.

Assisted reproductive technology (ART)—Infertility treatments such as in vitro fertilization and intracytoplasmic sperm injection.

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are required to express a disorder.

Azoospermia—The absence of sperm in the seminal fluid.

Azoospermia factor (AZF)—A region of the Y chromosome containing genes that are important for male fertility.

Cystic fibrosis (CF)—An inherited genetic disorder that affects many body systems and is caused by mutations in the CFTR gene that can also cause congenital bilateral absence of vas deferens and male infertility.

Globozoospermia—A genetic condition in which sperm have round heads and lack acrosomes, among other defects, resulting in male infertility.

Intracytoplasmic sperm injection (ICSI)—In vitro fertilization in which sperm is injected directly into the cytoplasm of the egg.

Klinefelter syndrome—A genetic disorder in which cells have two X chromosomes in addition to a Y chromosome, resulting in male infertility and possibly other problems; an XXY male.

Macrozoospermia—Macrocephalic sperm head syndrome; male infertility due to sperm with abnormally large heads and multiple (usually four) flagella; caused by mutations in the *AURKC* gene.

Nondisjunction—Failure of homologous chromosomes or sister chromatids to separate during meiosis or mitosis, resulting in cells with an abnormal complement of chromosomes.

Oligospermia—Production of fewer than normal amounts of sperm.

Seminal fluid—Fluid from the prostate and other sex glands that transports sperm.

Teratozoospermia—A condition in which at least 85% of sperm are abnormal; caused by mutations in several different genes.

Testicles—Two oval organs that produce sperm and are enclosed in the scrotum.

Vas deferens, pl. vasa deferentia—The tube that transports sperm from the testicle to the ejaculatory tube.

of macrozoospermia have been identified as resulting from at least four different mutations in both *AURKC* genes (homozygous mutations) that encode the enzyme aurora kinase C. This gene is essential for spermatogenesis—the reduction in chromosomes during meiosis that distributes only one chromosome from each chromosome pair to each sperm cell. *AURKC* mutations result in a failure of meiosis, so that the sperm have two or four sets of chromosomes instead of one. The *AURKC* mutations that cause macrozoospermia result in a non-functional enzyme or an enzyme that breaks down quickly in the testes, thereby blocking cell division during spermatogenesis. The extra chromosomes increase the size of the sperm head. If such an abnormal sperm cell does fertilize an egg, the embryo does not develop, or the pregnancy ends in miscarriage.

In globozoospermia, all of the sperm have abnormally round heads and other defects, including the lack of an acrosome and a defective nuclear membrane. About 70% of men with globozoospermia have mutations in the *DPY19L2* (*Dpy-19 Like 2*) gene, which produces a protein that is involved in elongating the sperm head and forming the acrosome during sperm-cell maturation. Globozoospermia can also be caused by mutations in the *SPATA16* gene (*spermatogenesis-associated 16*) and in the *PICK1* gene.

CATSPER1-related nonsyndromic male infertility is a condition in which fewer sperm are produced, or they are abnormally shaped, and the sperm have decreased motility (movement). It is called nonsyndromic because it does not cause any other symptoms. The *CATSPER1* gene produces a protein in flagella that is required for propelling the sperm forward and pushing them through the outside membrane of the egg during fertilization. Mutations in *CATSPER1* produce a protein that is abnormal, nonfunctional, or rapidly broken down, causing the sperm tails to move slowly. *CATSPER1* mutations are inherited in an autosomal recessive pattern. Abnormalities in sperm flagella can also be caused by mutations in the *DNAH1* gene that encodes heavy chain 1 of the axonemal dynein protein.

Syndromes

Congenital bilateral absence of vas deferens occurs when the two vasa deferentia fail to develop properly. This condition accounts for 1%–2% of all male infertilities. Males with this condition can only conceive children via ART. The condition may occur alone or in conjunction with mutations in the *CFTR* gene that causes CF. Although more than half of men with congenital bilateral absence of vas deferens have mutations in the *CFTR* gene, many of them do not have other symptoms of CF or have only mild respiratory or digestive problems. The *CFTR*

gene produces a protein that forms a channel for transporting chloride ions in and out of cells, which helps control water movement in tissues and is necessary for producing thin, flowing mucus for lubricating and protecting the airways, digestive system, and reproductive system, as well as other organs and tissues. *CFTR* mutations result in the production of thick, sticky mucus that clogs the vasa deferentia as they form in the fetus, resulting in their destruction before birth. Mutations in *CFTR* that cause CF are autosomal recessive. However, a second mutation in the *CFTR* gene, called R117H, is a dominant mutation. Depending on other characteristics of the *CFTR* gene, R117H mutations, as well as another mutation in the *CFTR* gene, can cause congenital bilateral absence of vas deferens even if the second *CFTR* gene is normal, and the male does not have CF.

Male infertility with sensorineural deafness is an autosomal recessive condition caused by deletions in the long arm of chromosome 15, resulting in the loss of several genes. In addition to hearing loss due to abnormalities in the inner ear, males produce sperm with decreased motility. Deletion of the *STRC* gene causes hearing loss, and deletion of the *CATSPER2* gene in the same region of the chromosome results in male infertility.

Congenital X-linked adrenal hypoplasia is caused by mutations in the *NROB1* gene that produces a protein called DAX1, which is important for the development of hormone-producing and hormone-secreting glands, including the adrenal glands, hypothalamus and pituitary in the brain, and the testes in males. Mutations in *NROB1* may delete the entire gene or produce an inactive DAX1 protein. This causes adrenal insufficiency and hypogonadotropic hypogonadism, in which hormone production is disrupted. The lack of male sex hormones leads to underdevelopment of the reproductive tissues and infertility. These mutations primarily affect males, since females have a second X chromosome with a normal gene that can compensate for the mutation.

Kallmann syndrome also causes hypogonadotropic hypogonadism, delayed puberty, anosmia (an inability to smell), and male infertility if untreated. Kallmann syndrome can be caused by mutations in several different genes. Most cases are sporadic, meaning that they are caused by new gene mutations rather than mutations inherited from a parent. However, some cases are inherited in an autosomal dominant, autosomal recessive, or X-linked recessive pattern.

Chromosome abnormalities

Male infertility is the most common symptom of Klinefelter syndrome, in which males have two X chromosomes and one Y chromosome instead of one X

QUESTIONS TO ASK YOUR DOCTOR

- Is the man or woman more likely to be the cause of infertility?
- How is male infertility diagnosed?
- Is genetic testing available for male infertility?
- Can assisted reproductive technologies overcome male infertility?

chromosome and one Y chromosome. This results in abnormal development of the male reproductive organs. The extra X chromosome results from an error during egg or sperm cell formation. Although testosterone therapy can improve other symptoms of Klinefelter syndrome, most men remain infertile.

48,XXYY syndrome, in which males have two X chromosomes and two Y chromosomes instead of one of each, causes a variety of medical and behavioral problems including a disruption of sexual development. The small testes do not produce sufficient testosterone (the male sex hormone) to promote puberty, and the abnormal functioning of the testes causes infertility. Although many genes are present only on the X or Y chromosome alone, genes in the pseudoautosomal regions are present on both X and Y chromosomes. Thus, males with 48,XXYY syndrome have extra copies of these genes, which contribute to the signs and symptoms of the syndrome. 48,XXYY is not inherited; rather, it occurs through an error in cell division called nondisjunction that leaves a sperm cell with extra chromosomes. In a small number of cases, the nondisjunction occurs soon after fertilization of a normal egg cell (with one X chromosome) by a normal sperm (with one Y chromosome).

Demographics

Male infertility affects more than 20 million men worldwide. About one-third of all infertilities are caused by male infertility, one-third by female infertility, and one-third by infertility in both the male and female or by unknown factors. However, only a fraction of male infertilities have genetic causes.

- Y chromosome infertility affects 1 man in 2,000–3,000 worldwide and accounts for 5%–10% of azoospermias and severe oligospermias.
- Macrozoospermia affects an estimated 1 in 10,000 males in North Africa. Its prevalence outside of North Africa is unknown.

- Globozoospermia is estimated to affect 1 in 65,000 males, but is most common in North Africa where it accounts for about 1 in 100 cases of male infertility.
- Congenital X-linked adrenal hypoplasia affects 1 in 12,500 newborns.
- Klinefelter syndrome occurs in about 1 in every 500–1,000 male newborns.
- 48,XXYY affects an estimated 1 in 18,000–50,000 males.

Signs and symptoms

Other than the inability to conceive a child, symptoms of male infertility depend on the underlying cause, but may include the following:

- low sperm count (fewer than 15 million sperm per milliliter of semen or fewer than 39 million per ejaculate)
- problems with sexual function
- pain, swelling, or lumps in the testicle area
- decreased facial or body hair

Diagnosis

Diagnosis of male infertility may include the following:

- a medical history of inherited disorders, sexual development, chronic disorders, illnesses, injuries, or surgeries
- examination of the genitals
- semen analysis, including sperm counts and abnormalities in sperm shape or motility
- sperm function tests for survival and attachment to and penetration of the egg
- genetic testing for chromosome abnormalities and/or gene mutations
- ultrasound examination
- hormone testing
- post-ejaculation urinalysis for sperm traveling backward into the bladder
- testicular biopsy
- new genetic tests for RNA elements in sperm that have been identified as essential for male fertility, including RNAs that are essential for sperm development, motility, energy production, fertilization, and embryo formation

Treatment and management

Treatment depends on the cause of the infertility. If healthy sperm are present in the testicles, as with infertility due to *CFTR* mutations, they may be retrieved from the testicles or epididymis (the ducts in which sperm mature before entering the vas deferens) and used for ICSI or in vitro fertilization.

Prognosis

Prognosis depends on the cause of the male infertility. Biological fatherhood is not possible if no healthy, mature sperm are produced.

Resources

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ORGANIZATIONS

American Society for Reproductive Medicine, 1209 Montgomery Hwy., Birmingham, AL 35216-2809, (205) 978-5000, (205) 978-5005, asrm@asrm.org, <http://www.reproductivefacts.org>

Eunice Kennedy Shriver National Institute of Child Health and Human Development, NICHD Information Resource Center, PO Box 3006, Rockville, MD 20847, (800) 370-2943, (866) 760-5947, NICHDInformationResourceCenter@mail.nih.gov, <https://www.nichd.nih.gov>

Margaret Alic, PhD

Male turner syndrome see **Noonan syndrome**

Malignant fever see **Malignant hyperthermia**

Malignant hyperpyrexia see **Malignant hyperthermia**

Malignant hyperthermia

Definition

Malignant hyperthermia (MH) is a condition that causes a number of physical changes to occur among genetically susceptible individuals when they are exposed to a particular muscle relaxant or certain types of medications used for anesthesia. The changes may include increased rate of breathing, increased heart rate, muscle

stiffness, and significantly increased body temperature (i.e., hyperthermia). Although MH can usually be treated successfully, it sometimes leads to long-term physical illness or death. Research has identified a number of genetic regions that may be linked to an increased MH susceptibility.

Description

Unusual response to anesthesia was first reported in a medical journal in the early 1960s, when physicians described a young man in need of urgent surgery for a serious injury. He was very nervous about exposure to anesthesia, since he had ten close relatives who died during or just after surgeries that required anesthesia. The patient himself became very ill and developed a high temperature after he was given anesthesia. During the next decade, more cases of similar reactions to anesthesia were reported, and specialists began using the term "malignant hyperthermia" to describe the newly recognized condition. The word "hyperthermia" was used because people with this condition often develop a very high body temperature rapidly. The word "malignant" referred to the fact that the majority (70%–80%) of affected individuals died. The high death rate in the 1960s occurred because the underlying cause of the condition was not understood, nor was there any known treatment (other than trying to cool the person's body with ice).

Increased awareness of malignant hyperthermia and scientific research during the following decades improved medical professionals' knowledge about what causes the condition, how it affects people, and how it should be treated. MH can be thought of as a chain reaction that is triggered when a person with MH susceptibility is exposed to specific drugs commonly used for anesthesia and muscle relaxation.

Triggering drugs that may lead to malignant hyperthermia include the following:

- halothane
- enflurane
- isoflurane
- sevoflurane
- desflurane
- methoxyflurane
- ether
- succinylcholine

Once an MH-susceptible person is exposed to one or more of these anesthesia drugs, he or she can present with a variety of signs. One of the first clues that a person is susceptible to MH is often seen when the person is given a muscle relaxant called succinyl choline. This drug generally causes some stiffness in the masseter (jaw) muscles

in most people. However, individuals with MH susceptibility can develop a much more severe form of jaw stiffness called masseter spasm when they receive this drug. They may develop muscle stiffness in other parts of their bodies as well. When exposed to any of the trigger drugs (inhalants for anesthesia), people with MH susceptibility can develop an increased rate of metabolism in the cells of the body, resulting in rapid breathing, rapid heartbeat, high body temperature (over 110°F), muscle stiffness, and muscle breakdown. If these signs are not recognized, treated, or able to be controlled, brain damage or death can occur due to internal bleeding, heart failure, or failure of other organs.

The series of events that occur after exposure to trigger drugs is activated by an abnormally high amount of calcium inside muscle cells. This is due to changes in the chemical reactions that control muscle contraction and the production of energy. Calcium is normally stored in an area called the sarcoplasmic reticulum, which is a system of tiny tubes located inside muscle cells. This system of tubes allows muscles to contract (by releasing calcium) and to relax (by storing calcium) in muscle cells. Calcium also plays an important role in the production of energy inside cells (i.e., metabolism). There are at least three important proteins located in (or nearby) the sarcoplasmic reticulum that control how much calcium is released into muscle cells and thus help muscles contract. One of these proteins is a calcium release channel protein that has been named the ryanodine receptor protein, or RYR. This protein (as well as the gene that tells the body how to make it) has been an important area of research. For some reason, when people with MH susceptibility are exposed to a trigger drug, they can develop very high levels of calcium in their muscle cells. The trigger drugs presumably stimulate the proteins that control the release of calcium, causing them to create very high levels of calcium in muscle cells. This abnormally high calcium level then leads to increased metabolism, muscle stiffness, and the other symptoms of MH.

The amount of time that passes between the exposure to trigger drugs and the appearance of the first symptoms of MH varies between different people. Symptoms begin within ten minutes for some individuals, although several hours may pass before symptoms appear in others. This means that some people do not show signs of MH until they have left the operating room and are recovering from surgery. In addition, some individuals who inherit MH susceptibility may be exposed to trigger drugs numerous times during multiple surgeries without any complications. However, they still have an increased risk to develop an MH episode during future exposures. This means that people who have an increased risk for MH susceptibility due to their family history cannot presume

that they are not at risk simply because they previously had successful surgeries. Although MH was frequently a fatal condition in the past, a drug called dantrolene sodium, which greatly decreased the rate of both death and disability, became available in 1979.

Genetic profile

Susceptibility to MH is generally considered to be inherited as an autosomal dominant trait. “Autosomal” means that males and females are equally likely to be affected. “Dominant” refers to a specific type of inheritance in which only one copy of a person’s gene pair needs to be changed in order for the susceptibility to be present. In this situation, an individual susceptible to MH receives a changed copy of the same gene from one parent (who is also susceptible to MH). This means that a person with MH susceptibility has one copy of the changed gene and one copy of the gene that works well. The chance that a parent with MH susceptibility will have a child who is also susceptible is 50% for each pregnancy. The same parent would also have a 50% chance to have a non-susceptible child with each pregnancy.

It is not unusual for people to not know they inherited a genetic change that causes MH susceptibility. This is because they typically do not show symptoms unless they are exposed to a specific muscle relaxant or certain anesthetics, which may not be needed by every person during his or her lifetime. In addition, people who inherit MH susceptibility do not always develop a reaction to trigger drugs, which means their susceptibility may not be recognized even if they do have one or more surgeries. Once MH susceptibility is diagnosed in an individual, however, it is important for his or her family members to know that they too have a risk for MH susceptibility, since it is a dominant condition. This means that individuals with a family member who has MH susceptibility should tell their doctor about their family history. Since MH may go unrecognized, it is important that anyone who has had a close relative die from anesthesia notify the anesthesiologist before any type of surgery is planned. People with a family history of MH susceptibility may choose to meet with a genetic counselor to discuss the significance of their family history as well. In addition, relatives of an affected person may consider having a test to see if they also inherited MH susceptibility.

Although there are many people who have the same symptoms of MH when exposed to trigger drugs, genetic research has shown that there are probably many genes, located on different chromosomes, that can all lead to MH susceptibility. This indicates that there is genetic heterogeneity among different families with MH susceptibility, meaning that different genes can lead to the same or

similar disease among different families. Researchers identified six different types of MH susceptibility. Although specific genes have been discovered for some of these types, others have been linked only to specific chromosomal regions.

Genetic classification of malignant hyperthermia includes the following:

- **MHS1**—Located on chromosome 19q13.1. Specific gene called *RYR1*. Gene creates the RYR protein.
- **MHS2**—Located on chromosome 17q11.2-24. Suspected gene called *SCN4A*.
- **MHS3**—Located on chromosome 7q21-22. Suspected gene called *CACNA2D1*. Gene creates part of the DHPR protein called the alpha 2/delta subunit.
- **MHS4**—Located on chromosome 3q13.1. Specific gene and protein unknown.
- **MHS5**—Located on chromosome 1q32. Specific gene called *CACNA1S*. Gene creates part of the DHPR protein called the alpha 1 subunit.
- **MHS6**—Located on chromosome 5p. Specific gene and protein unknown.

Over half of all families with MH susceptibility are believed to have MHS1 (i.e., have changes in the *RYR1* gene), while the rest have MHS2, MHS3, MHS4, MHS5, or MHS6. Only about 20% of all families tested have specific genetic changes identified in the *RYR1* gene. This is because there are many different types of genetic changes in the gene that can all lead to MH susceptibility, and many families have changes that are unique. As a result, genetic testing of the *RYR1* gene is complicated, time consuming, and often cannot locate all possible genetic changes. In addition, genetic testing for families may become more complex as knowledge about MH grows. Although MH susceptibility has typically been described as an autosomal dominant trait caused by a single gene that is passed from one generation to the next, MH susceptibility may actually depend upon various genetic changes that occur in more than one gene. Further research may clarify this issue.

While specific genes have been identified for some of the MH susceptibility types (i.e., *RYR1* and *DHPR* alpha 1 subunit), not all changes in these genes lead specifically to MH susceptibility. For example, although at least 20 different genetic changes that can lead to MH susceptibility have been identified in the *RYR1* gene, some people who have certain types of these changes actually have a different genetic condition called central core disease (CCD) that affects the muscles. Infants with this autosomal dominant condition typically have very poor muscle tone (i.e., muscle tension) as well as an

KEY TERMS

Anesthesia—Lack of normal sensation (especially to pain) brought on by medications just prior to surgery or other medical procedures.

Genetic heterogeneity—The occurrence of the same or similar disease, caused by different genes among different families.

Hyperthermia—Body temperature that is much higher than normal (i.e., higher than 98.6°F).

Masseter spasm—Stiffening of the jaw muscles. Often one of the first symptoms of malignant hyperthermia susceptibility that occurs after exposure to a trigger drug.

Metabolism—The total combination of all of the chemical processes that occur within cells and tissues of a living body.

Sarcoplasmic reticulum—A system of tiny tubes located inside muscle cells that allow muscles to contract and relax by alternatively releasing and storing calcium.

Trigger drugs—Specific drugs used for muscle relaxation and anesthesia that can trigger an episode of malignant hyperthermia in a susceptible person. The trigger drugs include halothane, enflurane, isoflurane, sevoflurane, desflurane, methoxyflurane, ether, and succinylcholine.

increased susceptibility to MH. Among families who have CCD, there are some individuals who do not have the typical muscle changes but have MH susceptibility instead. Future research may help scientists understand why the same genetic change in the *RYR1* gene can cause different symptoms among people belonging to the same family.

Demographics

The exact number of individuals who are born with a genetic change that causes MH susceptibility is not known. Until genetic research and genetic testing improve, this number will likely remain unclear. It is estimated that internationally 1 in 50,000 people who are exposed to anesthesia develop an MH reaction. Among children, it is estimated that 1 in 5,000 to 1 in 15,000 develop MH symptoms when exposed to anesthesia. MH has been seen in many countries, although there are some geographic areas in which it occurs more often in the local populations, including parts of Wisconsin, North Carolina, Austria, and Quebec.

Signs and symptoms

Although the specific symptoms of malignant hyperthermia can vary, the most common findings include the following:

- stiffness/spasms of jaw muscles and other muscles
- rapid breathing, causing decreased oxygen and increased carbon dioxide in the blood
- rapid or irregular heartbeat
- high body temperature (over 110°F)
- muscle breakdown (may cause dark or cola-colored urine)
- internal bleeding, kidney failure, brain damage, or death (if not treated successfully)

Diagnosis

The diagnosis of MH susceptibility can be made before or during a reaction to a triggering drug. Ideally, the diagnosis is made before a susceptible individual is exposed and/or develops a reaction. This is possible for people who learn they have an increased chance for MH because they have a relative with MH susceptibility. Testing these individuals requires a surgical procedure called a muscle biopsy, in which a piece of muscle tissue is removed from the body (usually from the thigh). Safe (i.e., non-triggering) anesthetics are used during the procedure. The muscle is taken to a laboratory and is exposed to halothane (a triggering anesthetic) and caffeine, both of which cause any muscle tissue to contract, or tighten. Thus, the test is called the caffeine halothane contracture test (CHCT). Muscle tissue taken from individuals with MH susceptibility is more sensitive to caffeine and halothane, causing it to contract more strongly than normal muscle tissue from non-susceptible people. This type of test is a very accurate way to predict whether a person has MH susceptibility or not. However, the test does require surgery and time to recover (typically 3 days), and it is expensive (approximately \$5,000 USD). In the United States, many insurance companies will pay for the testing if it is needed. Although the test is not available in every state or country, there are at least 40 medical centers worldwide that can perform the test.

Unfortunately, not all MH-susceptible people will learn from their family histories that they have an increased risk for MH before they are exposed to a trigger drug. For these individuals, the diagnosis of MH susceptibility is often made during surgery by the anesthesiologist (a physician specializing in anesthesia) who is providing the anesthesia medications. Other healthcare specialists also may notice symptoms of MH during or after surgery. Symptoms such as rapid breathing, rapid heart rate, and high body temperature can usually be detected with various machines or devices that examine basic body functions during

surgery. Muscle stiffness of the jaw, arms, legs, stomach, and chest may be noticed as well. These symptoms may happen during surgery or even several hours later. If the diagnosis is made during or after surgery, immediate treatment is needed to prevent damage to various parts of the body or death. If a person has a suspicious reaction to anesthesia, he or she may undergo a muscle biopsy to confirm MH susceptibility at a later date.

In spite of the fact that a number of important genes and genetic regions associated with MH susceptibility have been identified, testing a person's DNA for all of the possible changes that may cause this condition is not easily done for affected individuals and their families. Existing genetic testing identifies some changes that have been seen among families with MHS1 and MHS6. Research studies may provide information for families with MHS2, MHS3, MHS4, and MHS5 as well. Sometimes the testing requires DNA from only one affected person, but in other cases, many samples are needed from a variety of family members. Until genetic technology improves, the contracture test that is done on muscle tissue will likely remain the "gold standard" for diagnosis of MH susceptibility.

Treatment and management

The early identification of an MH episode allows for immediate treatment with an antidote called dantrolene sodium. This medication prevents the release of calcium from the sarcoplasmic reticulum, which decreases muscle stiffness and energy production in the cells. If hyperthermia develops, the person's body can be cooled with ice. In addition, the anesthesiologist will change the anesthetic from a trigger drug to a non-trigger drug. Immediate treatment is necessary to prevent serious illness and/or death.

Once a person with definite or suspected MH susceptibility is diagnosed (by an MH episode, muscle biopsy, or family history), prevention of an MH episode is possible. There are many types of non-triggering anesthetic drugs and muscle relaxants that can be used during surgical procedures. The important first step in this process is for people with known or suspected MH susceptibility to talk with their doctors before any surgery so that only non-triggering drugs are used. People with definite or suspected MH susceptibility should always carry some form of medical identification that describes their diagnosis in case emergency surgery is needed. The Malignant Hyperthermia Association of the United States provides wallet-sized emergency medical ID cards for its members.

Prognosis

Early diagnosis and treatment of MH episodes with dantrolene sodium has dramatically improved the prognosis for people who develop MH during or just after

surgery. When the condition was first recognized in the 1960s, no real treatment (other than cooling the person's body) was available, and only 20%–30% of people who developed MH survived. When the antidote (dantrolene sodium) became available in 1979, the survival rate increased to 70%–80%. However, 5%–10% of people who develop MH after exposure to a trigger drug still may die even with proper medication and care. Among those who do survive, some are disabled due to kidney, muscle, or brain damage. The best prognosis exists for people with definite or suspected MH susceptibility who are able to prevent exposures to trigger drugs by discussing their history with their doctors. Improved genetic testing in the future may help identify most or all people with inherited MH susceptibility, so they too may prevent exposures that trigger MH episodes.

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ORGANIZATIONS

- Malignant Hyperthermia Association of the United States, 1 N. Main St., PO Box 1069, Sherburne, NY 13460, (607) 674-7901, info@mhaus.org, <http://www.mhaus.org>

Pamela J. Nutting, MS, CGC

Manic-depressive psychosis see **Bipolar disorder**

Mannosidosis

Definition

Mannosidosis is a rare lysosomal storage disorder of either the alpha or beta form caused by the impaired function of either alpha-mannosidase or beta-mannosidase,

enzymes important in oligosaccharide metabolism. When the body is unable to break down chains of a mannose sugar properly, large amounts of sugar-rich compounds build up in the body cells, tissues, and urine, interfering with normal body functions and the development of the skeleton.

Description

Mannosidosis is a rare genetic disorder that develops in patients whose genes are mutated and are unable to make functional mannosidase enzyme. The enzyme has two forms, alpha and beta, resulting in alpha-mannosidosis and beta-mannosidosis. Alpha-mannosidosis occurs when the gene for the alpha form of the enzyme is mutated or deleted, and beta-mannosidosis occurs when the gene for the beta form of the enzyme is mutated or deleted. A different gene, *MAN2B1* or *MANBA*, controls production of each form of the enzyme. These enzymes are required by lysosomes (structures within the cell where proteins, sugars, and fats are broken down and then released back into the cell to make other molecules). Lysosomes need the enzyme to break down, or degrade, long chains of sugars. Mutations or deletions of the mannosidase enzymes result in the buildup of sugars within lysosomes. The accumulation of these sugars within lysosomes causes impaired cellular function and subsequent cell death.

First described in 1967, alpha-mannosidosis is characterized by mental disabilities, augmented facial features, ataxia, and immune dysfunction. The disorder has been further classified into three clinical subtypes. Infantile (type I) alpha-mannosidosis is a severe disorder that results in intellectual disability and physical deformities, and it can be deadly if not diagnosed and treated quickly. The moderate form (type II) presents before ten years of age with a markedly more gradual development of clinical phenotypes that also include intellectual disability, ataxia, and skeletal abnormalities. Type III, or adult alpha-mannosidosis, is the mildest form of the disorder and develops much more slowly with less effect on mental acuity and fewer skeletal abnormalities.

Beta-mannosidosis was identified nearly 20 years later in 1986. Patients with this form of the disorder are also intellectually disabled but over a wide range of severity, from mild to extreme. Beta-mannosidosis is not well understood, in part because it is such a rare disease. Roughly only 20 people worldwide have been diagnosed with the disorder.

Genetic profile

The two forms of mannosidosis, alpha and beta, are caused by changes on two different genes. Mutations in

the gene *MAN2B1*, on chromosome 19 (19p13.2-q12), results in alpha-mannosidosis. Beta-mannosidosis is caused by mutations in the gene *MANBA*. This gene is on chromosome 4 (4q22-25). Both genes, *MANB* and *MANB1*, are inherited as autosomal recessive traits. Therefore, if a man and woman each carry one defective gene, then 25% of their children will potentially develop the disorder. Previously there was no clear relationship between genotype and the clinically described phenotypes; however, several genome-wide association studies completed in 2015 established more than 127 separate mutations of the *MAN2B1* gene and discovered that one mutation (c.2248C.T [p.Arg750Trp]) accounted for 25% of the disease alleles in unrelated patients. In addition to the identification of these new gene mutation variants, researchers have shown a correlation of disease phenotype severity and the subcellular/lysosomal localization of the mutated/misfolded mannosidase enzyme proteins. A study demonstrated that study participants who had two null mutations—or mutations that caused inappropriate folding of the enzyme protein leading to the inability of the enzyme to reach the lysosomal compartment—were more likely to display more severe phenotypes. Patients who retained one mutant variant facilitating lysosomal entry and subsequent enzymatic function, even if the function was limited, displayed more moderate clinical phenotypes. The discovery that the subcellular location of nonfunctional/reduced-functional enzymes may play a role in the severity of cognitive and physical clinical symptoms may open the door to a more accurate classification system than the current three-tier system.

Demographics

Mannosidosis is a rare disorder, occurring in both men and women at a reported incidence rate of 1 in 500,000 for the alpha form and even less for beta-mannosidosis. The disorder does not affect any particular ethnic group but rather appears in a broad range of people. Alpha-mannosidosis has been studied in Scandinavian, Western and Eastern European, North American, Arabian, African, and Japanese populations. Researchers have identified beta-mannosidosis in European, Hindu, Turkish, Czechoslovakian, Jamaican-Irish, and African families.

Signs and symptoms

The various forms and types of mannosidosis all have one symptom in common: intellectual disability. Other signs and symptoms vary. Infants with alpha-mannosidosis appear normal at birth, but by the end of their first year, they show signs of intellectual disability, which progresses rapidly. Many infants diagnosed die due to degradation of their central nervous system.

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Enzyme replacement therapy (ERT)—A treatment method used to replace missing enzymes. It is possible to synthesize enzymes and then inject them intravenously into patients.

Hydrolysis—The breakdown of chemical bonds by the addition of water.

Lysosomal storage diseases—A group of more than 40 human genetic disorders that result from defects in lysosomal function.

Lysosome—A membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

Mannose—A type of sugar that forms long chains in the body and is important in metabolism and the glycosylation of proteins.

Mutation—An inherited or *de novo* change in the DNA sequence of the genome.

Individuals with the disorder may develop several symptoms that include dwarfism, shortened fingers, and skeletal changes of the facial region. In these children, the bridge of the nose is flat, the forehead is prominent, ears are large and low set, eyebrows are protruding, and the jaw juts out. Other symptoms include lack of muscle coordination, enlarged spleen and liver, recurring infections, and cloudiness in the back of the eyeball, which is normally clear. These patients often have vacuoles in their white blood cells, a clinical sign that sugars are being stored improperly.

The adult form occurs in 10%–15% of the cases of alpha-mannosidosis. The symptoms in adults are similar to those observed in infants but are less severe and develop more slowly. Patients with adult alpha-mannosidosis are often normal as babies and young children. However, in their childhood or teenage years, intellectual disability and physical symptoms become evident. These patients may also lose their hearing and have pain in their joints.

Beta-mannosidosis is characterized by symptoms that range from mild to severe. In all patients, however,

the most frequent signs are intellectual disability, lung infections, and hearing loss with speech difficulties. In mild cases, patients have red, wart-like spots on their skin. In severe cases, patients may have multiple seizures, and their arms and legs may be paralyzed. Because the symptoms of beta-mannosidosis vary so greatly, researchers suggest that the disorder may frequently be misdiagnosed.

Diagnosis

Both forms of mannosidosis are currently tested by an assay called thin-layer chromatography. This technique screens the patient's urine for abnormal types of sugar. It is a time-consuming and laborious assay that has led to the research and development of more sensitive, high-throughput diagnostic techniques such as high-pressure liquid chromatography (HPLC), matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF), and capillary electrophoresis coupled to a laser-induced fluorescence detector system (CE-LIF), all aimed at a faster and more sensitive diagnosis. It is also possible to perform genetic testing of a patient's blood cells to determine if the enzyme is present. If doctors suspect that a pregnant woman may be carrying a child with mannosidosis, they can use the aforementioned techniques to test cells in the amniotic fluid for enzyme activity.

Treatment and management

The discovery of the gene for alpha-mannosidosis in 1986 led to subsequent attempts to improve the non-effective treatment options available at that time. The first attempt at bone marrow transplantation (BMT) to cure alpha-mannosidosis was performed in 1987 but was unsuccessful and resulted in the death of the patient just 18 weeks after the procedure. Until 2012 no effective treatment options existed, and the symptoms such as intellectual disability and skeletal abnormalities were managed by supportive care, depending on the severity.

Patients with adult alpha-mannosidosis and beta-mannosidosis may show mild intellectual disability or behavior problems (such as depression or aggression) and may be able to function in society with minimal adversity. More severely afflicted individuals may require institutionalization. Skeletal abnormalities may require surgical correction, and recurring infections of the immune system are treated with antibiotics.

Medical advances in 2012 led to the development of viable hematopoietic stem cell transplantation (HSCT). This treatment remains the only efficacious treatment option. Due to the rarity of the disease, only a handful of these transplantations have been performed.

QUESTIONS TO ASK YOUR DOCTOR

- What type of testing is available for a mannosidase disorder, and should I get tested?
- How accurate are diagnostic tests?
- What therapies are available to treat mannosidosis, and what are the associated benefits and risks and costs?
- What is my risk of having children with mannosidosis?
- What resources are available for people who are diagnosed with mannosidosis?

Remediation of symptoms from the procedure is variable among patients, and not all patients survive. Because of the high incidence of harmful side effects and morbidity associated with HSCT, researchers have continued to search for more optimal therapeutic options. Ongoing human clinical trials are testing recombinant human alpha-mannosidase (RhLAMAN) enzyme replacement therapy (ERT), and results from the first 12 months of the 18 month trial showed that RhLAMAN ERT may be a safe new treatment option to decrease levels of oligosaccharide buildup and result in the improvement of motor as well as cognitive functions.

Prognosis

The future for patients with mannosidosis varies with the form of their disorder. Infants with alpha/beta-mannosidosis are not symptomatic at birth, and screening of newborns can identify individuals in need of BMT/ERT. Patients with mild forms of alpha- and beta-mannosidosis often survive into adulthood, but their lives are complicated by intellectual disability and physical deterioration. The advancement of BMT and ERT therapies has significantly improved the prognosis of patients diagnosed with the disorder if identified early enough.

Resources

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"Beta-mannosidosis." MedlinePlus. August 18, 2020. <https://medlineplus.gov/genetics/condition/beta-mannosidosis/> (accessed June 14, 2021).

ORGANIZATIONS

The Arc, 1825 K St. NW, Suite 1200, Washington, DC 20006, (202) 534-3700 or (800) 433-5255, (202) 534-3731, <http://www.thearc.org>

Climb: National Information Centre for Metabolic Disease, Climb Bldg., 176 Nantwich Rd., Crewe, Cheshire UK CWZ 6BG, (+44) (0)845 241 2173, <http://www.climb.org.uk>

ISMARD: The International Advocate for Glycoprotein Storage Diseases, 20880 Canyon View Dr., Saratoga, CA 95070, info@ismrd.org, <http://www.ismrd.org>

National MPS Society, PO Box 14686, Durham, NC 27709-4686, (919) 806-0101 or (877) MPS-1001, info@mpssociety.org, <http://www.mpssociety.org>

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Marfan syndrome

Definition

Marfan syndrome is an inherited disorder of the connective tissue that causes abnormalities of the eyes, cardiovascular system, and musculoskeletal system. It is named for the French pediatrician Antoine Marfan (1858–1942), who first described it in 1896.

Description

Marfan syndrome is sometimes called arachnodactyly, which means "spider-like fingers" in Greek, since one of the characteristic signs of the disease is disproportionately long fingers and toes. Marfan syndrome affects three major organ systems of the body: the heart and circulatory system, the bones and muscles, and the eyes. The genetic mutation responsible for Marfan was discovered in 1991. It affects the body's production of fibrillin, which is a protein that is an important part of connective tissue. Fibrillin is the primary component of the microfibrils that allow tissues to stretch repeatedly without weakening. Because the patient's fibrillin is abnormal, his or

her connective tissues are looser than usual, which weakens or damages the support structures of the entire body.

The most common external signs associated with Marfan syndrome include excessively long arms and legs, with the patient's arm span being greater than his or her height. The fingers and toes may be long and slender, with loose joints that can bend beyond their normal limits. This unusual flexibility is called hypermobility. The patient's face may also be long and narrow, and he or she may have a noticeable curvature of the spine. It is important to note that Marfan patients vary widely in the external signs of their disorder and in their severity; even two patients from the same family may look quite different. Most of the external features of Marfan syndrome become more pronounced as the patient ages, so that diagnosis of the disorder is often easier in adults than in children. In many cases, the patient may have few or very minor outward signs of the disorder, and the diagnosis may be missed until the patient develops ocular or cardiac symptoms.

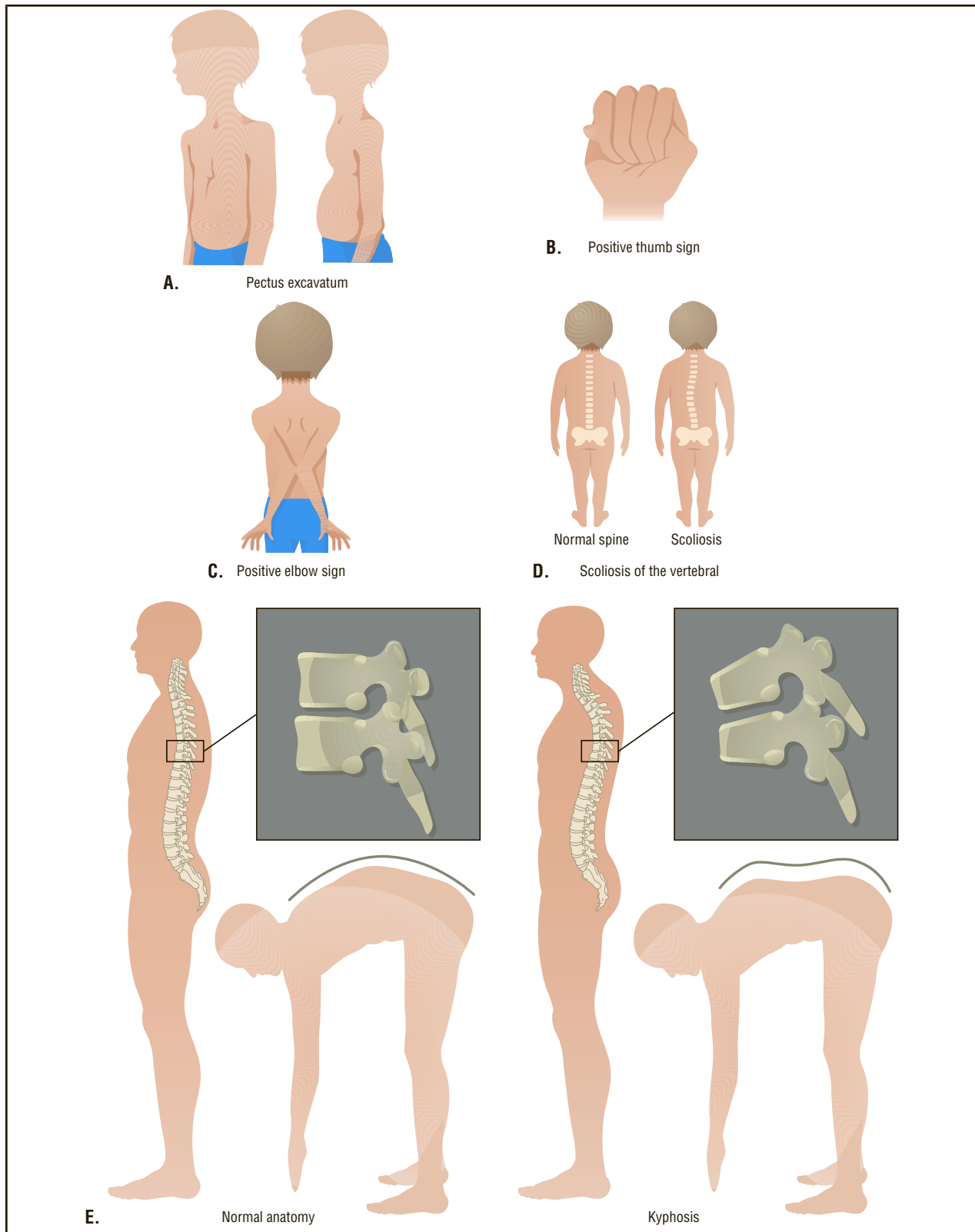
Marfan syndrome by itself does not affect a person's intelligence or ability to learn. There is, however, some clinical evidence that children with it have a slightly higher rate of attention-deficit and hyperactivity disorder (ADHD) than the general population. In addition, a child with undiagnosed nearsightedness related to the syndrome may have difficulty seeing the blackboard or reading printed materials, and thus may be restless and do poorly in school.

Risk factors

People at highest risk for Marfan syndrome are those who have a family history of the condition. If a person has it, each of their offspring has a 50% chance of having the altered gene that causes the condition. Marfan syndrome that occurs because of spontaneous new mutations (15% to 25% of the cases) cannot be prevented. However, for prospective parents with a family history of Marfan syndrome, genetic counseling is recommended. Older fathers are more likely to have new mutations appear on chromosome 15.

Genetic profile

Marfan syndrome is caused by a mutation in a single gene for fibrillin on chromosome 15, which is inherited in most cases from an affected parent. Only between 15% and 25% of cases result from spontaneous mutations. Mutations of the fibrillin gene, known as *FBNI*, are unique to each family affected by Marfan, which makes rapid genetic diagnosis impossible. More than 3,000 different mutations in this gene have been recorded. The syndrome is an autosomal dominant disorder, which



Five common clinical signs for Marfan syndrome. Pectus excavatum (A) refers to the inward curve of the chest. Positive thumb sign (B) is the appearance of the thumb tip when making a closed fist. Positive elbow sign (C) is the ability to touch one's elbows behind their back. Scoliosis (D) is a marked side-to-side curvature of the spine, and kyphosis (E) is the hunchback form resulting from an outward curvature of the spine (Gale)

means that someone who has it has a 50% chance of passing it on to any offspring.

Another important genetic characteristic of Marfan syndrome is its variable expression. This term means that the mutated *FBNI* gene can produce a variety of symptoms of very different degrees of severity, even in members of the same family.

Demographics

Marfan syndrome is one of the more common inheritable disorders. It appears that about one person in every 5,000 has Marfan syndrome including men and women of all races and ethnic groups.

Signs and symptoms

Cardiac and circulatory abnormalities

The most important complications of Marfan syndrome are those affecting the heart and major blood vessels; some are potentially life-threatening. About 90% of Marfan patients will develop cardiac complications. These include:

- **Aortic enlargement:** This is the most serious potential complication of Marfan syndrome. Because of the abnormalities of the patient's fibrillin, the walls of the aorta (the large blood vessel that carries blood away from the heart) are weaker than normal and tend to stretch and bulge out of shape. This stretching increases the likelihood of an aortic dissection, which is a tear or separation between the layers of tissue that make up the aorta. An aortic dissection usually causes severe pain in the abdomen, back, or chest, depending on the section of the aorta that is affected. Rupture of the aorta is a medical emergency requiring immediate surgery and medication.
- **Aortic regurgitation:** A weakened and enlarged aorta may allow some blood to leak back into the heart during each heartbeat. This condition is called aortic regurgitation. Aortic regurgitation occasionally causes shortness of breath during normal activity. In serious cases, it causes the left ventricle of the heart to enlarge and may eventually lead to heart failure.
- **Mitral valve prolapse:** Between 75% and 85% of patients with Marfan syndrome have loose or "floppy" mitral valves, which are the valves that separate the chambers of the heart. When these valves do not cover the opening between the chambers completely, the condition is called mitral valve prolapse. Complications of mitral valve prolapse include heart murmurs and arrhythmias. In rare cases, mitral valve prolapse can cause sudden death.
- **Infective endocarditis:** An infection of the endothelium, the tissue that lines the heart. In patients with Marfan syndrome, it is the abnormal mitral valve that is most likely to become infected.



The hands of a person suffering from Marfan's syndrome, showing abnormally elongated and slender fingers. A normal hand is shown at right for comparison. Marfan's syndrome is an inherited disorder of connective tissue characterized by long, slender fingers and toes and excessive height. Heart defects and dislocations of the lenses of the eye may also be present. (John Radcliffe Hospital/Science Source)

- **Other complications:** Some patients with Marfan syndrome develop cystic disease of the lungs or recurrent spontaneous pneumothorax, a condition in which air accumulates in the space around the lungs. Many patients eventually develop emphysema.

Musculoskeletal abnormalities

Marfan syndrome causes an increase in the length of the patient's bones, with decreased support from the ligaments that hold the bones together. As a result, the patient may develop various deformities of the skeleton or disorders related to the relative looseness of the ligaments, also known as hypermobility.

Disorders of the spine

- **Scoliosis (curvature of the spine):** A disorder in which the vertebrae that make up the spine twist out of line from side to side into an S-shape or a spiral. It is caused by a combination of the rapid growth of children with Marfan, and the looseness of the ligaments that help the spine to keep its shape.
- **Kyphosis:** An abnormal outward curvature of the spine, sometimes called hunchback when it occurs in the upper back. Patients with Marfan syndrome may develop kyphosis either in the upper (thoracic) spine or the lower (lumbar) spine.
- **Spondylolisthesis:** The medical term for a forward slippage of one vertebra on the one below it. It produces an ache or stiffness in the lower back.

- **Dural ectasia:** The dura is the tough, fibrous outermost membrane covering the brain and the spinal cord. The weak dura in patients with Marfan syndrome swells or bulges under the pressure of the spinal fluid. This swelling is called ectasia. In most cases, dural ectasia occurs in the lower spine, producing lower back ache, a burning feeling, or numbness or weakness in the legs.

Disorders of the chest and lower body

- **Pectus excavatum:** A malformation of the chest in which the patient's breastbone, or sternum, is sunken inward. It can cause difficulties in breathing, especially if Marfan has affected the heart, spine, and lung. It also usually causes concerns about appearance.
- **Pectus carinatum:** In other patients with Marfan syndrome, the sternum is pushed outward and narrowed. Although pectus carinatum does not cause breathing difficulties, it can cause embarrassment about appearance. A few patients may have a pectus excavatum on one side of their chest and a pectus carinatum on the other.
- **Foot disorders:** Patients with Marfan syndrome are more likely to develop pes planus (flat feet) or so-called "claw" or "hammer" toes than people in the general population. They are also more likely to have chronic pain in their feet.
- **Protrusio acetabulae:** The acetabulum is the socket of the hip joint. In patients with Marfan syndrome, the acetabulum becomes deeper than normal during growth for reasons that are not yet understood. Although protrusio acetabulae does not cause problems during childhood and adolescence, it can lead to a painful form of arthritis in adult life.

Disorders of the eyes and face

Although the visual problems that are related to Marfan syndrome are rarely life-threatening, they are important in that they may be the patient's first indication of the disorder. Eye disorders related to the syndrome include the following:

- **Myopia (nearsightedness):** Most patients with Marfan develop nearsightedness, usually in childhood.
- **Ectopia lentis:** The medical term for dislocation of the lens of the eye. Between 65% and 75% of patients with Marfan syndrome have dislocated lenses. This condition is an important indication for diagnosis of the syndrome, because there are relatively few other disorders that produce it.
- **Glaucoma:** This condition is much more prevalent in patients with Marfan syndrome than in the general population.

- **Cataracts:** Patients with Marfan are more likely to develop cataracts, and to develop them much earlier in life, sometimes as early as age 40.
- **Retinal detachment:** Patients with Marfan syndrome are more vulnerable to this disorder because of the weakness of their connective tissues. Untreated retinal detachment can cause blindness. The danger of retinal detachment is an important reason for patients to avoid contact sports or other activities that could cause a blow on the head or being knocked to the ground.
- **Other facial problems:** Patients with Marfan syndrome sometimes develop dental problems related to crowding of the teeth caused by a high-arched palate and a narrow jaw.

Other disorders

- **Striae:** Stretch marks in the skin caused by rapid weight gain or growth; they frequently occur in pregnant women, for example. Patients with Marfan syndrome often develop striae over the shoulders, hips, and lower back at an early age because of rapid bone growth. Although the patient may be self-conscious about the striae, these are not a danger to health.
- **Obstructive sleep apnea:** Refers to partial obstruction of the airway during sleep, causing irregular breathing and sometimes snoring. In patients with Marfan syndrome, obstructive sleep apnea is caused by the unusual flexibility of the tissues lining the patient's airway. This disturbed breathing pattern increases the risk of aortic dissection.

Diagnosis

There is no objective diagnostic test for Marfan syndrome, in part because the disorder does not produce any measurable biochemical changes in the patient's blood or body fluids, or cellular changes that could be detected from a tissue sample. The current standard of diagnostic criteria are set forth in the Ghent-2 nosology. This set of diagnostic criteria was updated in 2010 from the previously established Ghent-1 nosology described in 1996.

Examination

The diagnosis is established by taking a family history and a thorough examination of the patient's eyes, heart, and bone structure. The examination includes a slit-lamp eye examination by an ophthalmologist, and a work-up of the patient's spinal column by an orthopedic specialist. The importance of the slit-lamp examination is that it allows the doctor to detect a dislocated lens, which is a significant indication of the syndrome.

Tests

In terms of the cardiac examination, a standard electrocardiogram (EKG) is not sufficient for diagnosis; only the echocardiogram can detect possible enlargement of the aorta. Other tests include using magnetic resonance imaging (MRI) and computed tomography (CT) to check the heart valves and aorta. These scans also are used to check for dural ectasia, a typical complication of Marfan syndrome.

The symptoms of Marfan syndrome in some patients resemble the symptoms of homocystinuria, which is an inherited disorder marked by extremely high levels of homocysteine in the patient's blood and urine. This possibility can be excluded by a urine test.

In other cases, the diagnosis remains uncertain because of the mildness of the patient's symptoms, the absence of a family history of the syndrome, and other variables. These borderline conditions are sometimes referred to as marfanoid syndromes.

Treatment and management

Traditional

The treatment and management of Marfan syndrome are tailored to the specific symptoms of each patient. Some patients find that the syndrome has little impact on their overall lifestyle; others have found their lives centered on the disorder.

After a person has been diagnosed with Marfan syndrome, he or she should be monitored with an echocardiogram every six months until it is clear that the aorta is not growing larger. After that, the patient should have an echocardiogram once a year. If the echocardiogram does not allow the physician to visualize all portions of the aorta, CT or MRI may be used. In cases involving a possible aortic dissection, the patient may be given a transesophageal echocardiogram (TEE).

Children diagnosed with Marfan syndrome should be checked for scoliosis by their pediatricians at each annual physical examination. The doctor simply asks the child to bend forward while the back is examined for changes in the curvature. In addition, the child's spine should be x-rayed in order to measure the extent of scoliosis or kyphosis. The curve is measured in degrees by the angle between the vertebrae as seen on the x-ray. Curves of 20° or less are not likely to become worse. Curves between 20° and 40° are likely to increase in children or adolescents. Curves of 40° or more are highly likely to worsen, even in an adult, because the spine is so badly imbalanced that the force of gravity will increase the curvature.

KEY TERMS

Autosomal dominant—Refers to the pattern of inheritance in which only one copy of an allele that causes a disorder needs to be passed down to offspring for those offspring to also have the disorder phenotype.

Fibrillin—A glycoprotein secreted by fibroblasts into the extracellular matrix necessary for the deposition of elastin and the proper function of elastic fibers found in connective tissues.

Hypermobility—The ability to stretch one's joints farther than normal.

Nosology—A branch of medicine that aims to classify diseases by means of disease etiology (cause), pathogenesis (mechanism), and/or symptoms.

Scoliosis in 20° and 40° in children is usually treated with a back brace. The child must wear this appliance about 23 hours a day until growth is complete. If the spinal curvature increases to 40° or 50°, the patient may need surgery in order to prevent lung problems, back pain, and further deformity. Surgical treatment of scoliosis involves straightening the spine with metal rods and fusing the vertebrae in the straightened position.

Spondylolisthesis is treated with a brace in mild cases. If the slippage is more than 30°, the slipped vertebra may require surgical realignment.

Dural ectasia can be distinguished from other causes of back pain on an MRI. Mild cases are usually not treated. Medication or spinal shunting to remove some of the spinal fluid are used to treat severe cases.

Pectus excavatum and pectus carinatum can be treated by surgery. In pectus excavatum, the deformed breastbone and ribs are raised and straightened by a metal bar. After four to six months, the bar is removed in an outpatient procedure.

Protrusio acetabulae may require surgery in adult life to provide the patient with an artificial hip joint, if the arthritic pains are severe.

Patients with Marfan syndrome should consider wearing shoes with low heels, special cushions, or orthotic inserts. Foot surgery is rarely necessary.

Drugs

A patient may be given drugs called beta-blockers to slow down the rate of aortic enlargement and decrease the

risk of dissection by lowering the blood pressure and decreasing the forcefulness of the heartbeat. The most commonly used beta-blockers in patients with Marfan syndrome are propranolol (Inderal) and atenolol (Tenormin). Patients who are allergic to beta-blockers may be given a calcium blocker such as verapamil.

Because patients with Marfan syndrome are at increased risk for infective endocarditis, they must take a prophylactic dose of an antibiotic before having dental work or minor surgery, as these procedures may allow bacteria to enter the bloodstream. Penicillin and amoxicillin are the antibiotics most often used.

Pain in the feet or limbs is usually treated with a mild analgesic such as acetaminophen.

Alternative

Surgery may be necessary if the width of the patient's aorta increases rapidly or reaches a critical size (about 2 in., 5 cm). The most common surgical treatment involves replacing the patient's aortic valve and several inches of the aorta itself with a composite graft, which is a prosthetic heart valve sewn into one end of a Dacron tube. This surgery has been performed widely since about 1985; most patients who have had a composite graft have not needed additional surgery.

Patients who have had a valve replaced must take an anticoagulant medication, usually warfarin (Coumadin), in order to minimize the possibility of a clot forming on the prosthetic valve.

Visual and dental concerns

Patients with Marfan syndrome should have a thorough eye examination, including a slit-lamp examination, to test for dislocation of the lens as well as nearsightedness. Dislocation can be treated by a combination of special glasses and daily use of 1% atropine sulfate ophthalmic drops, or by surgery.

Because patients with Marfan syndrome are at increased risk of glaucoma, they should have the fluid pressure inside the eye measured every year as part of an eye examination. Glaucoma can be treated with medications or with surgery.

Cataracts are treated with increasing success by implant surgery. It is important to seek treatment at medical centers with eye surgeons who are familiar with the possible complications of cataract surgery in patients with Marfan syndrome.

All persons with Marfan syndrome should be taught to recognize the signs of retinal detachment (sudden blurring of vision in one eye becoming progressively worse

QUESTIONS TO ASK YOUR DOCTOR

- How do you plan to treat my Marfan syndrome?
- Are there treatment options?
- Is surgery necessary?
- What is the expected outcome?
- How do people inherit Marfan syndrome?

without pain or redness) and to seek professional help immediately.

Children with Marfan syndrome should be evaluated by their dentist at each checkup, for crowding of the teeth and possible misalignment, and referred to an orthodontist if necessary.

People with Marfan syndrome should avoid sports or occupations that require heavy weight lifting, rough physical contact, or rapid changes in atmospheric pressure (e.g., scuba diving). Weight lifting increases blood pressure, which in turn may enlarge the aorta. Rough physical contact may cause retinal detachment. Sudden changes in air pressure may produce pneumothorax. Regular noncompetitive physical exercise, however, is beneficial for patients with Marfan syndrome. Good choices include brisk walking, shooting baskets, and slow-paced tennis.

Social and lifestyle issues

Smoking is particularly harmful for patients with Marfan, because it increases their risk of emphysema.

In the past, women with Marfan syndrome were advised to avoid pregnancy because of the risk of aortic enlargement or dissection. The development of beta-blockers and echocardiograms, however, now allows doctors to monitor patients throughout pregnancy. It is recommended that patients have an echocardiogram during each of the three trimesters of pregnancy. Normal, vaginal delivery is not necessarily more stressful than a Caesarian section, but patients in prolonged labor may have a Caesarian birth to reduce strain on the heart. A pregnant woman with Marfan syndrome should also receive genetic counseling regarding the 50% risk of having a child with the syndrome.

Children and adolescents with Marfan syndrome may benefit from supportive counseling regarding appearance, particularly if their symptoms are severe and cause them to withdraw from social activities. Families may wish to seek counseling regarding the effects of

the syndrome on relationships within the family. Many people respond with guilt, fear, or blame when a genetic disorder is diagnosed in the family, or they may overprotect the affected member. Support groups are often good sources of information about Marfan syndrome; they can offer helpful suggestions about living with it as well as emotional support.

Prognosis

The prognosis for patients with Marfan syndrome has improved markedly. The life expectancy of people with the syndrome had increased to 72 years, up from 48 years in 1972. This dramatic improvement is attributed to new surgical techniques, improved diagnosis, and new techniques of medical treatment.

The most important single factor in improving the patient's prognosis is early diagnosis. The earlier that a patient can benefit from the new techniques and lifestyle modifications, the more likely he or she is to have a longer life expectancy.

In 2021, researchers have developed an animal model that may eventually lead to a treatment to prevent lens detachment in individuals who have eye complications. In addition, clinical trials are underway to treat various symptoms of Marfan syndrome. Participation in a clinical trial is voluntary and at no cost to the participant. All clinical trials receiving U.S. government funding, and some supported by private industry, are posted at <https://www.clinicaltrials.gov>. Foreign trials are listed at <https://www.orpha.net>.

Resources

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ORGANIZATIONS

National Marfan Foundation, 22 Manhasset Avenue, Port Washington, NY 11050, (516) 883-8712 or (800)

8-MARFAN, (516) 883-8040, staff@marfan.org, <https://www.marfan.org>

Stanford University Center for Marfan Syndrome and Aortic Disorders, 300 Pasteur Drive, 3rd Floor, Stanford, CA 94305-5233, (650) 725-8246, <https://stanfordhealthcare.org/medical-clinics/center-marfan-syndrome-related-aortic-disorders.html>

Rebecca J. Frey, PhD,
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Revised by Tish Davidson, AM

Marie-Strumpell spondylitis bechterew syndrome see **Ankylosing spondylitis**

Maroteaux-Lamy syndrome (MPS VI) see **Mucopolysaccharidoses**

Marshall-Smith syndrome

Definition

Marshall-Smith syndrome is a childhood condition involving specific facial characteristics, bone maturation that is advanced for the individual's age, failure to grow and gain weight appropriate for the individual's age, and severe respiratory (breathing) problems.

Description

Marshall-Smith syndrome (MSS) was first described in two males seen in 1971 by Drs. Marshall, Graham, Scott, and Smith. They noticed changes in the skeletal system of these patients. Bones normally mature through several stages, naturally progressing through these stages with time. Specifically, a young child's bones have more cartilage and less calcium deposits than an adult's bones. A child's bones appear less "dense" on an x-ray than an adult's bones. A constant feature of MSS is skeletal maturation that is advanced for age. For example, in 1993 a newborn child with MSS was found to have the bone age of a three-year-old child.

Specific facial features in MSS include a wide and prominent forehead, protruding and widely spaced eyes, a very small chin, and a small, upturned nose. Because individuals may not gain weight or grow well, they are often smaller than other children of the same age. There are often problems with structures in the respiratory tract (such as the larynx and trachea) and this can lead to difficulty with breathing. Pneumonia, or a lung infection, is common and can occur several times.

KEY TERMS

Cartilage—Supportive connective tissue which cushions bone at the joints or which connects muscle to bone.

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communication between the right and left cerebral hemispheres.

Gastrostomy—The construction of an artificial opening from the stomach through the abdominal wall to permit the intake of food.

Hirsutism—The presence of coarse hair on the face, chest, upper back, or abdomen in a female as a result of excessive androgen production.

Larynx—The voice box, or organ that contains the vocal cords.

Phalanges—Long bones of the fingers and toes, divided by cartilage around the knuckles.

Trachea—Long tube connecting from the larynx down into the lungs, responsible for passing air.

Tracheostomy—An opening surgically created in the trachea (windpipe) through the neck to improve breathing.

Umbilical hernia—Protrusion of the bowels through the abdominal wall, underneath the navel.

Significant mental and physical delays are almost always expected in MSS. Since children with MSS are often hospitalized for long periods of time to help treat respiratory problems, they may be slower to do physical things like crawling or walking.

No two patients with MSS have the exact same symptoms, as there is some variability with the condition. There are no alternate names for Marshall-Smith syndrome, though it is sometimes incorrectly referred to as Weaver syndrome, a separate condition with similar symptoms.

Families with MSS can be put under a great deal of stress, because long-term hospitalizations in the intensive care unit are common for children with MSS.

Genetic profile

The vast majority of people with MSS are unique in their family; there is usually no family history of the condition. Because of this, MSS is thought to be a random, sporadic event when it occurs. No specific gene has been associated with MSS, and other genetic background is

still largely unknown. Standard genetic testing, such as chromosome analysis and metabolic studies, typically are normal for patients with MSS.

In 1999, a group in Saudi Arabia reported a young girl with features of MSS who had a chromosome abnormality. She was found to have some duplication of the material on a region of chromosome 2. This has led researchers to believe that the gene for MSS may actually be on chromosome 2. This is the only individual with MSS found to have a chromosome abnormality. Current research is under way to determine the exact genetic cause for MSS.

Demographics

Marshall-Smith syndrome is very rare in the general population. In fact, no statistical rates are available for the condition. It appears to be present across the world, affecting males and females equally.

Signs and symptoms

The most medically serious complication in MSS is the associated respiratory problems. Structures in the respiratory system, such as the larynx and trachea, may not function properly because they can be “floppy,” soft, and less muscular than usual. Because of this, airways can become plugged or clogged, since air does not move through to clear them like usual. Mucus may start collecting, causing an increased amount of bacteria that can lead to pneumonia. Ear infections are common, because the bacteria can spread to the ears as well. Internal nasal passages may be narrower in people with MSS, which can pose difficulty with breathing.

Children with MSS may have problems with eating, due to similar reasons that they may have difficulty breathing. Additionally, they may have a weak “suck” and “swallowing” reflex, normally controlled by muscular movements. As mentioned earlier, another feature of MSS is lack of proper growth and weight gain. This can be in part due to the difficulty in feeding for these individuals, though they are often very small even at birth.

Advanced bone age is present in all people with MSS. In particular, the bones of someone with MSS appear more dense on an x-ray than they should, according to their age. While x-rays of their hands and wrists often determine a person’s “bone age,” people with MSS often have a generalized advanced bone age within their entire skeleton. They may also have broad middle phalanges of the hand, which can be seen on an x-ray.

Facial characteristics of people with MSS include those mentioned earlier, but other features may also occasionally be present. These can be blue-tinged sclerae (the

QUESTIONS TO ASK YOUR DOCTOR

- What are the medical problems my child is likely to have to confront as a result of having Marshall-Smith syndrome?
- What is her life expectancy likely to be as a result of this condition?
- Are there medications or procedures that can be provided to make her life more comfortable?
- Are there organizations for parents of children with Marshall-Smith syndrome?

white sections of the eyes), a large head circumference (measurement around the head), and a small, triangle-shaped face (with the point of the triangle being at the chin).

Occasionally, creases in the hands are deeper than usual in people with MSS. The first (big) toe can be longer and bigger than usual. Additional features include hirsutism and an umbilical hernia. Hearing loss can sometimes occur. Ears may be larger, have a crumpled appearance, or be lower on the head than usual.

Changes in the brain can occur in MSS. An individual was reported in 1997 to have a smaller optic nerve (the nerve that connects the eyes to the brain) than usual, and had some vision problems as a result. Some children may be missing the corpus callosum, a structure in the brain. Mental and physical delays are commonly present in MSS, and are usually quite significant. These may in part be due to the brain abnormalities that are sometimes seen. There may be partial to complete lack of speech for individuals with MSS, another sign of the mental delays.

Diagnosis

Because there is no genetic testing available for Marshall-Smith syndrome, all individuals have been diagnosed through a careful physical examination and study of their medical history.

Advanced skeletal age can be seen on x-rays of the patient's hands and wrists, since this is the typical way to assess bone age. A full x-ray survey of the body is a good way to assess age of other bones as well. Advanced bone age is always seen in Marshall-Smith syndrome, but it may also be present in other genetic syndromes. Sotos syndrome involves similar skeletal findings, but individuals are generally larger than usual and can have mental delays. Weaver syndrome includes advanced skeletal

maturation, but individuals are often larger than usual and have other specific facial characteristics (such as very narrow, small eyes). These and other conditions can be ruled out if the respiratory complications and facial characteristics seen in MSS are not present.

Treatment and management

As mentioned earlier, long hospitalizations are common for people with MSS. Most of these involve treating severe respiratory complications of MSS. These types of complications often necessitate placing a tracheotomy to assist with breathing. Manual removal of the mucus buildup by suctioning near the tracheotomy is common. Frequent pneumonia is common, and intravenous antibiotics are often the treatment, as in people without MSS. There is no specific treatment for the advanced bone age.

Because feeding can be difficult for children with MSS, a gastrostomy is often needed, and feeding is done directly through the gastrostomy tube. It is a challenge to make sure children with MSS maintain proper growth, and sometimes a gastrostomy is the only way to achieve this.

Prognosis

Marshall-Smith syndrome is considered a childhood condition because affected individuals do not typically survive past childhood. There is no long-term research on the disease due to its being rare and not typically present in adults.

Most children with MSS die in early childhood, often by three years of age, largely due to severe respiratory complications, and infections that may result from them. There have been reports of children surviving until age seven or eight, but these children did not have severe respiratory problems. These children give hope that the condition is variable, and not every person diagnosed with the condition will have a severely shortened lifespan.

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ORGANIZATIONS

- Human Growth Foundation, 997 Glencove Ave., Suite 5, Glenhead, NY 11545, (800) 451-6434, hgf1@hgfound.org, <http://www.hgfound.org>
- Little People of America, National Headquarters, 250 EL Camino Real, Suite 211, Tustin, CA 92780, (888) LPA-2001, info@lpaonline.org, <http://www.lpaonline.org>
- MAGIC Foundation, 6645 W. North Ave., Oak Park, Illinois 60302, (708) 383-0808, ContactUs@magicfoundation.org, <http://www.magicfoundation.org>
- MSS Research Foundation, Oeverbiesstraat 20, The Hague, NL The Netherlands 2548 WP, 31703356956, info@marshallsmith.org, <http://www.marshallsmith.org>

Deepti Babu, MS, CGC

Marshall syndrome

Definition

Marshall syndrome is a very rare genetic disorder with an autosomal dominant pattern that equally affects males and females. It is caused by an abnormality in collagen, which is a key part of connective tissue.

Description

Marshall syndrome was first described by Dr. D. Marshall in 1958, and it has been studied periodically by researchers since then. The disease is most apparent in the facial features of those affected, which include an upturned nose; eyes spaced widely apart, making them appear larger than normal; and a flat nasal bridge. This facial formation gives subjects a childlike appearance. The upper part of the skull is unusually thick, and deposits of calcium may appear in the cranium. Patients may also have palate abnormalities. In addition, they may experience early osteoarthritis, particularly in the knees.

Myopia (nearsightedness), cataracts, and glaucoma are common in Marshall syndrome. Moderate to severe hearing loss is often preceded by many incidents of otitis media (middle ear infection) and can occur in children as young as age three.

In the 40 years following Dr. Marshall’s discovery, some physicians argued that Marshall syndrome is

KEY TERMS

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light, resulting in blurry vision. Surgery may be performed to remove the cataract.

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Glaucoma—An increase in the fluid eye pressure, eventually leading to damage of the optic nerve and ongoing visual loss.

Myopia—Nearsightedness; difficulty seeing objects that are far away.

Osteoarthritis—A degenerative joint disease that causes pain and stiffness.

Saddle nose—A sunken nasal bridge.

actually a subset of Stickler syndrome, a more common genetic disorder. Individuals with both syndromes have similar facial features and symptoms. Other experts have argued against this view, stating that Marshall syndrome is a distinct disorder on its own. For example, most patients with Stickler syndrome have cataracts, while this problem is less common among those with Marshall syndrome. In addition, most subjects with Marshall syndrome have moderate to severe hearing loss, which rarely occurs among those with Stickler syndrome, who have normal hearing.

Genetic research performed in 1998 and 1999 revealed that both sides were correct. There are clear genetic differences between the two syndromes. There are also patients who have apparent overlaps of both syndromes.

In 1998, a study used genetic testing to establish that a collagen genetic mutation on *COL11A1* caused Marshall syndrome and that a change on *COL2A1* caused Stickler syndrome. A 2007 study found that other types of mutations on *COL11A1* could cause either syndrome.

A study in 1999 described a genetic study of 30 patients from Europe and the United States, all of whom were suspected to have either Marshall or Stickler syndrome. These genetic findings confirmed those of the previous (1998) study. Twenty-three novel mutations of *COL11A1* and *COL2A1* were found among the subjects. Some patients had genetic overlaps of both Marshall and Stickler syndromes.

Physical differences were also noted between the two syndromes. For example, all the patients with Marshall

syndrome had moderate to severe hearing loss, while none of the patients with Stickler syndrome had hearing loss. About half the patients with overlapping disorders of both diseases had hearing loss. All the patients with Marshall syndrome had short noses, compared to about 75% of the patients with Stickler syndrome. Palate abnormalities occur in all patients with Stickler syndrome, compared to only about 80% of those with Marshall syndrome. Also, about a third of the Stickler patients had dental abnormalities, compared to 11% of the patients with Marshall syndrome. Those with Stickler (71%) had a higher percentage of cataracts than those with Marshall syndrome (40%). Patients with Marshall syndrome were much more likely to have short stature than those with Stickler syndrome.

Genetic profile

The gene name for Marshall syndrome is Collagen, Type XI, alpha 1. The gene symbol is *COL11A1*. The chromosomal location is 1p21. Marshall syndrome is an autosomal dominant genetic trait, and the risk of an affected parent transmitting the gene to the child is 50%. Human traits are the product of the interaction of two genes from that condition, one received from the father and one from the mother. In dominant disorders, a single copy of the abnormal gene (received from either parent) dominates the normal gene and results in the appearance of the disease. The risk of transmitting the disorder from affected parent to offspring is 50% for each pregnancy regardless of the gender of the resulting child.

Demographics

Because of the rarity of this disease, very little demographic data is available. Fewer than 100 cases of individuals with this syndrome have been reported worldwide in medical literature. Some cases are probably undiagnosed because of the high expense of genetic testing. It is known that Marshall syndrome presents in infancy or early childhood and severe symptoms such as hearing loss and cataracts manifest before the age of ten years. Adults with the syndrome retain the facial traits that are characteristic of this disease, such as flat nose, large nasal bridge, and widely spaced eyes. Among those with Stickler syndrome, in contrast, these distinctive facial characteristics diminish in adulthood.

Signs and symptoms

Characteristic features of this disease are short upturned nose with a flat nasal bridge. Some patients also have glaucoma, crossed eyes, detached retinas, and protruding upper teeth. Patients often have short stature compared to other family members without the disease.

QUESTIONS TO ASK YOUR DOCTOR

- What is collagen, and what role does it play in Marshall syndrome?
- What are the most prominent signs and symptoms associated with Marshall syndrome?
- What kinds of treatment are available for the most serious symptoms of Marshall syndrome?
- Is there currently any type of research being conducted on a cure for Marshall syndrome?

Diagnosis

Individuals are diagnosed by their features as well as by the very early onset of serious eye and ear disease. Because Marshall syndrome is an autosomal dominant hereditary disease, physicians can also note the characteristic appearance of the biological parent of the child. Genetic testing is costly; thus, it is not ordered for most people. As a result, people may be diagnosed as possible Marshall syndrome or possible Stickler syndrome, based on their symptoms and appearance.

Treatment and management

Marshall syndrome cannot be cured; however, the symptoms caused by the disease should be treated. Children with Marshall syndrome should have annual eye and ear checkups because of the risk for cataracts and hearing loss. Cataract surgery is needed if cataracts develop. At present, the only treatment for the progressive hearing loss is a hearing aid. The flat “saddle nose” can be altered with cosmetic surgery. If a child with Marshall syndrome has osteoarthritis, doctors may advise against contact sports.

Prognosis

As patients with Marshall syndrome age, vision and hearing problems generally worsen. Many also develop osteoarthritis at an earlier age than do patients without Marshall syndrome, such as in the teens or 20s. Because there are so few identified cases, the life expectancy of afflicted individuals is unknown.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Christine Adamec

Martin-Bell syndrome see **Fragile X syndrome**

MCAD deficiency

Definition

Medium chain acyl-CoA dehydrogenase (MCAD) deficiency is a rare genetic disorder characterized by a deficiency of the MCAD enzyme. This enzyme is responsible for the breakdown of certain fatty acids into chemical forms that are useable by the human body. MCAD

deficiency accounts for approximately 1 to 3 of every 100 cases of sudden infant death syndrome (SIDS). MCAD deficiency is transmitted through a non-sex linked (autosomal) recessive trait. The first recognized cases of MCAD deficiency were reported in 1982.

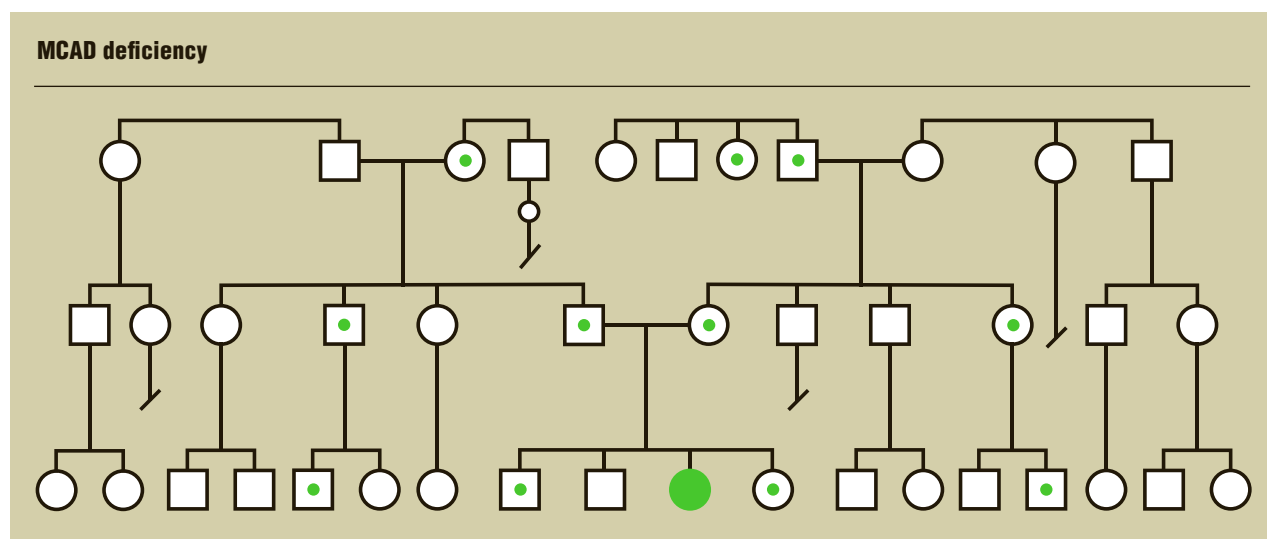
Description

MCAD is one of four enzymes in the mitochondria of the cells that are responsible for the breakdown of medium-chain fatty acids into acetyl-CoA. Medium-chain fatty acids are defined as fatty acids containing between 4 and 14 carbon atoms. Acetyl-CoA, the desired product of the breakdown of these fatty acids, is a two-carbon molecule. MCAD is the enzyme responsible for the breakdown of straight-chain fatty acids with 4 to 14 carbons. There are two other enzymes that are responsible for the breakdown of short straight-chain (less than 4 carbons) fatty acids, and long straight-chain (more than 14 carbons) fatty acids. These other two enzymes are not able to take over the function of MCAD when MCAD is deficient.

Individuals affected with MCAD deficiency produce a form of the MCAD enzyme that is not nearly as efficient as the normal form of MCAD. This lack of efficiency results in a greatly diminished, but still functional, capability to break down medium-chain fatty acids.

Genetic profile

The gene that is responsible for the production of MCAD is located on chromosome 1 at 1p31. Twenty-six different mutations of this gene have been identified as causing MCAD deficiency; however, 95%–98% of all cases are the result of a single point mutation. In this



MCAD deficiency: pedigree analysis chart. (Gale)

mutation, adenosine is substituted for guanine in base 985 (G985A), which causes a substitution of lysine (AAA) by glutamic acid (GAA) in residue 329 of the MCAD protein.

MCAD deficiency is a recessive disorder. This means that in order for a person to be affected with MCAD deficiency, he or she must carry two abnormal copies of the *MCAD* gene. In a population of individuals known to be affected with the G985A mutation, 81% were found to be homozygous for this mutation (two chromosomes, each with the same mutation). The remaining 19% were found to be heterozygous for the G985A mutation (only one chromosome carried the G985A mutation), but their other chromosomes carried one of the other MCAD gene mutations.

Demographics

MCAD deficiency is estimated to occur in approximately 1 out of every 13,000 to 20,000 live births. This estimate is confounded to a certain degree by the fact that up to 25% of all individuals affected with MCAD deficiency die the first time they exhibit any symptoms of the disease. Many of these children are often misdiagnosed with either sudden infant death syndrome (SIDS) or Reye syndrome. Unless an autopsy is performed, MCAD generally goes undetected in these individuals; and, even then, unless the physician performing the autopsy is familiar with MCAD deficiency, the cause of death may still be misreported.

MCAD deficiency is seen almost exclusively in Caucasians of Northern European descent (this includes people from every European country not bordering the Mediterranean Sea). Approximately 80% of the Caucasian population of the United States can be considered to be a part of this subpopulation. In this subpopulation, it is estimated that 1 in every 40 to 100 people is a carrier of the G985A mutation, and 1 in every 6,500 to 20,000 people is homozygous in this mutation. Homozygous individuals (carriers of two sets of the G985A mutation) should be affected with MCAD deficiency; however, the incidence rate of MCAD deficiency is lower than that predicted from the carrier populations. There are two possible reasons for the lower number of observed cases of MCAD deficiency than the carrier data suggests should occur. First, many individuals with MCAD deficiency may be misdiagnosed. Secondly, there may be a significant number of homozygous people who for unknown reasons remain unaffected (asymptomatic).

As a comparison, 1 in every 29 Caucasians is a carrier for cystic fibrosis, but only 1 in every 3,300 people in this subpopulation develops the disease.

The high frequency of a single mutation leading to MCAD deficiency, combined with the extreme similarity of the other known mutations to this mutation and the

high concentration of MCAD deficiency within a single subpopulation, suggests a founder effect from a single person in a Germanic tribe.

Because MCAD deficiency is a recessive disease, both parents must be carriers of this trait in order for their children to be affected. If both parents carry a copy of the mutated gene, there is a 25% likelihood that their child will be homozygous for MCAD deficiency. Genetically, the probability that an affected person will have a sibling who is also affected is also 25%. In population studies of known MCAD deficient individuals, it has been observed that an average of 32% of these individuals have at least one sibling either known to be affected with MCAD deficiency or to have died with a misdiagnosis of SIDS.

Signs and symptoms

There is no classic set of symptoms that characterize MCAD deficiency. The severity of symptoms observed in individuals affected with MCAD deficiency ranges from no symptoms at all (asymptomatic) to the occurrence of death upon the first onset of symptoms. The first symptoms of MCAD deficiency generally occur within the first three years of life. The average age of onset of the first symptoms is one year of age. Some individuals become symptomatic prior to birth. The onset of symptoms in adults is extremely rare.

Lethargy and persistent vomiting are the most typical symptoms of MCAD deficiency. The first episode of symptoms is generally preceded by a 12 to 16 hour period of stress. Most affected individuals show intermittent periods of low blood sugar (hypoglycemia) and higher than normal amounts of ammonia in the blood (hyperammonemia). An abnormally large liver (hepatomegaly) is also associated with MCAD deficiency.

Approximately half of all individuals showing symptoms of MCAD deficiency for the first time experience respiratory arrest, cardiac arrest, and/or sudden infant death. Between 20% and 25% of all MCAD deficiency affected infants die during their first episodes of symptoms.

Some individuals affected with MCAD deficiency are affected with a degenerative disease of the brain and central nervous system (encephalopathy). Seizures, coma, and periods of halted breathing (apnea) have also been seen in people with MCAD deficiencies.

Long-term symptoms of MCAD deficiency may include: attention deficit disorder (ADD), cerebral palsy, mental retardation, and/or developmental delays.

The severity of the symptoms associated this MCAD deficiency is linked to the age of the person when the symptoms first happen. The risk of dying from an onset of the disease is slightly higher in individuals who show the first symptoms after the age of one year. The highest risk ages

are the ages of 15 to 26 months. Seizures and encephalopathy are most frequently seen in affected individuals between the ages of 12 and 18 months. Seizures at these ages are often associated with future death during a symptomatic episode, recurrent seizures throughout life, the development of cerebral palsy, and/or the development of speech disabilities.

Diagnosis

The Departments of Health in Massachusetts and North Carolina require mandatory newborn screening for MCAD deficiency. California has a voluntary newborn screening policy. Additionally, Neo Gen Screening offers voluntary newborn screening at birthing centers throughout the Northeastern United States.

These newborn screening methods employ either a tandem mass spectrometry (MS/MS) blood test method or a PCR/FRET analysis. The MS/MS test discovers the presence of the G985A mutation in the *MCAD* gene by the difference in molecular weight in this gene versus the molecular weight of the normal *MCAD* gene.

In the PCR/FRET test, a sample of blood is drawn and the DNA is extracted. This DNA is then reproduced multiple times by the polymerase chain reaction (PCR amplification). Once enough sample has been made, the sample is labeled with a fluorescent chemical that binds specifically to the region of chromosome 1 that contains the *MCAD* gene. How this fluorescent chemical binds to the *MCAD* gene region containing the G985A mutation allows the identification of homozygous G985A, heterozygous G985A, and normal (no G985A mutations) *MCAD* genes (FRET analysis).

An older method for the detection of MCAD deficiency is a urine test that checks for elevated levels of the chemicals hexanoylglycine and phenylpropionylglycine.

Prenatal testing for MCAD deficiency is available using a test similar to the PCR/FRET blood test. In this case, the DNA to be studied is extracted from the amniotic fluid rather than from blood. Another prenatal test involves studying the ability of cultured amniotic cells to breakdown added octanoate, an 8-carbon molecule that requires MCAD to break it down.

Because MCAD deficiency is generally treatable if it is recognized prior to the onset of symptoms, most parents of a potentially affected child choose to wait until birth to have their children tested.

Treatment and management

Because individuals affected with MCAD deficiency can still break down short-chain and long-chain fatty acids at a normal rate and most have a diminished, but functional, ability to break down medium-chain fatty

KEY TERMS

Apnea—An irregular breathing pattern characterized by abnormally long periods of the complete cessation of breathing.

Carnitine—An amino acid necessary for metabolism of the long-chain fatty acid portion of lipids. Also called vitamin B7.

Enzyme efficiency—The rate at which an enzyme can perform the chemical transformation it is expected to accomplish. This is also called turnover rate.

Founder effect—Increased frequency of a gene mutation in a population that was founded by a small ancestral group of people, at least one of whom was a carrier of the gene mutation.

Hepatomegaly—An abnormally large liver.

Hyperammonemia—An excess of ammonia in the blood.

Hypoglycemia—An abnormally low glucose (blood sugar) concentration in the blood.

Medium-chain acyl-CoA dehydrogenase—Abbreviated MCAD, the enzyme responsible for the breakdown of medium chain fatty acids in humans. People affected with MCAD deficiency produce a form of MCAD that is not as efficient as the normal form of MCAD.

Medium-chain fatty acids—Fatty acids containing between 4 and 14 carbon atoms.

acids, a precipitating condition must be present in order for symptoms of MCAD deficiency to develop. The most common precipitators of MCAD deficiency symptoms are stress caused by fasting or by infection. At these times, the body requires a higher than normal breakdown of medium chain fatty acids. MCAD deficient individuals often cannot meet these increased metabolic demands.

The main treatments for MCAD deficiency are designed to control or avoid precipitating factors. Persons affected with MCAD deficiency should never fast for more than 10 to 12 hours and they should strictly adhere to a low-fat diet. Blood sugar monitoring should be undertaken to control episodes of hypoglycemia. During acute episodes, it is usually necessary to administer glucose and supplement the diet with carbohydrates and high calorie supplements.

Many individuals affected with MCAD deficiency benefit from daily doses of vitamin B7 (L-carnitine). This

vitamin is responsible for transporting long chain fatty acids across the inner mitochondrial membrane. Elevated levels of L-carnitine ensure that these individuals break down long chain fatty acids in preference to medium chain fatty acids, which helps prevent acute symptomatic episodes of MCAD deficiency. Additionally, L-carnitine helps remove toxic wastes from the bloodstream to the urine, so it is also pivotal in controlling hyperammonemia.

Some individuals affected with MCAD deficiency present symptoms for the first time when they receive the diphtheria-pertussis-tetanus (DTP) vaccine. It is important that any person suspected to be affected with MCAD deficiency should receive treatment for hypoglycemia in connection with the administration of this vaccine. Chicken pox and middle ear infections (otitis media) have also been shown to initiate symptoms of MCAD deficiency.

Prognosis

MCAD deficiency has a mortality rate of 20%–25% during the first episode of symptoms. If an affected individual survives this first attack, the prognosis is excellent for this individual to have a normal quality of life as long as appropriate medical treatment is sought and followed.

Resources

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ORGANIZATIONS

Fatty Oxidation Disorders (FOD) Family Support Group, PO Box 54, Okemos, MI 48805, (517) 381-1940, deb@fodsupport.org, <http://www.fodsupport.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, <http://www.rarediseases.org>

Organic Acidemia Association, 9040 Duluth St., Golden Valley, MN 55427, (763) 559-1797, mkstagni@gmail.com, <http://www.oaanews.org>

Paul A. Johnson

McCune-Albright syndrome

Definition

McCune-Albright syndrome is a disorder characterized by abnormalities in bone development, skin pigmentation, and endocrine gland function.

Description

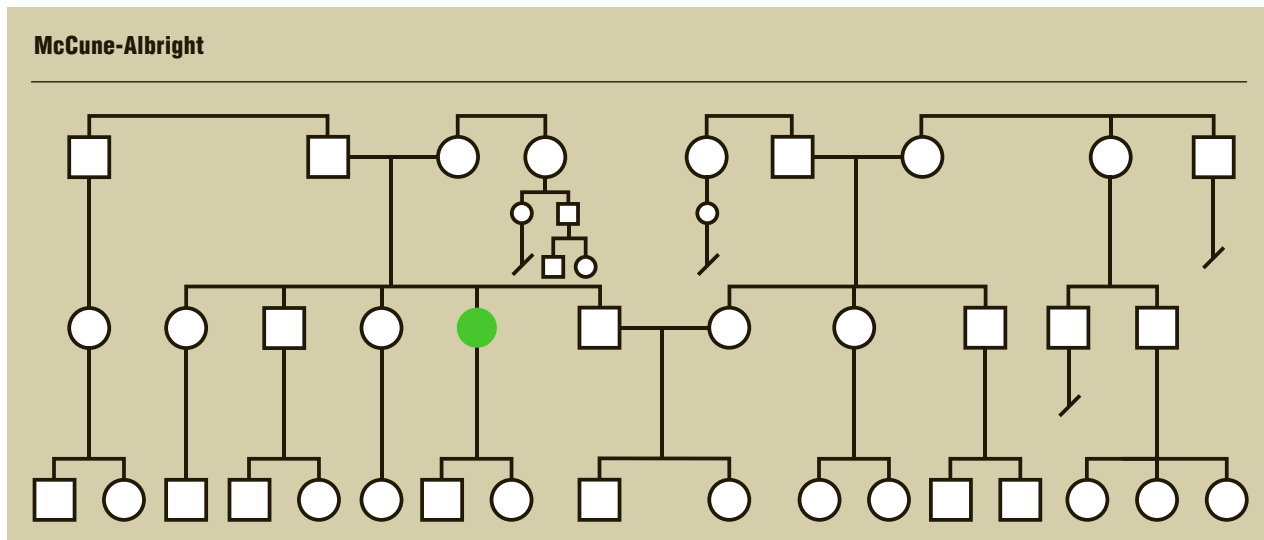
McCune-Albright syndrome (MAS) is an uncommon disorder in which a mutation distributed across various cell populations results in a wide variety of clinical features. The most notable features are abnormal bone development, pigmented skin spots, and endocrine gland dysfunction.

Genetic profile

McCune-Albright syndrome is not hereditary, but scientists have identified a specific genetic defect that causes MAS. The defect is a mutation in the *GNAS1* gene, which is associated with a type of G protein. These proteins are present in a wide variety of cells in the body. G proteins are part of the system of proteins and enzymes that regulate communication between cells and various agents such as hormones and the nervous system. If a cell's G protein is abnormal, this sets off a chain reaction that causes the cell to multiply inappropriately, and the subsequent cells produce too much hormone. The mutation first occurs in a single cell during the early stages of formation of the embryo. This cell multiplies into many other cells that eventually become part of the bones, skin, and endocrine glands. The severity of the syndrome is dependent on the percentage of cells involved. The earlier the mutation occurs, the more cells that will be affected. There is some evidence that a second mutation must occur before the clinical manifestations become evident.

Demographics

McCune-Albright syndrome is a rare genetic disorder with unknown incidence. It occurs equally in all races. Precocious puberty is far more common in affected girls than in boys, while other manifestations of the syndrome are believed to occur equally in both sexes. MAS has an estimated worldwide prevalence of between one in 100,000 and one in 1,000,000.



McCune-Albright: pedigree analysis chart (Gale)

Signs and symptoms

Three main features classically characterize McCune-Albright syndrome.

Abnormal bone development

Pockets of abnormal fibrous tissue develop within the bone, which may cause deformity, fractures, and nerve entrapment. Most of these lesions appear during the first decade of life. The pelvis and femur, or thighbone, are the most commonly involved areas of the skeleton. Bony abnormalities in the skull can cause blindness or deafness. The majority of patients with MAS have many of these lesions, hence the name polyostotic fibrous dysplasia.

In addition to these fibrous lesions, some patients develop osteosarcoma, which is a malignant tumor of the bone. Although it has not been proven, these tumors may originate from the fibrous lesions within the bone.

Pigmented skin spots

Patients with MAS typically have pigmented skin lesions called *café au lait* spots. These are flat areas of discoloration of the skin that may be associated with a variety of conditions. Those that are found in MAS have irregular borders. They are located on one side of the body, usually on the buttocks or lower back. Sometimes these lesions are present at birth.

Endocrine gland dysfunction

McCune-Albright syndrome is striking for its association with a number of endocrine abnormalities. Endocrine glands are those that secrete hormones directly into the bloodstream to be transported to other tissues of the

body. In MAS, one or more of these glands secrete abnormally high amounts of hormone.

The most common endocrine abnormality in MAS is excessive function of the gonads, which are ovaries in females and testicles in males. The ovaries secrete estrogen, and the testicles secrete testosterone. When these organs secrete too much estrogen or testosterone in children, the result is early puberty. Females are more commonly affected than males. In fact, early puberty in a girl is the hallmark sign of MAS. Typically, these girls develop secondary sexual characteristics, such as breasts and pubic hair, before the age of nine. Menses also begins early. Sometimes the normal sequence of development is disrupted, in that affected girls might have menses before breast or pubic hair development.

Hyperfunction of the pituitary gland also occurs in MAS, resulting in excess production of growth hormone and/or prolactin. Excess growth hormone leads to acromegaly, or marked overgrowth of certain bones and tissues, especially in the face and extremities. Some people with acromegaly grow to very tall stature. Acromegaly in MAS affects boys and girls equally. If too much prolactin is produced, then breast tissue will secrete milk inappropriately, in both boys and girls. This is called galactorrhea. In some patients, the pituitary gland dysfunction is caused by a tumor.

Other endocrine glands that may be hyperactive are the thyroid and adrenal glands. The thyroid gland produces thyroid hormones, which help regulate the body's metabolism. If excess thyroid hormones are produced, i.e., hyperthyroidism, then patients may have diarrhea, weight loss, nervousness, tremor, and rapid heartbeat. In

KEY TERMS

Dysplasia—The abnormal growth or development of a tissue or organ.

Pituitary gland—A small gland at the base of the brain responsible for releasing many hormones, including luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

some patients, thyroid nodules cause hyperthyroidism. The adrenal gland produces several hormones in the steroid hormone class, such as cortisol, aldosterone, and testosterone. Cortisol is most commonly over-produced. Similar to the pituitary gland, hyperfunction of the adrenal gland in MAS is sometimes caused by tumors.

Another feature of McCune-Albright syndrome is phosphate deficiency caused by excess excretion of phosphate in the urine. Since phosphate is a vital mineral for bone formation, this results in soft bones and some degree of pain. This condition is called rickets in children, and osteomalacia in adults. There are two theories that have been proposed to explain the loss of phosphate in the urine. First of all, it is thought that the fibrous bone lesions may produce an agent that circulates through the blood stream to the kidneys that makes the kidneys unable to retain phosphate. Secondly, perhaps the kidneys are intrinsically unable to retain the appropriate amount of phosphate.

It is important to emphasize the variability of clinical features among patients with MAS. Not every patient has the three features of bony lesions, pigmented skin spots, and endocrine abnormalities. Each patient is affected uniquely. There are rare subtypes of the syndrome in which patients have hepatitis, cardiac arrhythmias, or intestinal polyps.

Gastrointestinal issues

MAS may be associated with a broad spectrum of gastrointestinal (GI) diseases. Neonatal cholestasis and hepatitis have been reported in infants, and a variety of hepatobiliary abnormalities have been reported in adults, including hepatocellular adenomas, choledochal cysts, and inflammatory adenomas. However, the clinical spectrum and prevalence of MAS-associated GI disease are not well established. Gastric polyps may be asymptomatic or associated with symptoms of reflux. Activating GNAS mutations are known drivers for the development of intraductal papillary mucinous neoplasms (IPMNs). These pancreatic cysts have been reported in up to 40% of patients with MAS and have rarely been associated

with obstructive pancreatitis and diabetes. Gastrointestinal evaluation, including pancreatic imaging, should therefore be considered in all symptomatic patients.

One study described the clinical and radiographic GI abnormalities associated with MAS. The results of the study revealed that GI manifestations in MAS are common, and that patients with MAS may benefit from being evaluated for GI pathology. When compared with screened patients without GI disease, those with MAS-linked GI pathology had an increased frequency of acute pancreatitis, diabetes mellitus, and fibrous dysplasia. The optimal care for GI findings in MAS remains to be defined, but at the minimum, a thorough GI history at every visit and consideration of imaging with abdominal magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP) are warranted.

Diagnosis

There is no single test that is diagnostic for MAS. Certain clinical features can be easily observed, such as skin pigmentation and early puberty. X-ray can confirm the bony abnormalities. Blood tests for hormone levels can detect endocrine gland dysfunction.

Treatment and management

There is no specific treatment that cures the disease. Testalactone and fadrozole are drugs that inhibit estrogen production and have been successful in the short-term treatment of girls with early puberty, but long-term treatment has not been very effective. Patients with pituitary tumors may benefit from drugs to reduce tumor size, or surgery to remove the tumors. Thyroid nodules can be treated by surgical removal or destruction with radioactive iodine. Thyroid-inhibiting medications such as propylthiouracil and methimazole are also used for the treatment of MAS. In addition, adrenal tumors can be removed by surgery, and bone grafting, pinning, and casting are techniques used in the treatment of MAS.

Clinical trials

The National Institutes of Health (NIH) and other agencies sponsor clinical trials on MAS and related conditions.

Examples include:

- The evaluation of the effectiveness of Arimidex in the treatment of precocious puberty in girls with MAS. (NCT00055302)
- A study to determine the efficacy of Fulvestrant in the treatment of precocious puberty in girls with MAS. (NCT00278915).

QUESTIONS TO ASK YOUR DOCTOR

- What is McCune-Albright Syndrome (MAS)?
- What treatments are available for the symptoms I am suffering?
- What are the costs and potential side effects of these treatment options?
- What bones are most affected by MAS?
- What screening options are available to me if I have MAS, and I wish to have children?

- Screening and natural history of patients with polyostotic fibrous dysplasia and McCune-Albright Syndrome. (NCT00001727).

NIH constantly updates clinical trial information, and the most recent information on MAS trials can be found at: <http://www.clinicaltrials.gov>

Prognosis

The lifespan in patients with McCune-Albright syndrome is essentially normal. Women who experienced early puberty as girls are generally fertile.

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ORGANIZATIONS

Eunice Kennedy National Institute of Child Health and Human Development (NICHD), P.O. Box 3006, Rockville, MD 20847, (800) 370-2943, (866) 760-5947, NICHDInformationResourceCenter@mail.nih.gov, <http://www.nichd.nih.gov>

MAGIC Foundation, 4200 Cantera Drive, #106, Warrenville, Illinois 60555, (630) 836-8200 or (800) 362-4423, (708) 383-0899, contactus@magicfoundation.org, <http://www.magicfoundation.org>

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), 1 AMS Circle, Bethesda, MD 20892-3675, (301) 565-2966, (877) 226-4267, (301) 718-6366, NIAMInfo@mail.nih.gov, <http://www.niams.nih.gov>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 263-9938, <http://www.rarediseases.org>

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McCusick-Kaufman syndrome

Definition

McCusick-Kaufman syndrome (MKS) is a developmental disorder characterized by a group of conditions that includes congenital heart disease, buildup of fluid in the female reproductive tract, and extra toes and fingers.

Description

McKusick reported the first case of a disorder which he called hydrometrocolpos syndrome in 1964. Shortly thereafter, Kaufman described another individual with a very similar group of abnormalities. Subsequent writers combined these syndromes into one, calling it McKusick-Kaufman syndrome and characterizing its wide range of features.

MKS is the first human disorder to be attributed to a mutation occurring in a gene and affecting a type of molecule called a chaperonin. Chaperonins are sometimes called “protein cages” in that they protect cells by capturing and refolding misshapen proteins that could otherwise interfere with normal cellular functions.

Genetic profile

MKS is inherited in an autosomal recessive pattern, meaning that a child must inherit two altered genes, one from each parent, to be affected. An altered gene responsible for a rare developmental syndrome found predominantly among the Old Order Amish population has been identified. Mutations in the gene responsible for MKS have been identified on chromosome 20p12 in an Amish family. Scientists have isolated the McKusick-Kaufman syndrome gene by positional cloning.

Based on an earlier genetic analysis of the Old Order Amish population, a research group looked at a region of chromosome 20 thought to contain the gene responsible for the syndrome. A technique called sample sequencing was then used to find candidate genes in that region. One of those genes, dubbed *MKS*, was altered in a sample from an Amish person as well as in a sample from a non-Amish person diagnosed with MKS. In both people, errors or “misspellings” in the genetic code were found that would disturb the function of the *MKS* gene. It was observed that the chemical building blocks (amino acids) coded by the *MKS* gene appeared to be very similar to those that make up the chaperonins. Although the function of the protein made by the *MKS* gene is unclear, it appears to be involved in the production of proteins associated with the development of limbs, the heart, and the reproductive system.

In 2000, researchers identified a gene mutation that causes Bardet-Biedel syndrome (BBS), a rare genetic disorder that is related to MKS. BBS is believed to be due to a complete absence of the gene responsible for MKS.

Demographics

Between 1% and 3% of the Amish people of Lancaster County, Pennsylvania, are believed to be carriers of the disease, having just one copy of the altered gene.

KEY TERMS

Atresia—An abnormal condition in which a structure that should be hollow is fused shut.

Chaperonin—A molecule that captures and refolds misshapen proteins that might interfere with normal cellular functions; also called a protein cage.

Choanal atresia—A bony or membranous blockage of the passageway between the nose and pharynx at birth.

Cryptorchidism—A condition in which one or both testes fail to descend normally.

Dysplasia—The abnormal growth or development of a tissue or organ.

Genome—A term used to describe a complete representation of all of the genes in a species.

Hydrometrocolpos—An abnormal accumulation of fluids in the uterus and vagina.

Hydrops fetalis—A condition characterized by massive edema in a fetus or newborn.

Hypospadias—An abnormality of the penis in which the urethral opening is located on the underside of the penis rather than at its tip.

Polydactyly—The presence of extra fingers or toes.

Positional cloning—Cloning a gene simply on the basis of its position in the genome, without having any idea of the function of the gene.

Tracheo-esophageal fistula—Abnormal connection between the trachea and esophagus, frequently associated with the esophagus ending in a blind pouch.

The related Bardet-Biedel syndrome is estimated to occur between 1 in 125,000 and 1 in 160,000 people. Among an isolated community in Newfoundland, Canada, the prevalence is estimated to be ten times higher.

Signs and symptoms

Many abnormalities associated with MKS are visible in a physical exam. They include the following abnormalities:

- Limbs: polydactyly (extra fingers or toes)
- Genitourinary system in females: hydrometrocolpos (accumulation of fluids in the uterus and vagina), transverse vaginal membrane, vaginal atresia (absence of a vagina)
- Genitourinary system in males: hypospadias (abnormal opening of the urinary tract), prominent scrotal raphe

(ridges), micropenis, cryptorchidism (undescended testicles)

- Cardiac: congenital heart defects
- Head: pituitary dysplasia (abnormal development of the pituitary gland), choanal atresia (bony or membranous blockage of the passageway between the nose and pharynx), retinitis pigmentosa (overactive cells in the retina of the eye leading to blindness), tracheo-esophageal fistula (abnormal passage in the throat region)
- Skeleton: vertebral anomalies
- Abdomen: distension, peritoneal cysts, Hirschsprung megacolon (enlarged and poorly functioning large intestine)
- Other: nonimmune hydrops fetalis (massive build-up of fluids in a fetus or newborn)

Diagnosis

A diagnosis of McKusick-Kaufman syndrome is usually made at birth when a newborn is given a post-natal physical exam. The diagnosis is made by noting physical abnormalities such as: polydactyly, hydrometrocolpos, a transverse vaginal membrane, vaginal atresia, hypospadias, prominent scrotal raphe, micropenis, cryptorchidism, congenital heart defects, pituitary dysplasia, choanal atresia, tracheo-esophageal fistula, vertebral anomalies, abdominal distension, peritoneal cysts, Hirschsprung megacolon, or nonimmune hydrops fetalis. The probability of a correct diagnosis increases with each additional abnormality present. A diagnosis may sometimes be confirmed with a chromosomal analysis. Abnormal development of the pituitary gland (pituitary dysplasia) and vertebral abnormalities are visible in a CT or MRI scan. Peritoneal cysts are commonly diagnosed by ultrasonography.

Treatment and management

Treatment of MKS is limited to surgical correction of defects. Timing is often important. Many abnormalities, if uncorrected, can quickly become life threatening. For example, hydrops fetalis is often fatal. Genetic counseling before marriage is recommended for persons who are possible carriers of MKS. Affected rural and Amish girls should be delivered in settings that allow rapid surgical intervention and correction of abnormalities. Such actions could be lifesaving.

Prognosis

With appropriate genetic counseling and complete family histories, individuals born with MKS can receive prompt treatment. With rapid initial surgical intervention, most of these persons can live relatively normal lives.

QUESTIONS TO ASK YOUR DOCTOR

- What is the genetic cause for McKusick-Kaufman syndrome?
- What are the most common symptoms of this disorder?
- How is McKusick-Kaufman syndrome diagnosed in an infant?
- What types of surgery are used to treat the symptoms of McKusick-Kaufman syndrome, and what risks are associated with each procedure?

Some abnormalities, such as hypospadias, vaginal atresia, choanal atresia, tracheo-esophageal fistula, or Hirschsprung megacolon, may require multiple operations. Due to the risk of retinitis pigmentosa, vision should be monitored closely.

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ORGANIZATIONS

Hypospadias & Epispadias Association, 235 W. 102nd St., No. 5E, New York, NY 10025, <http://www.heainfo.org>

National Institutes of Health, Office of Rare Diseases Research, 6701 Democracy Blvd., Suite 1001, MSC 4874, Bethesda, MD 20892, (301) 402-4336, ordr@nih.gov, <http://www.rarediseases.info.nih.gov>

L. Fleming Fallon, Jr., MD, PhD, DrPH

Meckel syndrome see **Meckel-Gruber Syndrome**

Meckel-Gruber syndrome

Definition

Meckel-Gruber syndrome (MGS) is an inherited condition that causes skull abnormality, enlarged cystic kidneys, liver damage, and extra fingers and toes. Findings vary between affected infants (even in the same family), as well as between ethnic groups. Infants with MGS are usually stillborn or die shortly after birth.

Description

The first reports of MGS were published in 1822 by Johann Friedrich Meckel. G. B. Gruber also published reports of MGS patients in 1934 and gave it the name dysencephalia splanchnocystica. MGS is also known as Meckel syndrome and Gruber syndrome.

MGS affects many different organ systems including the central nervous system (brain and spinal cord), face, kidneys, liver, fingers and toes, and occasionally the bones of the arms and legs. Some researchers believe that abnormal development and differentiation of the embryonic mesoderm (the early tissue layer that contributes to the formation of the bones, cartilage, muscles, reproductive system, blood cells, heart, and kidneys) is related to MGS. The cells of the mesoderm must divide, migrate, associate, and specialize in a precise manner to form these body parts. A problem in any step of this process can lead to multiple abnormalities in various organ systems.

Since MGS causes severe birth defects and death in the newborn period, it can be devastating for families. Extensive examination and autopsy are often needed to confirm a diagnosis of MGS, delaying the family's answers regarding their child's death. Most parents do not know they are at risk until they have a child with MGS. This can cause feelings of anger, disbelief, and guilt.



This example of Meckel's diverticulum is the pouch (upper center) protruding from the wall of the small intestine. (CNRI/Science Source)

Genetic profile

The autosomal recessive inheritance pattern in MGS is well-documented. MGS affects males and females equally. Parents of affected children are assumed to be carriers and have a 25% chance of MGS recurrence in each pregnancy. A healthy brother or sister of an affected child has a two-thirds chance of being an MGS carrier.

Research involving families in Finland (where MGS is more common) led to the first MGS gene being mapped (localized) to the short arm of chromosome 17. This means that the gene location has been narrowed down to a small potential area, but the exact location and precise details about the gene are still unknown. Non-Finnish families did not show evidence of a causative gene linked to chromosome 17. This led to the search for a second MGS gene. Studies of Northern African and Middle Eastern families resulted in the second MGS gene being mapped to the short arm of chromosome 11. More research is being performed to learn more about the precise location of both MGS genes, gene changes that cause MGS, and the role of the genes in early development.

Demographics

MGS has an estimated incidence between 1 in 13,000 births and 1 in 140,000 births. This means that between 1 person per 50 and 1 person per 180 is an MGS carrier. The incidence varies among ethnic groups. Several ethnic populations have an increased incidence of MGS. The incidence in Finland is 1 in 9,000 births (1 person in 50 is a carrier). The incidence is also higher among Belgians and Bedouins in Kuwait with 1 affected birth in 3,500 (1 person in 30 is a carrier). The highest incidence is reported in the Gujarati Indians with 1 affected birth per 1,300 (1 person in 18 is a carrier). The incidence among Jews in Israel is 1 in 50,000 (1 person in 112 is a carrier). Cases of MGS have been reported in North America, Europe, Israel, Indonesia, India, Kuwait, and Japan.

Signs and symptoms

The three hallmark features of MGS are encephalocele, polycystic kidneys, and polydactyly. Approximately 90% of infants with MGS have an encephalocele. This is an opening in the skull that allows brain tissue to grow outside of the skull. Nearly 100% of infants with MGS have enlarged kidneys with cysts. Polydactyly (extra fingers and/or toes) is present in about 80% of affected children. The polydactyly is usually postaxial (the extra fingers/toes are on the same side of the hand/foot as the smallest finger/toe). In MGS, the polydactyly usually affects both the hands and feet. There may also be webbing of the fingers and toes—the skin between the fingers

KEY TERMS

Bile duct—A passageway that carries bile (fluid secreted by the liver involved in fat absorption) from the liver to the gallbladder to the small intestine.

Clubfoot—Abnormal permanent bending of the ankle and foot. Also called *talipes equinovarus*.

Trimester—A three-month period. Human pregnancies are normally divided into three trimesters: first (conception to week 12), second (week 13 to week 24), and third (week 25 until delivery).

or toes fails to separate—leaving the digits attached to each other.

Internal examination of babies with MGS revealed that virtually 100% have liver abnormalities. This can include halted development of the bile ducts, extra bile ducts, enlarged bile ducts, and loss of blood vessels. The liver is also usually enlarged. These liver changes are now considered by most to be another hallmark feature of MGS.

Babies with MGS often have similar facial features. Some reported features are eyes that are closer together or farther apart than usual, broad and flat nose, broad cheeks, and a wide mouth with full lips. Other features are commonly seen in MGS and are thought to be caused by a low amount of amniotic fluid surrounding the baby before birth. These features are sloping forehead, small jaw, low-set ears, and short, webbed neck. Low fluid prior to birth also frequently causes clubfoot in the newborn.

Other common features of MGS are abnormalities of the genitalia and cleft palate. The external (visible) genitalia are often small or ambiguous (not clearly male or female). There have also been reports of babies with MGS having both male and female reproductive parts (hermaphrodite). Cleft palate is seen in about 45% of babies with MGS. Cleft lip is less common but has been reported.

The symptoms of MGS are variable. Not all infants with MGS show the same signs, and the characteristic signs range in severity. Some features have been described in some babies with MGS but are not as common. These include heart defects, enlarged spleen, extra spleen, hydrocephaly (extra water in the brain), absence or underdevelopment of other brain structures, and arm and leg bones that are shortened, thickened, and bowed.

QUESTIONS TO ASK YOUR DOCTOR

- How early in a pregnancy can Meckel-Gruber syndrome be diagnosed, and how is that diagnosis made?
- What information can a genetic counselor provide my spouse and me about this genetic disorder?
- Are there treatments available that will prolong the life of a child with Meckel-Gruber syndrome and/or make the child's life more comfortable?
- What is the status of current research on Meckel-Gruber syndrome?

Diagnosis

Some of the features of MGS can be detected by prenatal ultrasound early in the second trimester. At that time, an encephalocele can often be seen as well as other brain abnormalities. Enlarged kidneys can also be detected at this time. As the pregnancy continues, a low amount of amniotic fluid becomes apparent. Enlarged kidneys make the abdomen appear and measure larger than usual. Cysts make the kidneys appear bright or white on an ultrasound instead of the usual gray color.

Measurement of the alpha-fetoprotein (AFP) level from either maternal blood or amniotic fluid may help to detect an encephalocele (although most encephaloceles are closed and do not elevate AFP levels). AFP can be measured in amniotic fluid after about 12 weeks of pregnancy and in maternal blood after about 15 weeks of pregnancy. AFP elevation in either test increases the chance of an encephalocele or other abnormality in the baby's skull or spine.

When signs of MGS are seen on prenatal ultrasound in the absence of a family history, MGS is often suspected but not confirmed until after birth and autopsy. A chromosome test can be performed before birth to rule out chromosome abnormalities such as trisomy 13. However, autopsy is usually needed to distinguish MGS from other syndromes with similar features. Every organ system of the baby is carefully examined for abnormal development.

Families at risk for recurrence of MGS can combine early ultrasound with either maternal blood AFP or amniotic fluid AFP for early detection. If early ultrasound reveals no signs of MGS, later scans are still recommended

because of the variability in expression and severity. No routine genetic tests are available to these families.

Treatment and management

There is no effective treatment or cure for MGS. Babies with MGS have extensive birth defects that require many surgeries to repair. Encephaloceles can be repaired by surgery after birth. Surgeries are most successful for infants with small skull abnormalities. Encephaloceles put infants at high risk for infection. The abnormalities seen in the kidneys and liver often leave the organs nonfunctional. There is often no way to repair the organs other than transplant. Even if all of these problems could be solved, infants with MGS often have underdeveloped lungs that cannot support life after birth. The lungs are underdeveloped because of the low amount of amniotic fluid prior to birth. Due to the extensive birth defects, the extensive surgeries needed to correct them, and the poor prognosis, babies born with MGS are given minimum care for comfort and warmth.

When MGS is suspected in an unborn baby, parents should be given information about the range of symptoms of MGS and the poor prognosis. Parents should also be cautioned that a diagnosis of MGS often cannot be confirmed until after birth. Prognosis can vary if the baby has atypical signs of MGS or if the baby has a different syndrome. Elective termination of affected pregnancies may be an option for some couples.

Prognosis

The prognosis for MGS is quite poor. Many infants with MGS are stillborn. Those that are born alive usually die shortly after birth in the first hours, days, or weeks of life. Death is usually due to inability to breathe (underdeveloped lungs), infection (opening in the skull), or organ failure (decreased function of kidneys and liver). MGS is variable, and there have been reports of infants with milder symptoms living longer. One infant with MGS lived until four months of age. Another lived to seven months of age after surgical repair of a small encephalocele. At birth he had cystic kidneys but normal kidney function. These two case reports show that longer survival is rare but possible because of the variable expression of MGS.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06180, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>.

Amie Stanley, MS

Meckel's diverticulum

Definition

Meckel's diverticulum is a congenital pouch (diverticulum) approximately 2 in. (4 cm) in length and located at the lower (distal) end of the small intestine. It was named for Johann F. Meckel, a German anatomist who first described the structure.

Description

The diverticulum is best described as a blind pouch that is a remnant of the omphalomesenteric duct or yolk sac that nourished the early embryo. It contains all layers of the intestine and may have ectopic tissue present from either the pancreas or stomach.

The rule of twos is the classical description. It is located about two feet from the end of the small intestine, is often about two inches in length, occurs in about 2% of the population, is twice as common in males as females, and can contain two types of ectopic tissue—stomach or pancreas. Many people who have a Meckel's diverticulum never have trouble, but those that do present in the first two decades of life, and often in the first two years.

There are three major complications that may result from the development of Meckel's diverticulum. The most common problem is inflammation or infection that mimics appendicitis. This diagnosis is defined at the time of surgery for suspected appendicitis. Bleeding caused by ectopic stomach tissue that results in a bleeding ulcer is the second most frequent problem. Bleeding may be brisk or massive. The third potential complication is obstruction due to intussusception, or a twist around a persistent connection to the abdominal wall. This problem presents as a small bowel obstruction.

However, the true cause is identified at the time of surgical exploration.

Genetic profile

Meckel's diverticulum is not hereditary. It is a vestigial remnant of the omphalomesenteric duct, an embryonic structure that becomes the intestine. As such, there is no genetic defect or abnormality.

Demographics

Meckel's diverticulum is a developmental abnormality that is present in about 2% of people, but does not always cause symptoms. Meckel's diverticula (plural of diverticulum) are found twice as frequently in men as in women. Complications occur three to five times more frequently in males.

Signs and symptoms

Symptoms usually occur in children under ten years of age. There may be bleeding from the rectum, pain and vomiting, or simply tiredness and weakness from unnoticed blood loss. It is common for a Meckel's diverticulum to be mistaken for the much more common condition appendicitis. If there is obstruction, the abdomen will distend and there will be cramping pain and vomiting.

Diagnosis

The situation may be so acute that surgery is needed on an emergency basis. This is often the case with bowel obstruction. With heavy bleeding or severe pain—whatever the cause—surgery is required. The finer points of diagnosis can be accomplished when the abdomen is open for inspection during a surgical procedure. This situation is called an acute abdomen.

If there is more time (not an emergency situation), the best way to diagnose Meckel's diverticulum is with a nuclear scan. A radioactive isotope injected into the bloodstream accumulates at sites of bleeding or in stomach tissue. If a piece of stomach tissue or a pool of blood shows up in the lower intestine, Meckel's diverticulum is indicated.

Treatment and management

A Meckel's diverticulum that is causing discomfort, bleeding, or obstruction must be surgically removed. This procedure is very similar to an appendectomy.

Prognosis

The outcome after surgery is usually excellent. The source of bleeding, pain, or obstruction is removed, so

KEY TERMS

Appendectomy—The procedure to surgically remove an appendix.

Appendicitis—Inflammation of the appendix.

Appendix—A portion of intestine attached to the cecum.

Catecholamines—Biologically active compounds involved in the regulation of the nervous and cardiovascular systems, rate of metabolism, body temperature, and smooth muscle.

Cecum—The first part of the large bowel.

Congenital—Refers to a disorder that is present at birth.

Connective tissue—A group of tissues responsible for support throughout the body; includes cartilage, bone, fat, tissue underlying skin, and tissues that support organs, blood vessels, and nerves throughout the body.

Distal—Away from the point of origin.

Diverticulae—Sacs or pouches in the walls of a canal or organ. They do not normally occur, but may be acquired or present from birth. Plural form of diverticula.

Ectopic—Tissue found in an abnormal location.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Intussusception—One piece of bowel inside another, causing obstruction.

Isotope—Any of two or more species of atoms of a chemical element with the same atomic number and nearly identical chemical behavior but with differing atomic mass and physical properties.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Linkage analysis—A method of finding mutations based on their proximity to previously identified genetic landmarks.

Peptic ulcer—A wound in the bowel that can be caused by stomach acid or a bacterium called *Helicobacter pylori*.

Tortuous—Having many twists or turns.

Volvulus—A twisted loop of bowel causing an obstruction.

the symptoms also disappear. A Meckel's diverticulum will not return.

Resources

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"Pediatric Meckel Diverticulum." Medscape. <https://emedicine.medscape.com/article/931229-overview> (accessed June 14, 2021).

ORGANIZATIONS

American Academy of Family Physicians (AAFP), 11400 Tomahawk Creek Pkwy., Leawood, KS 66211-2680, (913)

906-6000 or (800) 274-2237, (913) 906-6075, <http://www.aafp.org>

American Academy of Pediatrics, 141 Northwest Point Blvd., Elk Grove Village, IL 60007-1098, (847) 434-4000 or (800) 433-9016, (847) 434-8000, csc@aap.org, <http://www.aap.org>

American College of Gastroenterology, 6400 Goldsboro Rd., Ste. 200, Bethesda, MD 20817, (301) 263-9000, info@acg.gi.org, <http://www.gi.org>

American College of Surgeons, 633 N. St. Clair St., Chicago, IL 60611-3211, (312) 202-5000 or (800) 621-4111, (312) 202-5001, postmaster@facs.org, <http://www.facs.org>

American Medical Association (AMA), AMA Plaza, 330 N. Wabash Ave., Chicago, IL 60611-5885, (800) 621-8335, <http://www.ama-assn.org/ama>

L. Fleming Fallon, Jr., MD, PhD, DrPH

Mediterranean anemia see **Beta-thalassemia**

Medium-chain acyl-coenzyme A see **MCAD deficiency**

Meier-Gorlin syndrome (MGORS) see **Primordial dwarfism**

Melanoma

Definition

Melanoma is a type of cancer most often found in the skin, but occasionally in the eye, throat, or intestines. Its name is derived from the Greek word for black. Melanocytes, the pigmented cells that produce a brownish-black pigment known as melanin and are responsible for racial variations in skin color, the color of moles, and tanning in response to sun exposure, are the cells that give rise to melanoma. In malignant melanoma, the melanocytes become cancerous and may spread throughout the body to invade other organs and tissues.

Demographics

Melanoma accounts for only 4% of skin cancers in the United States; however, it is responsible for 75% of deaths from skin cancer. According to the National Cancer Institute (NCI), 106,110 new cases of melanoma will be diagnosed in the United States in 2021 (about 62,260 cases in men, and 43,850 in women), or about 5.6% of all cancers; and 7,180 people will die from the disease (4,600 men, and 2,580 women), or about 1.2% of all cancer deaths. There are about 500 cases of melanoma diagnosed in children each year in the United States. Melanoma was considered a rare form of cancer until the 1970s, but its rate among Caucasians in the United States has tripled since 1985. Unlike many cancers, which are declining in incidence as of 2021, the incidence of primary cutaneous malignant melanoma has been steadily increasing since 1980, possibly related to increased sun exposure and the popularity of tanning salons. Currently, the risk is about 22.8 per 100,000 people in the general American population.

Melanoma affects all age groups but is most commonly seen in adult patients; the average age at the time of diagnosis is 65 as of 2021. Nonetheless, the rate of melanoma is rising more rapidly among young people than among older adults; melanoma is now the most common cancer diagnosed in young adults between the ages of 25 and 29. The current overall lifetime risk of melanoma in the United States is about 2.6% (one person in 38) for Caucasians; 0.1% (one in 1,000) for African Americans; and 0.6% (one in 167) for Hispanics/Latinos.

One of the more unusual findings in the United States in recent years is the rapid increase of deaths from melanoma in older males. Although the death rate among younger men (age 44 or younger) has dropped since the late 1990s, most likely as a result of public health education campaigns about the dangers of sun exposure, it has risen 66% in men between the ages of 45 and 64, and 157% in men over 65. By age 80, American men are three times as likely to die of melanoma as are women of the same age.

According to the Melanoma Network of Canada, melanoma is the seventh most commonly diagnosed cancer in Canada. The network estimates that 8,200 Canadians (4,500 men, and 3,700 women) will be diagnosed with melanoma in 2021, and that 1,300 (870 men and 430 women) will die from this form of cancer.

The highest rates of melanoma in the world, however, are not found in the United States or Canada but in Australia and New Zealand. According to Melanoma Institute Australia, melanoma could be called Australia's national cancer. In 2021, the institute estimates that 16,000 Australians will be diagnosed with melanoma, and 1,300 will die from it. It is the single most common cancer in Australians between the ages of 15 and 39.

Description

The epidermis, the uppermost layer of skin, contains melanocytes, the cells that make melanin, which is the pigment that gives skin its hue. Melanin is responsible for the color of a person's skin, hair, and eyes. There are between 1,000 and 2,000 melanocytes in each square millimeter of human skin. The difference in skin color between fair-skinned and darker-skinned people is not based on the number of melanocytes in the skin but on their level of activity. When skin is exposed to the sun, the melanocytes become more active, produce more melanin, and cause the skin to darken—that is, they cause a suntan. When a cancerous tumor develops in tissue containing melanocytes, a person is said to have melanoma.

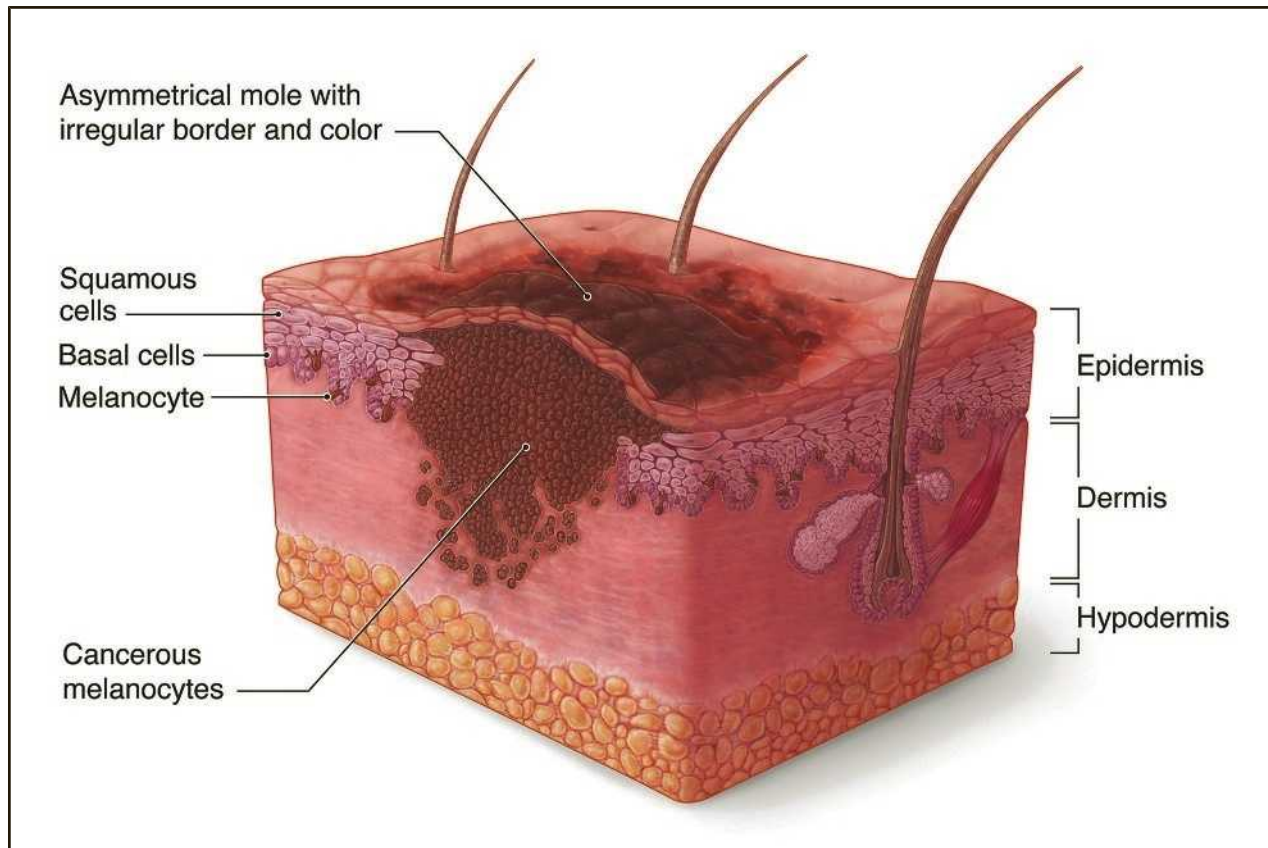
Most cases of melanoma occur in the skin (cutaneous melanoma), but sometimes melanoma can also occur in the colored layer of eye tissue—a condition known as intraocular or uveal melanoma.

Cutaneous melanoma

Between 70% and 80% of cutaneous melanomas arise from normal skin; the remaining 20% to 30% develop in moles (also called nevi). Moles are benign growths or collections of melanocytes on the skin surface. According to the American Academy of Dermatology, most individuals have about 30 moles on their skin. The number and type of moles that individuals have may increase the risk of melanoma. People with more than 50 moles or with moles that are unusual and irregular-looking (doctors call these dysplastic nevi or atypical moles) are at increased risk of developing melanoma.

There are four major types of cutaneous (skin-based) melanoma:

- Superficial spreading melanoma accounts for 70% of all cases of melanoma and typically occurs in younger people. This type of melanoma takes a long time to penetrate the top layer of skin, and the first sign of it is a



Melanoma, a type of skin cancer that develops in melanocytes, creating asymmetrical moles with irregular borders and discoloration. Melanocytes produce melanin, the pigment that gives color to the skin. Prolonged exposure to ultraviolet (UV) light can damage melanocyte DNA, causing cells to replicate out of control and even spread to other parts of the body. (Evan Oto/ Science Source)

flat or slightly raised skin lesion. The lesion may be discolored with irregular borders and may develop out of a previously benign mole. It is most likely to occur on the trunk in men, the legs in women, and the upper back in men and women.

- Lentigo maligna is another form of melanoma that is most often found in older adults. It begins as a flat or slightly raised tan, brown, or dark brown skin discoloration that remains close to the skin's surface. Once the malignancy spreads, it is referred to as lentigo maligna melanoma. It accounts for 5% to 10% of melanoma cases.
- Acral lentiginous melanoma is the most common type of melanoma in African Americans and Asians, and is least common among Caucasians. It accounts for 7% to 10% of melanomas. The black or brown discoloration of acral lentiginous melanoma first spreads along the surface of the skin, often under the nails or on the soles of the feet or palms of the hands.
- Nodular melanoma, which accounts for 15% to 20% of all melanoma cases, is the most aggressive form of melanoma, and by the time it is diagnosed, it may have spread to other areas of the body. This type of melanoma

starts as a lump that is usually black in color. Nodular melanoma is found most frequently on the trunk, legs, and arms, and most often affects older people.

Superficial spreading melanoma, lentigo maligna melanoma, and acral lentiginous melanoma begin as in situ malignancies, which means they affect only the top layers of skin. Eventually, these forms of melanomas may become invasive and spread to other areas of the body. Nodular melanoma is often invasive by the time it is diagnosed, however.

Intraocular (uveal) melanoma

Intraocular melanoma, or melanoma within the eye, is a cancer that develops in the parts of the eye that contain melanocytes—the iris and other nearby structures that belong to the uvea, the middle pigmented layer of the eye. About 5% of uveal melanomas develop in the iris, with the majority being found in the posterior uvea. Melanomas in the iris usually involve mutations in the *BRAF* gene, while melanomas in the posterior uvea are more often caused by *GNAC/GNA11* mutations. There are about 2,500 cases of

KEY TERMS

Adjuvant therapy—Treatment given to patients who are at risk of having microscopic untreated disease present but have no obvious symptoms.

Breslow depth—A measurement of the thickness of a cutaneous melanoma, used in staging the cancer. It is named for Alexander Breslow, an American pathologist who first identified it as a prognostic factor for melanoma in 1970.

Cutaneous—Pertaining to or affecting the skin. Most melanomas are cutaneous cancers.

Dendritic cells (DCs)—Accessory cells in the mammalian immune system that acts as messengers between the adaptive and innate immune systems. Their name is derived from their tree-like shape.

Electrodessication—A surgical technique for removing skin cancers by drying out tissue with an electric current and then removing the dead tissue with a curette.

Fitzpatrick phototype scale—A set of six skin types based on the skin's response to the ultraviolet radiation in sunlight. The scale was devised in 1975 by Thomas Fitzpatrick, a dermatologist at Harvard University. Fitzpatrick types I and II are at the greatest risk of melanoma.

Genome—The total amount of genetic information within an organism's chromosomes, including its genes and DNA sequences.

Immunotherapy—A form of treatment that uses biologic agents to enhance or stimulate normal immune function.

Melanocytes—Skin cells derived from the neural crest that produce the protein pigment melanin.

Metastasis (plural, metastases)—A tumor growth or deposit that has spread via lymph or blood to an area of the body remote from the primary tumor.

Mohs surgery—A form of microscopically controlled surgery that allows for the precise removal of cancerous tissue. It is commonly used to treat various types of skin cancer, particularly in areas of the body where preserving as much tissue as possible is essential. Mohs surgery is also known as micrographic surgery.

Nevus (plural, nevi)—The medical term for mole; it is derived from the Latin word for birthmark.

Oncogene—A gene that has the potential to cause cancer.

Oncology—The branch of medicine concerned with the study, diagnosis, treatment, and prevention of cancer.

Resection—The act of removing an organ or tissue surgically.

Spitz nevus—A benign reddish or reddish-brown skin lesion that is difficult to distinguish from melanoma and is usually removed for that reason. Spitz nevi are named for Sophie Spitz, an American pathologist who first described them in 1948.

Targeted therapy—In cancer treatment, a type of drug therapy that blocks tumors by interfering with signaling pathways or specific molecules that the cancer cells need for growth. Also called biologic therapy, targeted therapy is less harmful to normal cells than traditional chemotherapy.

Uvea—The medical term for the pigmented middle layer of the three layers of tissue comprising the eye. The uvea includes the iris, the ciliary body, and the choroid. Melanomas that develop in these structures are called uveal melanomas.

Xeroderma pigmentosum (XP)—A rare inherited skin disorder in which the skin cells lack an enzyme needed to repair damage to the cell's DNA caused by sunlight. People with XP are 1,000 times more likely to develop melanoma than people without the disorder.

intraocular melanoma diagnosed per year in the United States; it is most likely to develop in people with blue eyes and fair skin. Uveal melanoma is more common in Denmark and other Scandinavian countries than in the United States. It is slightly more common in men than in women. The average age of a person diagnosed with this type of melanoma is 55.

Intraocular or uveal melanomas can grow slowly for years without producing any symptoms, although they eventually cause blurred vision, seeing double, a sensation

of having a foreign body in the eye, gradual loss of sight, and sometimes pain in the eye. This type of melanoma often spreads from the eye to the liver, the lungs, or even the central nervous system before it is diagnosed. Most patients die from the spread of the cancer to these vital organs rather than from the effects of the cancer on the eye itself. About half of all patients diagnosed with intraocular melanoma die within 10 years after diagnosis and treatment. The standard forms of treatment for this type of cancer are radiation therapy and surgical removal of the affected eye.

Risk factors

Malignant melanoma occurs in people of all ages and ethnicities. However, certain factors put people at greater risk of developing this disease:

- Belonging to Fitzpatrick phototypes I and II: people who have fair skin; red or blond hair; and blue or green eyes. The Fitzpatrick phototypes are a set of six skin types based on the skin's response to the UV radiation in sunlight. The scale was devised by an American dermatologist in 1975.
- Being older than age 20; the rate of melanoma rises sharply after age 50.
- History of excessive sun exposure, exposure to artificial ultraviolet light (such as in tanning beds), or a history of severe (blistering) sunburns in childhood.
- Living in areas that get high levels of ultraviolet radiation, such as mountainous regions or countries closer to the Equator.
- Having a previous personal history of melanoma or another type of skin cancer.
- Having extensive scars or burns on the skin. Fragile skin is more easily damaged by sun.
- Occupational exposure to certain chemicals in the environment, including arsenic and some types of weed killers.
- Having a job that requires working outdoors during daylight hours.
- Having a close relative with melanoma; about 20% of cases of melanoma are familial.
- Having a high number of moles (50 or more).
- Having moles that are unusual in appearance or irregular in shape.

Having certain procedures or health conditions that weaken the immune system may also predispose a person to developing melanoma. Compared to people in the general population, those who have undergone organ transplants have a threefold risk of melanoma. Having human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), other forms of cancer, or autoimmune diseases that require immunosuppressive treatments can also increase a person's risk of developing malignant melanoma.

A rare inherited condition known as xeroderma pigmentosum (XP) increases a person's risk of malignant melanoma. People with XP lack an enzyme that is needed to repair damage caused by sunlight to the DNA in skin cells. Without this protective enzyme, the DNA in individual skin cells can undergo mutations leading to melanoma and other types of skin cancer. XP is inherited in an autosomal recessive manner; it can be caused by

mutations in any of nine genes (*DDB2*, *ERCC1*, *ERCC2*, *ERCC3*, *ERCC4*, *ERCC5*, *POLH*, *XPA*, or *XPC*). The average life expectancy of a person with XP is 37 years.

Causes and symptoms

Causes

ULTRAVIOLET RADIATION. The development of melanomas from normal skin is not completely understood. As of 2021, researchers think there may be two pathways to malignant melanoma, one involving exposure to sunlight and the other with melanocyte proliferation triggered by other factors. This hypothesis is based on the difference in distribution of moles on the body between patients who develop melanomas on the face and neck, and those who develop melanomas on the trunk or legs. A small percentage of melanomas arise within burn scar tissue. Researchers do not fully understand the relationship between deep burns and an increased risk of skin cancer. In general, however, melanoma is caused by the interaction of ultraviolet (UV) radiation from the sun and the melanin in melanocytes. UV radiation can damage the DNA in skin cells both directly and indirectly. Researchers have found that 92% of melanomas are caused by indirect damage to DNA, and 8% by direct damage.

When the DNA in a skin cell is damaged by UV radiation, the cell can undergo a series of mutations that lead to abnormal multiplication of new cells. In some cases, the changed DNA makes the cell more vulnerable to the damaging effects of UV radiation.

Melanomas grow in two stages or phases. The first is a phase of outward or radial growth. The second phase, which is much more dangerous, is a phase of vertical growth into deeper layers of tissue. It is during this second phase of growth that melanomas become harder to treat and more likely to spread to other parts of the body.

ENVIRONMENTAL CHANGES. Melanoma was a rare form of cancer until the twentieth century. The earliest known surgical removal of a melanoma was performed in 1787 by a British surgeon, but the disease was little studied until the 1840s and 1850s, when two other British doctors described the stages of melanoma and found that it runs in some families. The connection between melanoma and sun exposure was not made until 1956, when an Australian doctor named Henry Lancaster found that the high intensity of sunlight is a risk factor for melanoma. In the 1970s, scientists began to notice that the ozone layer—a layer of oxygen molecules consisting of three atoms of oxygen in the upper atmosphere—was becoming thinner. The ozone layer helps to block a high-energy type of ultraviolet radiation known as UVB from reaching the surface of the earth, so doctors began

to wonder whether a thinner ozone layer contributed to an increased rate of skin cancers.

As of 2021, however, doctors do not think that the rise in cases of melanoma is due primarily to changes in the ozone layer. One reason is that depletion of the ozone layer is most severe over Antarctica, which is not a heavily populated continent. It is also likely that the increase in the number of reported cases of melanoma since the 1990s is due in part to better diagnostic instruments and earlier diagnosis. A third reason is that recent advances in genetics indicate that heredity plays a larger role in melanoma than was thought to be the case in the 1980s. Still another reason is growing recognition that tanning beds, first introduced in the 1970s and increasingly popular until the early 2000s, are a major factor in increased rates of melanoma, particularly among young women. In 2015, Australia banned commercial tanning salons across the country, while the United States leaves regulation of commercial tanning to the individual states. As of 2021, 42 states and the District of Columbia either ban the use of tanning salons by teenagers below age 18 or require teens to obtain parental permission.

GENETIC FACTORS. The development of melanoma is thought to have a strong genetic link, since about 20% of people who develop melanoma also have family members with the disease. Researchers have identified mutations in genes on chromosomes 1, 9, and 12 as linked to familial melanoma, including a gene called *BRAF* that plays a role in the development of melanoma. A mutated form of *BRAF* is thought to switch on the malignant cells, allowing them to grow and divide. A positive family history of one or two first-degree relatives having had melanoma substantially increases the patient's risk for developing the disease. There is also a syndrome known as dysplastic (atypical) nevus syndrome that is characterized by atypical moles in children under age 10. Such individuals have to be monitored closely for the development of malignant melanoma.

There are mutations in about half of familial melanoma patients of the tumor-suppressing gene *CDKN2A* (also known as the *p16* gene) on chromosome 9. Mutations in another tumor suppressor gene known as *CDK4* have also been linked to melanoma. Still other genes linked to an increased risk of melanoma include *RBI*, *NF1*, *PTEN/MMAC1*, and *NRAS*. Mutations in the *NRAS* gene on chromosome 1 are found in 15% to 20% of melanomas; these melanomas are more aggressive and have a poorer prognosis than tumors without the mutation.

In addition to the genetic mutations in melanoma cells associated with early UV damage to the skin, there is evidence that more radical alterations occur at a rapid pace in end-stage disease, resulting in chaotic changes to

the genome that include increased ploidy (the number of complete chromosomes in a cell), doubling of the entire genome, and mutations in genes that ordinarily protect the integrity of the genome.

Symptoms

The first sign of melanoma is a mole, discolored lump, or other growth found on the skin. Melanomas can occur anywhere on the body, but they are most often found on the backs of men and the legs of women. Generally, melanomas are black or brown, but they may be red, skin-colored, or white. Some may develop pinkish or bluish patches mixed in with darker areas.

Changes in a mole's appearance over time may also indicate malignant melanoma. Sometimes, a growth or mole may bleed, ooze, or itch, which indicates malignancy. Having satellite moles, new moles that grow near an existing mole, may also point to this form of skin cancer. Early-stage melanomas may itch or shed small flakes of skin, while more advanced melanomas may bleed or ooze fluid as well as itch. Advanced melanomas may also become hard or lumpy in texture. However, melanomas usually do not cause pain.

People with moles, lumps, or growths that fit these criteria should be checked by a doctor.

Diagnosis

Diagnosis of melanoma begins with careful examination of the skin.

Examination

Anyone who finds an abnormal mark or mole on the skin should contact their health care provider for a skin examination. About 80% of all skin cancers are first noticed by the patient. The doctor or nurse will carefully examine all moles, birthmarks, and pigmented areas over the person's entire body, including the back, legs, hands, feet, and scalp.

Doctors often use the ABCDE mnemonic when making a diagnosis of melanoma. The letters stand for the following signs:

- **Asymmetry:** Melanomas are usually asymmetrical, with one half different from the other. A normal mole is round, whereas a suspicious mole is unevenly shaped.
- **Border:** The edges of a melanoma may be ragged or blurred. A normal mole has a clear-cut border with the surrounding skin, whereas the edges of a suspect mole are often irregular or scalloped.
- **Color:** A malignant melanoma often has several colors or shades, whereas benign moles are typically one color. Normal moles are uniformly tan or brown, but cancerous

moles may appear as mixtures of red, white, blue, brown, purple, or black.

- **Diameter:** Cancerous moles are usually larger than a pencil eraser or pea (about 6 millimeters or 1/4 inch).
- **Evolution:** A mole that changes over time in color or shape or develops itchiness or bleeding should be reported to the doctor.

A family doctor can often spot suspicious-looking changes in a patient's skin, but they will usually refer the patient to a dermatologist for a definite diagnosis. Dermatologists are doctors with specialized training in diagnosing and treating skin disorders.

To diagnose cutaneous melanoma, a dermatologist will first use a dermatoscope, which is a special palm-sized instrument with a magnifying lens and built-in light. Most modern dermatoscopes allow the doctor to toggle between polarized and nonpolarized light in order to study a mole or other skin feature in detail. The use of dermatoscopes has increased the accuracy of diagnosing malignant melanoma considerably, because the doctor can make digital images of suspicious moles or skin areas and save them for comparison with images from later checkups.

Tests

As of 2021, there are no blood or other body fluid tests that can be used to diagnose melanoma. The diagnosis is usually made by a combination of tissue analysis and (for advanced-stage disease) imaging studies. Most patients who consult a doctor have an early-stage melanoma, and extensive testing is not usually warranted. It is important to see a doctor promptly when melanoma is suspected, however; the pausing of routine office visits during COVID-19 lockdowns has already resulted in a growing number of patients whose melanomas increased in severity, with consequent worsening of outcomes.

In regard to genetic testing, most people who develop melanoma do *not* have a genetic mutation associated with this type of cancer. The American Academy of Dermatology does, however, recommend genetic counseling and possibly genetic testing for patients with one or more of the following characteristics:

- Three or more melanomas that grew deep into the skin or spread, especially if the first melanoma was diagnosed before age 45.
- Three or more blood relatives on one side of the patient's family who have had melanoma or cancer of the pancreas.
- Two or more Spitz nevi, which are benign red or reddish-brown colored patches of skin that can be difficult to distinguish from melanomas; they are usually removed by dermatologists even though they are benign.

- One or more Spitz nevus in addition to a close relative diagnosed with uveal melanoma, mesothelioma, or meningioma.

If the patient has signs or symptoms of more advanced disease, or if the lesion has penetrated deeply into the skin, imaging studies may be appropriate. These would involve CT scans of the abdomen, the chest, or regional nodal areas, or a CT or MRI of the brain. A positron emission tomography (PET) scan may also be used to look for melanoma metastases. PET scans involve the use of radioactive glucose to look for cancer cells, as cancers take up sugar more rapidly than normal tissues do.

Procedures

BIOPSY. If the dermatoscope images suggest that the patient may have melanoma, the next step is to take a sample of the abnormal mole or area of skin to be sent to a laboratory for analysis under a microscope. This procedure is called a biopsy. In the case of melanoma, the doctor will remove the entire mole rather than just a portion of it, in order to obtain an accurate measurement of its depth. It is important to establish the exact thickness of penetration of the primary tumor. If a skin lesion is suspicious, full-thickness excisional biopsy is the approach recommended. Shave biopsies and biopsies that remove only a portion of the suspect area are inappropriate. Often, in an early case, the excision involves just the suspicious lesion with minimal normal skin, but it should be a full vertical excision of the skin. Biopsies are done under topical or local anesthesia.

To evaluate whether the melanoma may have spread beyond the skin, the doctor may perform a sentinel lymph node biopsy. A sentinel lymph node is the lymph node closest to the melanoma, the one to which it is most likely to spread.

STAGING. Malignant melanoma is curable if caught early. When a melanoma is not removed in its early stages, however, cancer cells will start to grow downward from the skin surface and invade healthy tissue. The disease can then spread to other parts of the body. Measuring a cancer's size, thickness, and likelihood of spreading is called staging. Melanomas are graded in five stages, from 0 to 4. The chief factor in determining a patient's chances of recovery is the thickness of the melanoma, known as the Breslow depth or Breslow measurement.

The five stages of melanoma are defined by the American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (or TNM) system:

- **Stage 0:** The cancerous cells are found only in the outer layer of skin (Tis) and have not spread to nearby lymph nodes (N0) or other parts of the body (M0). At this stage,

the cancer is called melanoma in situ. The five-year survival rate is 99.9%.

- **Stage I:** The melanoma is no more than 2/25 of an inch thick (2 mm) and may or may not be ulcerated (T1 or T2a). It has not spread to nearby lymph nodes (T0) or other parts of the body (M0). Five-year survival rate is 98%.
- **Stage II:** The tumor is more than 1 mm thick (T2b or T3) or may be 4 mm thick (T4) but has not spread to nearby lymph nodes (N0) or distant organs (M0). Survival rate is 81%.
- **Stage III:** The melanoma has spread to nearby lymph nodes or to skin just outside the original tumor (satellite tumors). Stage III is subdivided into four substages (IIIA, IIIB, IIIC, and IIID) according to the tumor's thickness, the number of lymph nodes affected, and whether or not the tumor is ulcerated. In none of these substages has the tumor spread to other parts of the body (M0). Survival rate after five years is 65%.
- **Stage IV:** The primary tumor may be any size (any T). Melanoma cells have spread to other organs (M1), most often the lungs, liver, brain, and bones; to lymph nodes (any N); or to skin areas far away from the original tumor. The 5-year survival rate is 25%.

Treatment

Traditional

SURGERY. The only definite cure for malignant melanoma is surgical removal of the cancerous mole or patch of skin before the melanoma reaches a depth of 1 millimeter. The surgeon will remove a margin of normal skin surrounding the melanoma, as well as the tumor itself, to make sure that no cancerous cells are left behind.

A procedure known as microscopically controlled excision—also known as Mohs surgery after the physician who developed it in 1938—can be used to examine each layer of skin as it is removed to ensure that the proper amount is taken. Depending on the amount of skin removed, the cut is either closed with stitches or covered with a skin graft. When surgical excision is performed on such visible areas as the face, cosmetic surgery may also be performed to minimize the scar. Other techniques for removing skin tumors include burning; freezing with a probe containing liquid nitrogen (cryosurgery); or laser surgery. For skin cancer that is localized and has not spread to other areas of the body, excision may be the only treatment needed.

For advanced melanoma that has moved beyond the original tumor site, the local lymph nodes may be surgically removed. In some cases in which the melanoma

has penetrated deeply into a finger or toe, amputation of the digit may be necessary, but these cases are rare.

IMMUNOTHERAPY. Immunotherapy in the form of interferon or interleukin was used in the past as adjuvant therapy for advanced melanoma to stimulate the immune system. However, these agents had severe side effects that some patients could not tolerate. As of 2021, interferon is used only infrequently, because newer agents have proven much more effective.

One newer drug used in immunotherapy for advanced-stage melanoma is ipilimumab (Yervoy), a synthetic version of an immune system antibody. Ipilimumab works by blocking CTLA-4, a protein on the surface of T cells that acts as a brake on T cell activation. In 2014, the Food and Drug Administration (FDA) approved two new drugs that act in similar ways: pembrolizumab (Keytruda) and nivolumab (Opdivo); and in 2016, the FDA approved the use of ipilimumab and nivolumab as combination immunotherapy for patients with inoperable stage IV melanoma.

In 2015, the FDA approved a new type of immunotherapy called oncolytic virus therapy, which uses a herpesvirus altered in a laboratory, to infect and kill cancer cells. The only drug in this class as of 2021 is talimogene laherparepvec, or T-VEC (Imlygic), which is injected directly into the tumors of metastatic melanoma. It stimulates the patient's immune system to attack cancer cells and kill them directly.

TARGETED THERAPY. Targeted therapy is a newer type of treatment for advanced melanoma. It is a type of drug therapy that blocks the growth of skin cancers by interfering with signaling pathways or specific molecules that the cancer cells need for growth. There are several types of targeted therapy drugs used for melanoma as of 2021. One group targets melanoma cells with mutations in the *BRAF* gene; it includes drugs like vemurafenib (Zelboraf), encorafenib (Braftovi), and dabrafenib (Tafinlar), which attack the BRAF protein directly and shrink metastatic tumors, thus prolonging the patient's survival time.

Newer targeted therapy drugs include the MEK inhibitors, which inhibit the action of two enzymes known as MEK1 and MEK2, which work together with the BRAF protein to regulate cell growth. MEK inhibitors approved by the FDA include trametinib (Mekinist), cobimetinib (Cotellic), and binimetinib (Mektovi). The next step in development of targeted therapy is to combine BRAF inhibitors and MEK inhibitors. As of 2021, the FDA has approved three such combinations: dabrafenib-trametinib (Tafinlar-Mekinist); encorafenib-binimetinib (Braftovi-Mektovi); and vemurafenib-cobimetinib (Zelboraf-Cotellic).

Some acral melanomas contain mutations in the *c-KIT* proto-oncogene; they may respond to treatment

with imatinib (Gleevec) or nilotinib (Tasigna), drugs that are known to affect cells with *c-KIT* mutations.

TOPICAL MEDICATIONS. Some early-stage melanomas may be treated with imiquimod (Zyclara), a topical medication applied as a cream. It is used most often in areas where surgery would be disfiguring. More recently, researchers in Italy reported success in treating a patient with later-stage melanoma with imiquimod, and a group of dermatologists in Michigan reported similar success in combining imiquimod with shave excision and electrodesiccation in treating metastatic melanoma.

RADIOTHERAPY. Though radiation therapy has a minimal role in the primary treatment of malignant melanoma, for patients who have metastatic disease it may be helpful in symptom relief in patients who have developed tumor deposits in such areas as the brain or bone. Therapy that is intended to relieve the symptoms of the disease, rather than cure it, is called palliative therapy.

CHEMOTHERAPY. Chemotherapy can be used to treat metastatic melanoma; however, it is not usually used as first-line therapy, because melanomas are much more resistant to chemotherapy than other cancers. The chemotherapeutic agent dacarbazine, or DTIC, seems to be the most effective agent. Combination chemotherapy may be an option. Other chemotherapy drugs that may be used include vinblastine, carboplatin, and temozolomide. Chemotherapy is more often administered in combination with targeted therapy than used by itself.

VACCINES. Vaccines for metastatic melanoma are being studied in clinical trials but were still considered experimental as of 2021. Promising candidate vaccines are made from dendritic cells (DCs), specialized cells in the immune system that stimulate T cells to attack cancerous tumors. There are 88 clinical trials of dendritic cell vaccines against melanoma registered with the National Institutes of Health as of mid-2021. Most of these trials combine administration of the vaccines with cancer chemotherapy to patients with advanced melanoma.

Alternative and complementary therapies

There are no established alternative treatments for skin cancer. Preventive measures that can be helpful include regular skin self-examination; minimizing exposure to the sun and sunburn; and eating a diet high in antioxidants.

Patients diagnosed with melanoma may benefit from some complementary therapies such as prayer, meditation, humor therapy, art therapy, pet therapy, and aromatherapy. While these approaches should not be used as replacements for conventional treatments, they can help to lift the patient's spirits.

QUESTIONS TO ASK YOUR DOCTOR

- Have you ever had a patient who asked you to look at a suspicious mole or skin lesion?
- If so, did you refer the patient to a dermatologist?
- Why do you think the rate of melanoma keeps rising in North America and countries like Australia?
- The FDA first proposed federal legislation banning minors from using tanning salons anywhere in the United States in 2015. Do you think such legislation is a good idea, or should regulation of tanning salons continue to be left to the states?

Look Good Feel Better is a free public service program approved by the American Cancer Society; it helps patients with any kind of cancer cope with changes in their looks related to cancer treatment. It began in 1987 when a doctor asked the president of the Personal Care Products Council to help a patient who was so depressed by her appearance during chemotherapy that she refused to leave her hospital room. The president sent a makeup artist to visit the patient, who was so delighted with her makeover that she began to respond better to her cancer treatment. Look Good Feel Better has expanded to include programs for teens, men, and Spanish-speaking patients; groups are available in all 50 states, the District of Columbia, and Puerto Rico. The main website is <http://www.lookgoodfeelbetter.org>.

Prognosis

The prognosis of melanoma is influenced by a number of factors, according to the AJCC:

- Thickness of the primary melanoma (Breslow's depth); the thicker the tumor, the worse the prognosis.
- Presence of ulceration or bleeding of the primary melanoma. Ulceration or bleeding increases the risk of metastasis.
- Number of lymph nodes involved.
- Location of the primary melanoma: location on the extremities has a better prognosis than a location on the head, neck, or chest.
- Metastasis to distant sites, with metastases to the lungs or skin having a better prognosis than metastases to the brain, liver, or bones.
- Patient's sex: Women have better prognoses in most cases than men.

- Patient's age: Younger patients have better prognoses than older adults.
- Presence of genes that are considered unfavorable; these include *MCM6* and *TIMELESS* as well as *BRAF*, *CDKN2A*, and *NRAS*.

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- American Academy of Dermatology (AAD), P.O. Box 1968, Des Plaines, IL 60017, (888) 462-DERM (3376), (847) 240-1280, (847) 240-1859, mrc@aad.org, <https://www.aad.org>
- American Cancer Society (ACS), 250 Williams Street NW, Atlanta, GA 30303, (800) 227-2345, <https://www.cancer.org/>
- American Society of Clinical Oncology (ASCO), 2318 Mill Road, Suite 800, Alexandria, VA 22314, (888) 282-2552, (703) 299-0158, (703) 299-0255, <https://www.asco.org/>
- Melanoma Institute Australia, 40 Rocklands Road, Wollstonecraft, NSW, Australia 2065, +61 2 9911 7200, +61 2 9954 7290, info@melanoma.org.au, <https://www.melanoma.org.au/>
- Melanoma Network of Canada, 482 South Service Road E. Unit 110, Oakville, Ontario, Canada L6J 2X6, (877) 560-8035, info@melanomanetwork.ca, <https://www.melanomanetwork.ca/>
- National Cancer Institute (NCI), 9609 Medical Center Drive, Rockville, MD 20850, (800) 422-6237, (301) 435-3848, NCInfo@nih.gov, <https://www.cancer.gov/>
- National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, <https://www.genome.gov/about-nhgri/Contact>, <https://www.genome.gov/>
- Skin Cancer Foundation, 205 Lexington Avenue, 11th Floor, New York, NY 10016, (212) 725-5176, <https://www.skincancer.org/about-us/contact-us/>, <https://www.skincancer.org/>

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) 463-6332, <https://www.fda.gov/>

Rebecca J. Frey, PhD

Melnick-Fraser syndrome see **Branchiootorenal syndrome**

Menkes syndrome

Definition

Menkes syndrome is a sex-linked recessive condition characterized by seizures and neurological deterioration, abnormalities of connective tissue, and coarse, kinky hair. Affected males are often diagnosed within the first few months of life and die in early childhood.

Description

Menkes syndrome is also known as Menkes disease and kinky hair syndrome. It was originally described in 1962, based on the report of a family of English and Irish descent who had five male infants with a distinctive syndrome of progressive neurological degeneration, peculiar hair, and failure to thrive. Each of the boys appeared normal at birth but after several months, developed seizures and began to regress in their physical skills. Each child died at an early age, with the oldest surviving to be three-and-one-half years old. In 1972, Menkes syndrome was linked to an inborn copper deficiency. It is now clear that this lack of copper, an essential element for normal growth and development, inhibits the work of specific enzymes in the body. The clinical signs and symptoms of Menkes syndrome are a direct result of these biochemical abnormalities.

Approximately 90%–95% of patients with Menkes syndrome have a severe clinical course. This represents classical Menkes syndrome. Males with milder forms of Menkes syndrome have also been described. The mildest presentation is now known as occipital horn syndrome (OHS), which is allelic to Menkes syndrome; both conditions are due to different mutations in the same gene. Mutations responsible for OHS primarily cause connective tissue abnormalities and have significantly milder effects on intellectual development. Individuals with OHS live longer than those with classical Menkes syndrome.

Genetic profile

Menkes syndrome is an X-linked recessive condition. The gene, which was identified in 1992, is located on the long arm of the X chromosome at band 13.3

(Xq13.3). It is extremely unusual for a female (with two X chromosomes in her cells) to be affected, although it has been reported. Males, who have only one X chromosome, make up the overwhelming majority of patients.

Approximately one-third of affected males are due to a new mutation in the mother's egg cell. There is usually a negative family history, or no other affected male family members. When the mutation occurs as an isolated, random change, the mother's risk of having another affected son is low.

On the other hand, the remaining two-thirds of affected males are born to carrier mothers. Often, there is a family history of one or more affected male relatives (e.g., uncle, brother, cousin), all of whom are related to one another through the maternal side. Carrier females are normal but face a risk of passing on the gene for Menkes syndrome to their children. A carrier mother has a 25% risk of having an affected son, a 25% risk of having an unaffected carrier daughter, a 25% risk of having a normal son, and a 25% risk of having a normal, non-carrier daughter. These risks apply to each pregnancy.

The Menkes syndrome gene, also known as *MNK* or *ATP7A*, is a large gene known to encode a copper-transporting protein. Individuals with Menkes syndrome have low levels of copper in their blood. Their cells are able to take in copper but the metal is unable to leave the cell and be delivered to crucial enzymes that require copper in order to function normally. As a result, copper accumulates in the body tissues, and clinical abnormalities occur. Most symptoms of Menkes syndrome, such as skeletal changes and abnormal hair, may be explained by the loss of specific enzymes. However, the reasons for the brain degeneration are still not entirely clear.

A variety of mutations that cause Menkes syndrome have been identified in the *MNK* gene. Unfortunately, almost every family studied has had a unique mutation. This makes genetic testing difficult, particularly if the mutation in the family has not yet been determined. OHS is also caused by mutations in the *MNK* gene.

Demographics

Menkes syndrome is relatively rare, with an estimated incidence of 1 in 100,000–250,000 male births. Among the 3.5 million infants born annually in the United States, approximately 15–35 males have Menkes syndrome.

Signs and symptoms

Infants with classical Menkes syndrome appear normal at birth and continue to develop normally for roughly the first eight to ten weeks of life. At approximately two

to three months of age, affected infants begin to lose previously attained developmental milestones, such as head control and a social smile. They lose muscle tone and become hypotonic, or floppy, develop seizures, and begin to fail to thrive. Changes in the appearance of their face and hair become more apparent. A diagnosis of Menkes syndrome is often made around this time.

Menkes syndrome has several clinical features.

Neurologic features include:

- mental deterioration and handicap due to structural and functional brain abnormalities
- seizures
- inability to regulate body temperature (hypothermia)
- feeding and sleeping difficulties
- decreased muscle tone

Connective tissues typically display:

- tortuous blood vessels due to abnormal formation of blood vessel walls
- abnormalities of bone formation, as noted by x-ray (skull, long bones, and ribs)
- bladder diverticulae
- loose skin, particularly at the nape of neck, under the arms, and on the trunk
- loose joints

Other clinical features are:

- unusual facial features (jowly, pudgy cheeks, large ears)
- abnormal hair, including the eyelashes and eyebrows
- light skin and hair coloring (hypopigmentation)
- delayed eruption of teeth
- impaired vision
- normal hearing

The hair of individuals with Menkes syndrome deserves special discussion, particularly since this condition is sometimes called kinky hair syndrome. Abnormal hair is not typically evident during the first few months of life. However, around the time that the other physical signs of the disorder become more apparent, the hair takes on an unusual appearance and texture. On magnified inspection, it is short, sparse, coarse, and twisted. It has been likened to the texture of a steel wool cleaning pad. It shows an unusual orientation, referred to as *pili torti*, a 180 degree twist of the hair shaft. It is usually fragile and breaks easily. The hair of all affected individuals shows these characteristic changes; it is likewise present in some women who are known gene carriers.

Death occurs early in males with Menkes syndrome, often by the age of three years in classical disease. Longer survival is not unusual and is most likely due to recent

improvements in medical care. Severity of disease and its rate of progression are fairly consistent among untreated males in a single family.

Diagnosis

An initial diagnosis of Menkes syndrome is usually suspected based on the combination of physical features. As these features are generally subtle in the newborn period, they may be missed—particularly if there is no prior family history of the condition.

A common prenatal and newborn history has been recognized among affected infants. The histories often include: premature labor and delivery; large bruises on the infant's head after an apparently normal, uncomplicated vaginal birth; hypothermia; low blood sugar (hypoglycemia); and jaundice. Hernias may be present at either the umbilicus or in the groin area. These findings are non-specific and occur in normal pregnancies and unaffected infants. However, their presence may alert a knowledgeable physician to the possibility of Menkes syndrome, especially when other clinical signs are also present.

A clinical diagnosis is strongly supported by decreased serum levels of copper and ceruloplasmin, a protein in the blood to which the majority of copper is attached. Abnormal results, however, do not confirm the diagnosis since both copper and ceruloplasmin levels may also be low in normal infants during the first few months of life. A definitive diagnosis of Menkes syndrome is possible by either specific biochemical analysis to measure the level of copper accumulation in the cells, or by identification of the responsible mutation in the *MNK* gene. Both types of analysis represent highly specialized testing and are available only through a limited number of laboratories in the world.

Prenatal diagnosis, in the context of a family history of the disorder, is possible. Ideally, a woman's carrier status will have been determined prior to a pregnancy as carrier detection may be difficult and time-consuming. Mutation analysis is the most direct and accurate way to determine carrier status. In order for this to be possible, the *MNK* mutation in an affected family member must have been previously determined. Linkage analysis is another possibility but requires blood samples from other family members, including the affected relative, to facilitate interpretation of results. If the affected relative is deceased, a stored DNA sample may be used.

Other, non-molecular methods of carrier detection include analysis of hair samples to look for areas of *pili torti*, increased fragility, or hypopigmentation. Skin cells cultured in the laboratory may be used to measure the accumulation of radioactive copper. However, these

KEY TERMS

Catecholamines—Biologically active compounds involved in the regulation of the nervous and cardiovascular systems, rate of metabolism, body temperature, and smooth muscle.

Connective tissue—A group of tissues responsible for support throughout the body; includes cartilage, bone, fat, tissue underlying skin, and tissues that support organs, blood vessels, and nerves throughout the body.

Diverticulae—Sacs or pouches in the walls of a canal or organ. They do not normally occur, but may be acquired or present from birth. Plural form of diverticula.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Linkage analysis—A method of finding mutations based on their proximity to previously identified genetic landmarks.

Tortuous—Having many twists or turns.

approaches are not always reliable, even in known carriers.

If a woman is found to be a non-carrier, prenatal testing for Menkes syndrome is generally not necessary in any of her pregnancies. However, in the event that a woman is a confirmed carrier, prenatal testing such as chorionic villus sampling (CVS) or amniocentesis may be offered. Ultrasound examinations alone will not assist in making a diagnosis. CVS or amniocentesis will determine the fetal sex: if female, additional testing is usually not recommended since carrier daughters would be expected to be normal. Carrier testing on the daughter may be performed after birth, if desired, or postponed until later in life.

Further testing is offered when a fetus is male. If mutation studies cannot be performed because the mutation in the family is unknown, biochemical analysis may be attempted. Biochemical testing has serious drawbacks, and a correct diagnosis may not always be possible. Tissue obtained during CVS normally has a very low copper content and is very susceptible to contamination by maternal tissue or by outside sources, such as laboratory instruments or containers. As a result, if the copper level exceeds a certain level, an unaffected pregnancy could

potentially be falsely identified as affected. Specific handling precautions are necessary to minimize this risk.

Similar concerns exist for a sample obtained by amniocentesis. Ordinarily, the cells obtained from this procedure are cultured and grown in the laboratory. A measurement is taken of the total amount of accumulated copper over a certain period. The timing of amniocentesis in the pregnancy is critical because the amniotic fluid cells do not grow as rapidly after a gestational age of 18 weeks. Problems in cell growth cause significant difficulties in the interpretation of the biochemical results.

Other methods of diagnosis are being investigated. Promising methods include an assessment of the concentration of copper in a sample of the placenta (extremely high in affected pregnancies), and the level of catecholamines (low) in a sample of blood from the umbilical cord. Both methods, which are fast, reliable, and performed immediately after delivery, clearly require a high level of suspicion of the disorder. In most cases, this will be based on a history of a previous affected son, abnormal or unclear prenatal testing results, or both. Women who do not have a family history of Menkes syndrome, and are therefore not expected to be at-risk, are not offered this testing.

Treatment and management

The underlying, critical problem for patients with Menkes syndrome is an induced copper deficiency. Copper uptake is normal but the gene abnormality prevents the release of copper to the appropriate enzymes in the cells. Copper accumulates in the intestinal system, and patients are unable to meet their most basic nutritional needs. The most serious effects are apparent during the first year of life when growth of the brain and physical development are occurring most rapidly. Copper is required in order for both of these processes to occur normally.

Treatment of Menkes syndrome has focused on providing patients with an extra source of copper to try to deliver it to the enzymes that need it for normal function. Studies at the National Institutes of Health (NIH) have focused on the use of a copper-histidine compound in affected males. Copper-histidine is normally present in human serum and is most likely the form in which copper is absorbed by the liver. Also, in the laboratory, the presence of histidine in serum has been shown to increase the uptake of copper. Daily injections are the most successful form of treatment to date.

Two conclusions have been drawn from this work: (1) Treatment is more successful when started at an early age. Most, but not all, treated boys have achieved more normal developmental milestones and have had milder mental impairment. (2) Treatment is much less effective

QUESTIONS TO ASK YOUR DOCTOR

- What is the expected lifespan for a child born with Menkes syndrome?
- If my sister had a child with this disorder, is there any way of knowing what the probability is of my having a child with the same disorder?
- What are the most common signs and symptoms associated with Menkes syndrome?
- Can you recommend brochures, pamphlets, or other sources of information about this disorder?

if started after the age of several months, or when neurologic symptoms have already begun. While milder improvements in the areas of physical development, personality, and sleeping habits have been reported in boys whose treatment started later, the degree of mental handicap has not been significantly altered.

A separate study in 1998 lent further support to these results. This study followed four affected males with classical Menkes syndrome, all of whom were started on copper-histidine treatment soon after birth. Three of the four males were born into families with other affected relatives; the fourth child was diagnosed at the age of three weeks. All four showed significant improvements in their development and clinical course. None of them experienced entirely normal development, but their remaining clinical abnormalities were similar to those seen in patients with occipital horn syndrome. The oldest survivor of the group was 20 years old.

This information strongly supports the importance of nutritional therapy in the care of patients with Menkes syndrome. Early treatment is best but requires early diagnosis. It should also not be seen as a “cure.” It has been shown to lessen the severity of the syndrome but not eliminate it. Thus, prenatal diagnosis, and its possible limitations, should continue to be discussed with prospective parents known to be at risk. Mutation studies should be performed, whenever possible, to increase the accuracy of testing results.

Prognosis

Death often occurs by the age of three years in untreated males with classical Menkes syndrome, although longer-term survivors have been reported. Treatment with supplemental copper has resulted in improved physical development, milder mental handicap, and extended lifespan in some affected males. However, not all patients have responded to the same extent.

Additionally, patients treated after the onset of symptoms have done worse than those treated before symptoms occur. Research is continuing to refine the best dosage of copper-histidine, determine the optimal timing and route of treatment, and develop newer treatment strategies.

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ORGANIZATIONS

- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Mental retardation see **Smith-Fineman-Myers syndrome**

Mermaid syndrome see **Sirenomelia**

Metaphyseal dysplasia

Definition

Metaphyseal dysplasia, also known as metaphyseal chondrodysplasia, is a very rare disorder in which the outer part of the shafts of long bones is unusually thin with a tendency to fracture. Aside from valgus knee deformities (commonly known as knock-knee), many patients with metaphyseal dysplasia exhibit few or no symptoms. The disorder comes in a variety of forms, some of which cause serious problems including intellectual disability, blindness, and deafness.

Description

Metaphyseal dysplasia is frequently mistaken for craniometaphyseal dysplasia, a disorder characterized by

the thickening of the bones of the head. Metaphyseal dysplasia is genetically distinct from craniometaphyseal dysplasia and has only mild effects on the skull. In fact, metaphyseal dysplasia is so subtle that often it cannot be detected by clinical observation and is uncovered only when x-rays are taken for another purpose. The signs are immediately visible on x-rays, particularly the cone-like flaring that occurs on the tubular bones of the leg. This flaring is similar in shape to the Erlenmeyer glass flasks used in laboratories.

Another name for metaphyseal dysplasia is Pyle's disease, after Edwin Pyle, an orthopedic surgeon who first described it in 1931.

There are eight varieties of metaphyseal dysplasia. They are classified as Jansen type, Schmid type, McKusick type, metaphyseal anadysplasia, Shwachman-Diamond metaphyseal dysplasia, adenosine deaminase deficiency, Spahr-type metaphyseal chondrodysplasia, and metaphyseal acroscaphodysplasia.

Genetic profile

Inheritance of metaphyseal dysplasia is typically autosomal recessive, meaning that both parents are carriers of an abnormal gene when a child exhibits symptoms. Children inheriting the gene from one parent become carriers. When both parents are carriers, each child has a 25% chance of having the disorder and a 50% chance of being a carrier. In the case of Jansen type metaphyseal dysplasia, the chromosomal gene locus is 3p22-p21.1. In Schmid type metaphyseal dysplasia, the locus is 6q21-q22.3. For McKusick type (cartilage-hair hypoplasia), it is 9p13. In adenosine deaminase deficiency, the locus is 20q-13.11. The modes of inheritance for Jansen type, Schmid type, and adenosine deaminase deficiency are all autosomal dominant, meaning that a child may inherit the disorder if just one parent is a carrier. For all other varieties of metaphyseal dysplasia, the modes are autosomal recessive, with the possible exception of metaphyseal anadysplasia, which may be X-linked recessive. In that case, whenever one parent is a carrier of the disorder, each child would have a chance of either inheriting it or being a carrier.

The Schmid type of metaphyseal dysplasia has been connected to a mutation in the *COL10A1* gene, which codes for type X collagen $\alpha 1$ chain, which—although not fully understood—does play a role in the ossification of collagen. This mutation has been linked to a substitution mutation.

Demographics

This disorder is very rare, and the number of recorded cases is too small to draw firm demographic conclusions. There appears to be no preference based on sex.

KEY TERMS

Carrier—An individual who possesses an unexpressed abnormal gene of a recessive genetic disorder.

Dysplasia—The abnormal growth or development of a tissue or organ.

Metaphysis—An area of softer bone and cartilage in long bones between the diaphysis (shaft) and epiphysis (end).

Splay—Turned outward or spread apart.

Signs and symptoms

The characteristic sign of metaphyseal dysplasia is splaying of the long bones, more severely than in craniometaphyseal dysplasia. Gross Erlenmeyer flask flaring is seen in the tubular bones of the leg, particularly in the femur. Unlike craniometaphyseal dysplasia, few signs occur in the skull in metaphyseal dysplasia, apart from protrusions over the eye sockets.

Metaphyseal dysplasia is also marked by expanded bones of the rib cage and pelvis and by changes in the angle of the lower jaw. The humerus bone of the arm tends to be unusually broad. Other signs include scoliosis (a sideways curvature of the spine) and osteoporosis (a condition that makes bones brittle). Patients may complain of muscle weakness or joint pain. Dentists may notice malocclusion, an inability of the teeth to properly close. Some spinal changes are possible, associated with the flaring of tubular bones. These may include platyspondyly, a broadening of the vertebrae.

Jansen type

In addition to the mentioned signs, Jansen type metaphyseal chondrodysplasia is characterized by short arms, legs, and stature (short-limbed dwarfism), which become apparent during early childhood. Affected children experience a gradual stiffening and swelling of their joints. Often, they develop a characteristic “waddling gait” and a stance that appears as if they were squatting. Some facial abnormalities may be evident at birth. These include prominent, widely spaced eyes, a receding chin, or a highly arched palate. Some affected adults develop unusually hardened bones in the back of the head, which sometimes results in deafness and/or blindness. Abnormal cartilage development may harden into rounded bone masses that may be noticeable on the hands, feet, and elsewhere. Other signs and symptoms associated with Jansen type metaphyseal chondrodysplasia include clubbed fingers, a fifth finger permanently fixed in a bent position, fractured ribs,

intellectual disability, psychomotor retardation, and high blood levels of calcium. Curvature of the spine in these patients may be front-to-back as well as sideways. Testing the blood and urine for calcium can assist in confirming a diagnosis. Jansen type metaphyseal chondrodysplasia was formerly referred to as metaphyseal dysostosis. This type of metaphyseal dysplasia is possibly due to a deleterious mutation in the gene *Zfp521*, which codes for a parathyroid related protein receptor that has a large role in the proliferation and differentiation of cells at the growth plate, leading to these skeletal abnormalities.

Schmid type

Like Jansen type metaphyseal chondrodysplasia, Schmid type metaphyseal chondrodysplasia is also characterized by short-limbed dwarfism. Other special features may include an outward flaring of the lower rib cage, bowed legs, leg pain, a normal spine, and a hip deformity that causes the thigh bone to angle toward the body's center. Schmid type metaphyseal chondrodysplasia was first discovered in 1943 in a family of Mormons that had experienced 40 cases of the disorder over four generations. The first affected ancestor was traced back to 1833. This type of metaphyseal dysplasia is caused by a mutation of the *COL10A1* gene located on chromosome 6 due to a deletion that causes a frameshift.

McKusick type

Like Jansen type and Schmid type, McKusick type metaphyseal chondrodysplasia is marked by short-limb dwarfism. Other features include thin, light-colored hair, loose-jointed fingers, elbows that cannot be fully extended, Hirschsprung disease (a birth defect in which the usual nerve network fails to develop around the rectum, and in some cases, the colon), and abnormalities of the immune system. In the shin, the tibia bone is uncharacteristically shorter than the fibula. Patients are at increased risk of developing cancers, especially of the skin and the lymph nodes. McKusick type metaphyseal chondrodysplasia is also known as cartilage hair hypoplasia syndrome. The disorder was first recognized in 1965 among the Old Order Amish.

Metaphyseal anadysplasia

First noticed in 1971, metaphyseal anadysplasia is a form of metaphyseal dysplasia that starts early. Instead of appearing after puberty, some signs are found to be present at birth, but disappear after several years. In the thigh bones of patients studied, there was an unusually low level of red blood cell production.

Shwachman-Diamond syndrome

In addition to the skeletal system, Shwachman-Diamond syndrome also affects the pancreas. It is

QUESTIONS TO ASK YOUR DOCTOR

- Can you explain the meaning of the term "metaphyseal dysplasia"?
- How is this disorder transmitted from one generation to the next?
- How do the various types of metaphyseal dysplasia differ from each other?
- Are people with metaphyseal dysplasia able to live a normal life and if not, what are the most serious problems they will face?

characterized by inadequate absorption of fats because of abnormal pancreatic development and bone marrow dysfunction. Other unusual symptoms and signs include short stature, liver abnormalities, and low levels of any or all blood cells. Reduced levels of white blood cells may cause these patients to be vulnerable to repeated bouts with pneumonia, otitis media, and other bacterial infections. Shwachman-Diamond syndrome is also referred to as Shwachman-Bodian syndrome, Shwachman-Diamond-Oski syndrome, Shwachman syndrome, and congenital lipomatosis of the pancreas. Some researchers call it pancreatic insufficiency and bone marrow dysfunction.

Adenosine deaminase deficiency

A deficiency of adenosine deaminase (ADA), an essential, broadly distributed enzyme, causes severe combined immunodeficiency disease. This can bring about a wide range of effects, including asthma; pneumonia; sinusitis; diarrhea; problems with the liver, kidneys, spleen, and skeletal system; and failure to thrive. ADA deficiency is similar to McKusick type metaphyseal chondrodysplasia in that both disorders include skeletal changes and problems with cellular immunity. ADA deficiency earned a special place in genetics history in 1990, when, in the first application of gene therapy in humans, it was corrected using genetically engineered blood.

Spahr type metaphyseal chondrodysplasia

This is one of several disorders that used to be called metaphyseal dysostosis. It is extremely rare, and its features include severely bowed legs and short-statured dwarfism. In some cases, the bowing of the knees is so severe as to require surgical correction. Spahr type is very similar to Schmid type metaphyseal chondrodysplasia, except that inheritance is believed to be autosomal

recessive in Spahr type, unlike Schmid type, which is autosomal dominant.

Metaphyseal acroscyphodysplasia

This variety is also referred to as wedge-shaped or cone-shaped epiphyses of the knees. Its features include severely retarded growth, psychomotor retardation, abnormally small arms and legs, extremely short fingers, and curvature of the knees.

Metaphyseal dysplasia with maxillary hypoplasia and brachydactyly (MDMHB)

This type of metaphyseal dysplasia is an autosomal dominant pattern of inheritance classified by maxillary hypoplasia (softened facial bone), brachydactyly (shortness of the fingers and toes), metaphyseal flaring and thin diaphyseal cortices of long bones, increased size of the medial half of the clavicles, and malformed teeth, among other skeletal abnormalities. Studies have shown that this form of metaphyseal dysplasia is likely due to a duplication mutation of the *RUNX2* gene, which codes for the protein that regulates osteoblasts and chondrocytes.

Diagnosis

Diagnosis is usually by x-ray, in which the bone deformities of metaphyseal dysplasia are very noticeable, even if not apparent in a normal clinical examination. A medical doctor will look for valgus knee deformities. A radiologist will look for Erlenmeyer-flask-shaped femur bones and ensure that any deformities to cranial bones are minor in order to rule out craniometaphyseal dysplasia. The radiologist will also watch for abnormally broad humerus, radius, and ulna bones.

Treatment and management

Metaphyseal dysplasia cannot be directly treated, but some individual symptoms, such as osteoporosis or joint problems, may be treated or surgically corrected.

Prognosis

In many cases, patients with metaphyseal dysplasia may be symptomless and very healthy. Other patients, including those with Jansen type metaphyseal chondrodysplasia, may have more severe complications including blindness, deafness, or intellectual disability.

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Methemoglobinemia, beta-globin type

Definition

Methemoglobinemia, beta-globulin type, formerly known as congenital methemoglobinemia, is an autosomal dominant inherited blood disorder. Its most distinctive characteristic is a cyanotic appearance, a bluish tint to the skin and mucous membranes. The condition is also known as hemoglobin M disease or blue baby syndrome.

Description

Methemoglobinemia is a malformation of the molecules associated with transporting oxygen to tissues and organs for the proper function of these tissues and organs. There are many types of methemoglobinemia, both hereditary and acquired. Acquired methemoglobinemia is often associated with drug use. Congenital methemoglobinemia, such as in the case of beta-globin type, is due to a mutation in the gene that codes for the correct synthesis of hemoglobin, an important molecule for the

binding of oxygen and then the releasing of it in its target tissue. More specifically, the iron portion of the heme molecule is not able to transform into its correct state, the ferrous state, for the proper binding and transfer of oxygen, so it remains in the ferric state. This causes a higher than normal (more than 1%) methemoglobin in the red blood cells. The defining and most prominent characteristic of methemoglobinemia is cyanosis, which may range from mild discoloration of the skin to an intense bluish color due to a lack of oxygen in the tissue. Symptoms of methemoglobinemia beta type appear as early as the age of three or four months.

Genetic profile

Methemoglobinemia beta type is due to a mutation in the *HBB* gene inherited as an autosomal dominant disorder. The hemoglobin molecule consists of four subunits, two of which are designated as alpha-globin and two of which are beta-globin. The hemoglobin, beta (*HBB*) gene carries instructions for the synthesis of the beta-globin unit of hemoglobin. Mutations in this gene result in the formation of an altered form of hemoglobin called M hemoglobin, which bonds abnormally with heme and reduces the molecule's ability to carry oxygen molecules. The *HBB* gene is located on the short arm of chromosome 11. Other disorders associated with mutations of this gene include sickle cell anemia and beta thalassemia, among others.

Signs and symptoms

The normal red color of blood is caused by hemoglobin-bonded oxygen (oxyhemoglobin). Hemoglobin with reduced amounts of oxygen retains the original color of the hemoglobin molecule itself, which is bluish brown. As a consequence, the common and predominant feature of methemoglobinemias such as methemoglobinemia beta-globin type is the bluish color imparted to the skin and mucous membranes, caused by blood vessels being close to the surface, a condition known as cyanosis. Symptoms are directly related to the amount of methemoglobin present in the blood and may range from simple cyanosis to neurological and/or cardiac symptoms due to hypoxia, and after that, death. A second cause of the disorder is mutations in the alpha-globin unit of the hemoglobin molecule that result in deficient production of the essential enzyme nicotinamide adenine dinucleotide (NADH) cytochrome b5 reductase. Four types of this form of congenital methemoglobinemia have been identified, depending on the locations of the body in which the defective enzyme occurs; therefore, differential diagnosis can occur via genetic testing.

KEY TERMS

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a nonsex chromosome is required for a disease or inherited trait to develop in an individual.

Congenital—Refers to a disorder that is present at birth.

Cyanosis—A bluish discoloration of the skin and mucous membranes.

Heme—An organic molecule that contains a single atom of iron and is responsible for the oxygen-carrying ability of hemoglobin.

Hemoglobin—A protein-iron compound in the blood that carries oxygen to the cells and carries carbon dioxide away from the cells.

Methemoglobinemia—A medical condition of the blood characterized by the presence of an altered form of hemoglobin, known as methemoglobin.

Plethora—An overabundance of something, in this case blood in the body.

Prevalence—The number of individuals living with a particular illness within a particular population at any given time. Prevalence is often expressed in terms of the number of individuals per 100 or per 1,000 members of the population.

Splenomegaly—Enlargement of the spleen.

Demographics

No estimates are available for the prevalence or incidence of methemoglobinemia beta-globin type either worldwide or in the United States. The disease is, however, classified as rare.

Diagnosis

The presence of cyanosis strongly suggests the possibility of methemoglobinemia beta-globin type. An initial follow-up test consists of a blood test for the presence of methemoglobin. The presence of this substance at concentrations greater than about 1% is considered evidence of methemoglobinemia. A simple confirmatory test is to bubble pure oxygen gas through the blood sample. Failure of the blood to turn red (evidence of its oxygenation) is considered confirmation of methemoglobinemia. Associated factors may be an overabundance of blood in the body (plethora) and enlargement of the spleen (splenomegaly). The differential diagnosis of methemoglobinemia beta-globin type

QUESTIONS TO ASK YOUR DOCTOR

- Are there signs or symptoms that indicate that more aggressive treatment for methemoglobinemia beta-globin type should be considered?
- What treatments are available for a patient in such circumstances?
- Although methemoglobinemia is generally a benign condition, are there circumstances in which more serious medical problems can arise?
- Under what circumstances are treatments with methylene blue and/or ascorbic acid indicated and recommended?

from other forms of methemoglobinemia and acquiring cyanosis can be done via genetic sequencing since there is now a known gene association.

Treatment and management

As of 2015, treatment of methemoglobinemia beta-globin type included methylene blue and ascorbic acid. Ascorbic acid (vitamin C) and methylene blue have been found to be partially successful in the treatment of certain cases. Although the condition is generally benign, the most serious cases are sometimes treated with exchange transfusions, in which large quantities of the patient's blood are removed and replaced with blood from a donor.

Prognosis

Methemoglobinemia beta-globin type is typically benign and does not normally require treatment. Patients should be observed for any change in condition and referred for medical treatment if any change is noted.

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Methylenetetrahydrofolate reductase variant (MTHFR gene variant)

Definition

Methylenetetrahydrofolate reductase variants (MTHFR gene variants) are variants in the MTHFR gene that can result in reduced levels or malfunction of an enzyme called MTHFR. Most of these variants do not cause disease, but some result in high levels of the amino acid homocysteine. Some MTHFR variants may cause an increased risk of problems such as blood clots, high blood pressure, stroke, and heart disease. (Not all studies have found this association.) A few rare variants cause autosomal recessive homocystinuria, a genetic disorder that can feature developmental delays, seizures, eye disorders, blood clots, and bone fragility.

Description

The MTHFR gene contains the instructions for the production of methylenetetrahydrofolate reductase (MTHFR), an enzyme that the body uses to convert folate (vitamin B9) to a form that helps convert the amino acid homocysteine to methionine. The amino acid methionine is involved in a various processes in the body, including making proteins and other compounds. Methionine can also be obtained through diet. Some variants in the MTHFR gene can decrease the levels of MTHFR or cause it not to function properly, which results in higher amounts of homocysteine and lower amounts of methionine in the blood, a condition that can produce increased health risks in some people.

Genetic profile

The two most common MTHFR gene variants are C677T and A1298C. Like most genes, people normally

inherit two copies of the MTHFR gene, one from their mother and one from their father. Individuals with a C677T variant in both copies of their MTHFR genes can have slightly increased levels of homocysteine. The levels of homocysteine can be normal if they get enough folate from their diet. Individuals with one A1298C and one C677T variant tend to have slightly increased homocysteine, which can resolve with folate supplementation. Individuals with one C677T variant can have homocysteine levels that are slightly higher than normal but not as high as those with two C677T variants. Individuals with one or two A1298C variants tend to have normal levels of homocysteine.

At least 40 rare variants in the MTHFR gene can cause autosomal recessive homocystinuria. People with autosomal recessive homocystinuria have inherited one of these rare variants from their mother and one from their father. Their parents are called carriers since they each have one normal copy of their MTHFR gene and one copy with the rare variant. Two carriers have a one-in-four (25%) chance of having a child with homocystinuria, one-in-two chance (50%) of having a child who does not have the disease but is a carrier, and one-in-four (25%) chance of having a child with two normal copies of the gene. Carriers do not have homocystinuria but may be at increased risk for blood clots and strokes. C677T and A1298C are not associated with autosomal recessive homocystinuria.

Demographics

In the United States, the C677T variant is found in less than 1% of African Americans, but is more common among whites and found in 20% or more among Hispanics and Italians. The A1298C variant is less common than the C677T variant. About 17% of people in the United States have a combination of the C677T and A1298C variants. The variants that cause autosomal recessive homocystinuria are very rare.

Signs and symptoms

For most people, the common MTHFR variants C677T and A1298C are unlikely to cause problems even if they have increased levels of homocysteine. Some studies have found that higher levels of homocysteine and lower levels of methionine may cause an increased risk of blood clots, high blood pressure, stroke, and heart disease.

Women with two copies of the C677T variant appear to be at slightly increased risk of having a child with a neural tube defect (NTD). This severe defect causes the child to be born with an opening in the spine or skull, exposing the spinal cord or brain and possibly causing brain and nerve damage.

KEY TERMS

Amino acid—Organic compounds the body uses for many different processes. There are about 500 known amino acids but only 20 of them are related to DNA and combine together to form proteins.

Autosomal recessive—Condition caused by a pathogenic variant (mutation) in both copies of a particular gene. Two carriers of an autosomal recessive condition have a one-in-four (25%) chance of passing it on to their children.

Carrier—Person who has a pathogenic variant in one copy of a gene that causes an autosomal recessive condition. Carriers often do not have symptoms. Two carriers of an autosomal recessive condition have a one-in-four (25%) chance of passing it on to their children.

DNA (deoxyribonucleic acid)—The genetic material that contains the instructions for creating proteins.

DNA base—One unit in a DNA sequence. The four DNA bases are adenine (A), cytosine (C), guanine (G), and thymine (T). The sequence of these bases is the genetic code that contains the instructions for creating proteins.

DNA sequence—The sequence of DNA bases that contains the instructions for creating proteins. A three base sequence in the DNA contains the instructions for making a particular amino acid. For example, CGC codes for the amino acid alanine. Proteins are made up of one or more amino acids strung together. The instructions for a particular protein are made up of a number of three base sequences.

Enzyme—Type of protein that speeds up a chemical reactions that happen in the body.

Gene—A sequence of bases in a DNA sequence that contains the instructions for one protein.

Hyperhomocysteinemia—Increased levels of homocysteine in the blood.

Neural tube defect (NTD)—Severe birth defects in which there is an opening in the skull or spine that exposes the brain or spinal cord. This exposure can result in damage to the brain or spinal cord.

Pathogenic variant—Any change in the sequence of a genome that causes disease.

Variant—Change in the sequence of DNA.

Some more severe and rare variants cause autosomal recessive homocystinuria, a condition associated with high levels of homocysteine. Homocystinuria resulting from MTHFR variants has a childhood or adult onset and

QUESTIONS TO ASK YOUR DOCTOR

- Should I be taking folate?
- What MTHFR gene variant(s) do I have?
- What treatments exist for homocystinuria?

is associated with developmental delay, eye disorders, blood clots, and bone fragility. Carriers of these rare variants do not have homocystinuria but may be at increased risk for blood clots and strokes.

Diagnosis

Genetic testing can identify MTHFR gene variants. Some health providers suggest testing for common MTHFR variants for people with unexplained blood clots. If autosomal recessive homocystinuria is suspected, then urine testing typically shows extremely elevated homocysteine and lower levels of methionine. Sequencing of the whole MTHFR gene to look for and identify variants is recommended since many rare variants can cause this condition. Testing for variants in other genes that can more commonly cause this disorder may also be recommended.

Treatment and management

Supplementation with folate (vitamin B9) and vitamin B6 and B12 may reduce the risk for clots, strokes, and heart disease in some individuals with mild variants such as C677T and A1298C. Women with MTHFR variants who plan to have children, like all women, should take 400 micrograms (mcg) of folic acid each day prior to getting pregnant. This supplementation may decrease the risk of neural tube defects.

People with autosomal recessive homocystinuria caused by MTHFR variants are treated with folate, methionine, and vitamins B6 and B12. They may also be treated with Betaine, a drug that decreases homocysteine levels in the blood. Treatment should be started as early as possible.

Prognosis

Most people with the common and mild C677T and A1298C variants do not have symptoms. Some may have increased risk of heart disease, blood clots, and strokes. This risk may be reduced by folate (vitamin B9) and vitamin B6 and B12 supplements. The risk of neural tube defects may be lower in women with MTHFR variants who take folate prior to pregnancy.

Early treatment of autosomal recessive homocystinuria can prevent symptoms and improve the prognosis. Later treatment cannot reverse symptoms but can make the symptoms milder.

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ORGANIZATIONS

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Methylmalonic acidemia

Definition

Methylmalonic acidemia (MMA) is an autosomal recessive disorder that causes defects in metabolism. Individuals who have the disease cannot metabolize vitamin B12. The first recognized cases of MMA were described in 1967. Some non-genetic cases have been reported in which the affected individuals were vegetarians who had been on prolonged cobalamin (vitamin B12) deficient diets.

Description

Methylmalonic acidemia (MMA) is characterized by an accumulation of methylmalonic acid in the blood stream, which leads to an abnormally low pH (high acidity) in nearly every cell in the body (metabolic acidosis). A higher-than-normal accumulation of ketones in the blood stream (ketosis) similar to that seen in instances of diabetes mellitus is also associated with MMA. If left untreated, metabolic acidosis is often fatal.

Methylmalonic acid is an intermediate in the metabolism of fats and proteins. This compound can accumulate in the bodies of individuals with MMA because of a partial or complete inability to convert methylmalonyl-CoA to succinyl-CoA in the tricarboxylic acid (TCA) cycle.

MMA is one of the genetic disorders that affect mitochondrial metabolism. The mitochondria are organelles inside cells that are responsible for energy production and respiration at the cellular level. One of the most important processes in the mitochondria is the TCA, because it produces the majority of the ATP (chemical energy) necessary for maintenance (homeostasis) of the cell. Before glucose enters the TCA cycle, it is broken down into acetyl-CoA, which is then further broken down in the TCA cycle to yield carbon dioxide, water, and ATP. When some fatty acids and certain amino acids from proteins (specifically isoleucine, valine, threonine, methionine, thymine, and uracil) are broken down in preparation to enter the TCA cycle, they provide propionyl-CoA rather than acetyl-CoA. This propionyl-CoA is then converted into methylmalonyl-CoA, which is next converted to succinyl-CoA. It is succinyl-CoA that enters the TCA cycle to eventually yield carbon dioxide, water, and the ATP needed by the cells.

The conversion of methylmalonyl-CoA to succinyl-CoA involves the apoenzyme methylmalonyl-CoA mutase. One of the cofactors required by this apoenzyme is cobalamin (vitamin B12). Genetic MMA is a result of either a deficiency in the methylmalonyl-CoA mutase or a defect in the mechanism inside the cells that converts

dietary vitamin B12 into its useable form for this metabolic reaction.

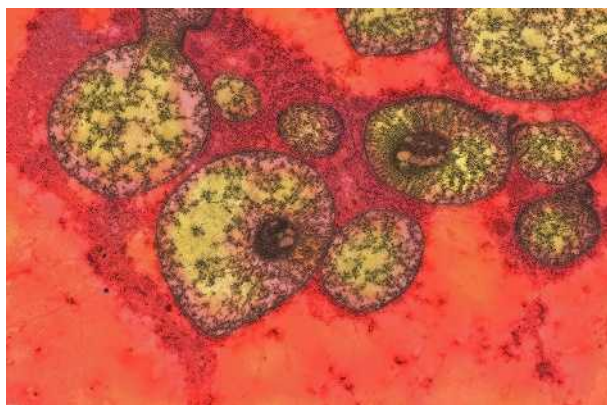
An enzyme is a chemical that facilitates (catalyzes) the chemical reactions; it is neither a substrate nor a product in the chemical reaction. As a result, enzymes are not used up in chemical reactions, and one molecule of an enzyme may be used to facilitate the same chemical reaction multiple times. All of the enzymes necessary for catalyzing the various reactions of human life are produced within the body by genes. In the case of the enzyme deficiency that causes MMA, the enzyme consists of a genetically produced apoenzyme and a cofactor (vitamin B12) that comes from dietary sources.

Genetic profile

The gene responsible for MMA has been mapped to chromosome 6 in the human genome and is called *MUT*. At least 30 mutations in this gene have been identified that lead to a broad spectrum of clinical symptoms and severities. Approximately 60% of the cases of MMA are due to mutations in the *MUT* gene. Genetic MMA is recessive, meaning that two copies of the mutated gene are required for the disease to present.

Demographics

The exact frequency of MMA is not known. It is believed to occur with a frequency of approximately one in every 48,000 live births in the United States. As in all recessive non-sex linked (autosomal) genetic disorders, both parents must carry the gene mutation in order for their child to have the disorder. Therefore, in cases where the parents are related by blood (consanguineous), the occurrence rate is higher than in the rest of the



Colored transmission electron micrograph (TEM) of tissue showing abnormally shaped and structured mitochondria in the liver. Methylmalonic acidemia is a metabolic disorder that disrupts normal amino acid metabolism. (Patricia M. Zervas, NIH Office of Research Services/Science Source)

population. Parents with one child affected by MMA have a 25% likelihood that their next child will also be affected with MMA.

There is no observed increase in likelihood for the disease on the basis of sex or ethnicity in cases of MMA.

Signs and symptoms

The abnormally high levels of acid in the blood of individuals affected with MMA can produce drowsiness, seizures, and, in severe cases, coma and/or stroke. Prolonged acidemia can cause intellectual disability. In the very rare instances of a complete apoenzyme absence, MMA is associated with sudden infant death syndrome (SIDS) and at least one known case of sudden child death at the age of 11 months.

Dehydration and failure to thrive are generally the first signs of MMA. These symptoms are accompanied by lethargy, lack of muscle tone (hypotonia), and “floppiness” in newborns.

Developmental delay is typically experienced in all individuals affected with MMA if treatment is not started early in life.

Some individuals affected with MMA have facial dysmorphisms. These include a broad nose, a high forehead, a skin fold of the upper eyelid (epicanthal folds), and a lack of the normal groove in the skin between the nose and the upper lip (the philtrum). In a few individuals affected with MMA, skin lesions resulting from yeast infections (candidosis) may be present, particularly in the mouth and facial area. Occasionally, enlargement of the liver (hepatomegaly) is seen in MMA-affected individuals.

When observed in individuals with MMA, uncoordinated muscle movements (choreoathetosis), disordered muscle tone (dystonia), slurred speech (dysarthria), and difficulty swallowing (dysphagia) may be signs of an acidemia-induced stroke.

Diagnosis

In newborns, a history of poor feeding, increasing lethargy, and vomiting are typical symptoms of MMA. In older infants, an episode of lethargy, often accompanied by seizures, is symptomatic. In children or adolescents, the symptoms may include muscle weakness, loss or diminishment of sensation in the legs, and/or blood clots.

Kidney (renal) disease may be observed in affected individuals with long-untreated MMA.

A blood test to detect high levels of methylmalonic acid is a decisive test for MMA. Researchers at

KEY TERMS

Apoenzyme—An enzyme that cannot function without assistance from other molecules called cofactors.

ATP—Adenosine triphosphate. The molecule used by the cells of the body for energy.

Autosomal recessive disorder—A disorder where two copies of a dysfunctional gene must be inherited in order for the trait to present. The gene is present on the non-sex chromosomes.

Cofactor—A substance that is required by an enzyme to perform its function.

Ketosis—An abnormal build-up of compounds called ketones in the blood. This condition usually indicates a problem with blood sugar regulation.

Metabolic acidosis—High acidity (low pH) in the body due to abnormal metabolism, excessive acid intake, or retention in the kidneys.

Methylmalonic acid—An intermediate product formed when certain substances are metabolized.

Sudden infant death syndrome (SIDS)—The unexpected, sudden death of a child under one year of age. Often called “crib death.”

TCA cycle—Formerly known as the Krebs cycle, a process by which glucose and other compounds are broken down into forms that are directly useable as energy in the cells.

the National Institutes of Health (NIH) have developed a breath test (the 1-13C-propionate breath test) that measures how well patients with methylmalonic acidemia (MMA) respond to receiving liver or combined liver and kidney transplantation. The test can also be used to assess the severity of the disease in people and help determine whether they would benefit from surgical or experimental genomic therapies that target the liver. Propionate oxidative capacity, as measured with 1-13C-propionate breath testing, predicts disease severity and clinical outcomes, and it could be used to assess the therapeutic effects of liver-targeted genomic therapies for MMA and related disorders of propionate metabolism. MMA may also be detected via a urine test for abnormally high levels of methylmalonate.

Prenatally, MMA may be diagnosed by measuring the activity of the apoenzyme methylmalonyl-CoA mutase in cultured cells grown from the cells obtained during an amniocentesis.

QUESTIONS TO ASK YOUR DOCTOR

- How is MMA likely to affect my quality of life?
- When should treatment begin for newborns or infants?
- If MMA runs in my family or my spouse's family, what is the chance my children will have the disease?
- What are the side effects of common treatments for MMA?

In one MMA-related case, a woman named Patricia Stallings was sentenced to life imprisonment for the presumed poisoning of her infant son with ethylene glycol, an ingredient in antifreeze. It was not until she gave birth in prison to a second son who was properly diagnosed with MMA that forensic investigators discovered that what was initially thought to be ethylene glycol in her first son's system was, in fact, methylmalonic acid. All charges against Ms. Stallings were dropped, and she was released from prison. This was an extreme case, but it certainly shows the importance of proper medical diagnosis of MMA.

Family history is often used to diagnose MMA when there are affected siblings or siblings who died shortly after birth for unclear reasons.

Treatment and management

Individuals affected with MMA are generally placed on low- or no-protein diets supplemented with carnitine, cobalamin (vitamin B12), and alkalinizing agents such as bicarbonate to neutralize the excess acid caused by MMA. Intravenous administration of glucose may be necessary during acute attacks. In individuals who do not respond to carnitine and/or cobalamin, the anti-bacterial drug metronidazole may be prescribed. This drug kills some of the naturally occurring bacteria in the lower digestive tract and thereby reduces the production of propionate, a precursor chemical to methylmalonic acid. In cases of severe MMA, kidney and/or liver transplants may be called for.

Prognosis

With appropriate care and diet, MMA is a controllable disease that does not kill or permanently disable people beyond the first year of life. If unchecked, MMA can lead to permanent, irreversible disabilities or conditions or even death. Some infants affected with extremely

severe genetic mutations are stillborn or die prior to an appropriate diagnosis of MMA being made.

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ORGANIZATIONS

- National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 263-9938, <http://www.rarediseases.org>
- Organic Acidemia Association, 9040 Duluth Street, Golden Valley, MN 55427, (763) 559-1797, (866) 539-4060, mkstagni@gmail.com, <http://www.oaanews.org>

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Microbiome

Definition

The human microbiome refers to the entirety of genetic material of all of the micro-organisms (bacteria,

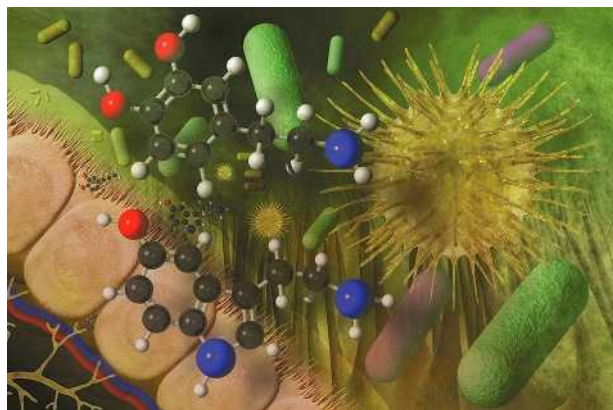


Illustration of microbiome (gut bacteria), which make chemicals such as dopamine (above) and serotonin (below) that neurons use to communicate with each other. (Carol and Mike Werner/Science Source)

bacteriophage, fungi, protozoa, and viruses) found on or inside the human body. The term was first used by microbiologist Joshua Lederberg in 2001.

Description

There are trillions of microbes living on and inside the human body. In fact, the human body has more microbes than individual cells. According to researcher Dr. Martin J. Blaser at the New York University School of Medicine, “The current estimate is that humans have ten trillion human cells and about 100 trillion bacterial cells.” These organisms conduct necessary functions such as aiding in digestion, protecting from illness, and enhancing the reproductive system. Scientists have known for many years that bacteria play an important role in health. Of the thousands of known bacteria, only approximately 100 are known to be harmful to humans. Using the microbiome, researchers are investigating the role of bacteria and other microbes in promoting and protecting health.

In 2007, researchers at the National Institutes of Health (NIH) began the Human Microbiome Project to study microbiomes within the human body and the genetics of these organisms. Their goal was to “characterize microbial communities found at multiple human body sites and to look for correlations between changes in the microbiome and human health.” This project has led to the discovery of the significance of genetic information from the 10,000-plus different species of microbes that live in and on the human body. It has identified more than eight million unique microbial genes associated with the human microbiome in healthy adults. These microbes contribute more genes used in human survival than the entire human genome. These microorganisms are crucial to human survival, and by studying them, scientists have

recognized the fact the humans need these organisms far more than previously thought. Our microbiome helps us by producing vitamins, controlling our immune system, protecting us against microbes that cause disease, and digesting our food.

Genetic profile

Using several scientific methodologies, researchers have identified some genetic information of the microbiome and how it affects humans. One such method is utilizing the large databases of human genomic data, such as the National Center for Biotechnology Information’s (NCBI) non-redundant Clusters of Orthologous Groups (COG) or the Kyoto Encyclopedia of Genes and Genomes (KEGG) databases and comparing specific sections of the genetics of a micro-organism isolated from the microbiome. The advantage to this method is that it may identify interactions between micro-organisms or between host and micro-organism; however, it is limited because of sections of missing data and gaps in the genome that are not yet identified.

Another method to identify genetic factors of the human microbiome is to use catalogues of known genes within the microbiome. Researchers are compiling data to create more comprehensive catalogues as genes are identified. As technology progresses, scientists expect not only to identify more of the genetics of the microbiome but also to identify more of the significance of micro-organism/host interactions. One such interaction is the AMR gene and antibiotic resistance.

Demographics

Every human, regardless of gender or race, has a microbiome associated with his or her body. There is far more variability within the microbiome than in the human genome, making it an even more individualized set of genetic material. According to Dusko Ehrlich, project coordinator of MetaHIT, a program created to study the genomics of the intestinal tract, “There’s a 0.1% difference in our genomes, but there may be a 50% difference in our metagenome.”

Signs and symptoms

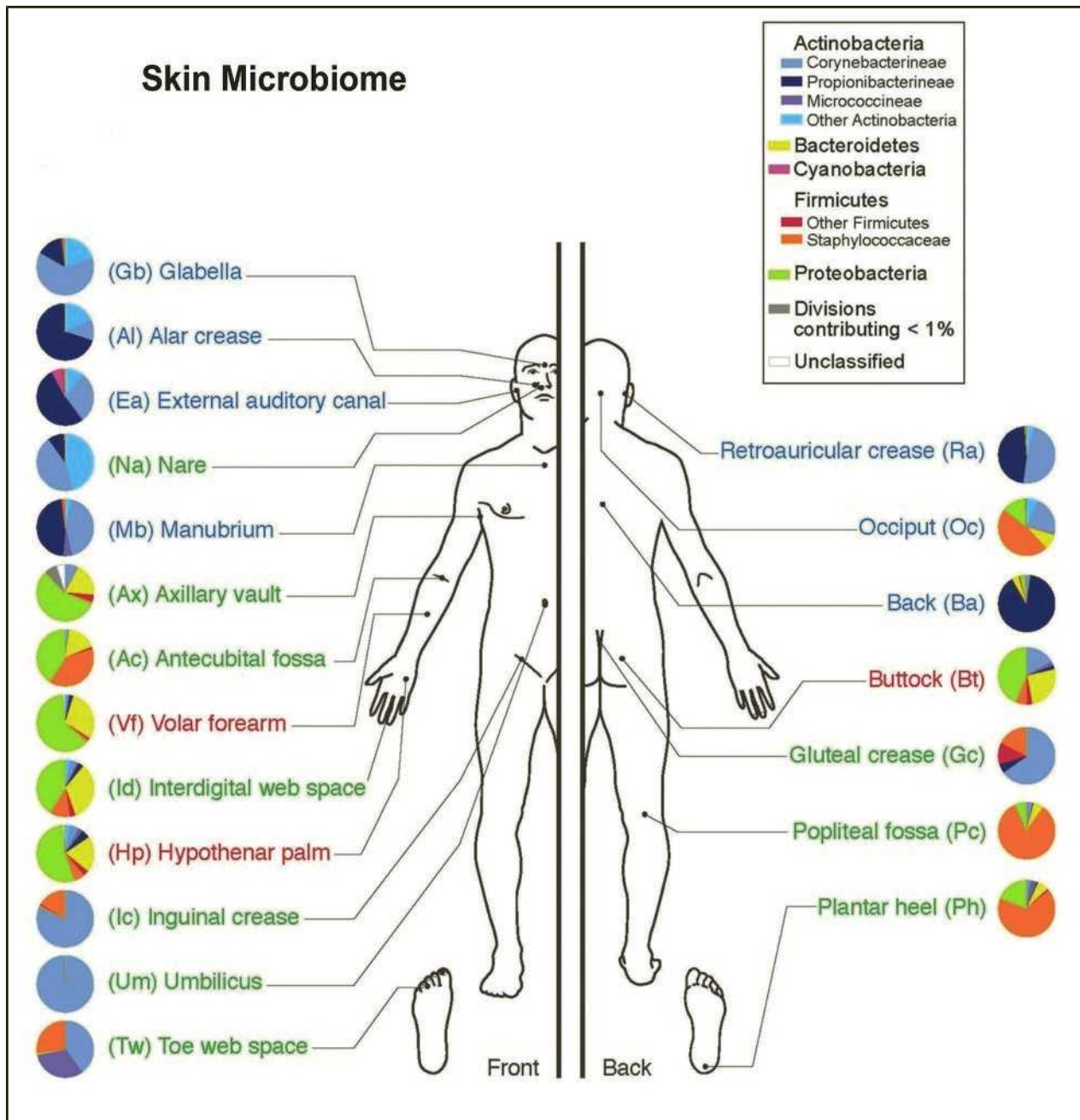
When the microbiome is in balance and working in harmony, there is less chance of illness. However, when the microbiome becomes unbalanced, there is an increased chance of symptoms. The type of symptoms will be determined by the type of imbalance and the part of the body involved. For example, microbe imbalance in the gut can lead to intestinal problems. If the microbe imbalance is present in the respiratory tract, then asthma symptoms may occur. If the bacteria in the gut contain mutations in

antibiotic resistant genes (ARGs), then the body may be susceptible to drug-resistant infections. Other studies have shown a link between changes in the microbiome of the gut and conditions such as obesity and anxiety.

The Microbiome and Disease

Each person's microbiome is unique, and this can influence their health and susceptibility to different

diseases. For example, when our microbiome is not working properly, it can increase our risk of autoimmune diseases like diabetes, arthritis, multiple sclerosis, and muscular dystrophy. Autoimmune diseases occur when your immune system attacks your body by mistake. A faulty microbiome can result in the accumulation of disease-causing microbes, which causes this abnormal immune response. Since we can pass down our microbiome to our children, an



The skin can be thought of as an ecosystem of diverse microorganisms, including bacteria, fungi, viruses, and mites, that live in various creases and sections of body. If the balance gets disrupted, skin disorders or infections can occur. (Science Source)

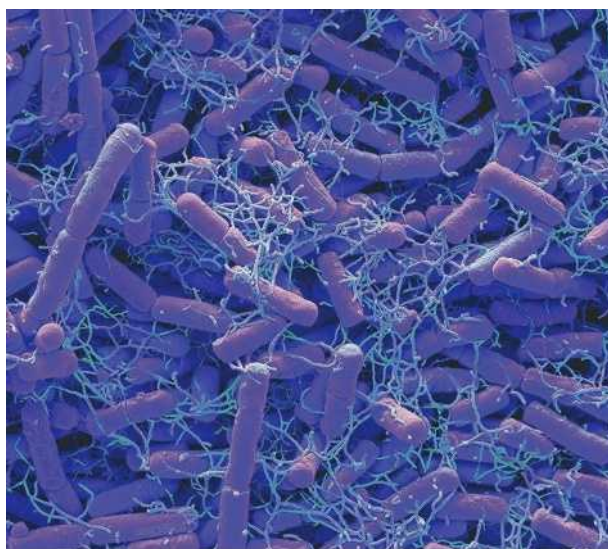
increased risk for autoimmune diseases may be passed down in families.

The composition of the microbiome influences the development of allergies and asthma, which result from an over-reaction of the immune system. People who have less-diverse microbiomes have fewer species to recognize as foreign but safe, and they are more likely to over-react to allergens. Individuals who have more exposure to microbes tend to have a more diverse microbiome, which can help prevent allergies and asthma. For example, living in a home with dogs seems to increase the diversity of the bacteria in the microbiome and decrease the risk of childhood allergies.

Another condition affected by the microbiome is irritable bowel syndrome (IBS). IBS affects the intestines and causes cramping, bloating, gas, diarrhea, and constipation. The microbiome in the digestive tract can help protect the body from pathogens by producing antibacterial substances like short chain fatty acids (SCFA). IBS patients typically have changes in their gut microbiome. These changes can cause inflammation of the stomach and intestines (gastroenteritis) as the result of a microbe infection. This inflammation can lead to the development of IBS. People with diarrhea-predominant IBS are more likely to have an overgrowth of bacteria in the small intestine. People with constipation-predominant IBS are more likely to have higher levels of microbes that produce methane. Methane gas decreases the contraction of the intestines which can lead to constipation.

The microbiome in the gut appears to affect the functioning of the brain and the nervous system. Research suggests that there is a communication loop between the central and peripheral nervous system and the enteric nervous system (ENS). The ENS controls the function of the gastrointestinal system. This communication is bidirectional, or a loop that links the emotional and cognitive centers of the brain with peripheral digestive functions. The health of your microbiome can, therefore, influence brain and mental health. Changes in the microbiome of IBS patients may contribute to the intestinal pain found in IBS. This is because the microbiome appears to regulate pain in the peripheral and central nervous system. Researchers believe that it may be possible to decrease chronic pain and improve mental and brain health by affecting the gut microbiome through diet and medications.

Large-scale changes of the microbes in the digestive tract and its microbiome appear to be associated with obesity. Changes in digestive tract microbes can alter the metabolism of the host. When that occurs, it may cause inflammation, insulin resistance, and an increase in stored fat. Studies have also found that obese twins may have



Microbiome. Colored scanning electron micrograph (SEM) of bacteria cultured from a fingertip. There are around 1000 species of bacteria from 19 phyla found on human skin. Skin flora is usually non-pathogenic, and either commensal (not harmful to their host) or mutualistic (beneficial). One benefit bacteria can offer is preventing transient pathogenic organisms from colonizing the skin surface, either by competing for nutrients, secreting chemicals against them, or stimulating the skin's immune system. However, resident microbes can cause skin diseases and enter the blood system, creating life-threatening diseases, particularly in immunosuppressed people. (Steve Gschmeissner/Science Source)

fewer types of bacteria in their microbiome and more enzymes that help them more efficiently extract calories. This can lead to more weight gain when consuming less food. Restoration of the microbes in the digestive tract to a healthy state may reduce symptoms and lead to weight loss.

An individual's diet seems to affect the health of their microbiome, which in turn effects the risk of disease. One study found that people who ate more dairy desserts, red meat, and processed foods were more likely to have gut bacteria that were associated with an increased risk of diseases like heart disease and diabetes. Those who ate foods like high-fiber vegetables, nuts, fish, and eggs had gut bacteria that were associated with a lower risk of disease. Processed foods, whether they were plant-based or not, were associated with unhealthier gut bacteria.

A child's exposure to certain chemicals like phthalates, which are found in detergents, plastic clothing, and personal products like shampoo, and polyfluoroalkyl substances, which are found in stain- and water-repellent fabrics, may influence their microbiome. One study found that children with high levels of phthalates in their blood had fewer and less variety of gut bacteria and that

KEY TERMS

Bacteriophage—A virus that can destroy a bacterium.

Metagenome—Genetic material taken directly from an environment.

Microbe—A microorganism.

Microbiota—Microscopic living organisms.

Prebiotic—Chemicals or compounds that induce growth in micro-organisms.

Probiotic—Micro-organisms believed to provide health benefits to humans.

Protozoa—One type of a class of single-celled organism.

Single nucleotide polymorphism (SNP)—A type of single-gene mutation.

those with high levels of phthalates had fewer fungi. A reduction in bacteria and fungi may cause health problems. This study also found that children with higher levels of chemicals in their blood had gut bacteria that are used to clean up toxic chemicals. These types of bacteria are not usually found in the human gut.

The Microbiome and Antibiotic Resistance

The microbiome has also been linked to antibiotic resistance, which happens when bacteria cannot be controlled by antibiotics. The overuse of antibiotics has given rise to many strains of bacteria that are resistant to the antibiotics that are currently available. This is a global threat. These bacteria become resistant through the development of antibiotic resistant genes (ARGs). The human digestive tract is a reservoir of bacteria with ARGs that are resistant to antibiotics. This antibiotic resistance can be passed on to other people. For example, antibiotic resistance can be passed down to a child during birth through exposure to antibiotic resistant bacteria. Interestingly, some research suggests that children born by caesarean section, are more likely to have antibiotic resistance, because they were more exposed to bacteria acquired in the hospital. In this manner, scientists believe that the ARGs that lead to antibiotic resistance are passed from generation to generation. However, a vaginal birth can also expose the child to beneficial bacteria from the mother's microbiome.

Diagnosis

Research into the benefits of the microbiome as a diagnostic tool is ongoing. In 2012, Swedish scientists

showed that the microbial genes in the digestive tract may be a better predictor of risk for developing type 2 diabetes than measurements such as waist-to-hip ratio and body mass index. Also in 2012, researchers from the MetaHIT project presented data to suggest that digestive-tract bacteria were more accurate at predicting obesity and leanness than individual genetic variants. These results have led researchers at the University of Colorado to surmise that microbiomes may help to more accurately diagnose other digestive tract and immune system disorders such as Crohn's disease, which is often misdiagnosed.

Treatment and management

Researchers have discovered that prebiotics and probiotics may help prevent health issues by helping to balance the microbiome. Probiotics are beneficial bacteria, and prebiotics are plant fibers that help feed the healthy bacteria. You can get probiotics from supplements and also from fermented foods like yogurt, sauerkraut, kombucha, and kimchi. Prebiotics can be found in many fruits and vegetables, especially those that contain fiber and resistant starch that your body cannot digest. Some research suggests that prebiotics and probiotics may be effective treatment for some psychological disorders and for digestive disorders such as irritable bowel syndrome (IBS).

Fecal microbiota transplantation (FMT), can also help balance the microbiome. FMT restores the healthy bacteria in the colon by injecting stool into the colon from a healthy donor. FMT can cure often-fatal, drug-resistant infections such as *Clostridium difficile* (*C. difficile*). Antibiotic therapy can upset the balance of the microbiome and allow the *C. difficile* to multiply. The fecal material from the healthy individual, on the other hand, can help to regrow the needed micro-organisms and re-establish a balanced microbiome. This can lead to eradication of the sick bacteria or at least a reduction in its numbers so that symptoms subside. FMT has also been used to treat colitis, constipation, and IBS.

Many researchers think the future of medical treatment may be found in the organisms and genetics of the microbiome. In 2014, a major pharmaceutical company announced a partnership with a biotech company in order to study the microbiome with the goal of developing tests for liver and digestive disease. Other research is seeking to develop small proteins to work with the microbiome to treat conditions like diabetes and autoimmune illnesses. 4D Pharma and Merck are partnering in the development of medicines made up of strains of gut bacteria originally from healthy human donors. These bacteria will be put into capsules and taken orally.

QUESTIONS TO ASK YOUR DOCTOR

- Would I benefit from taking probiotics?
- What, if any, imbalance do I have in the microorganisms in my body?
- Are there tests to perform that can measure the micro-organisms in my body?

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Deborah L. Nurmi, MS

Revised by Lisa M. Andres, MS, CGC

Microcephalic osteodysplastic primordial dwarfism type 2 (MOPD2) see **Primordial dwarfism**

Microcephaly

Definition

Microcephaly is a condition in which the size of the skull and the brain is abnormally small. According to the American Academy of Neurology, the specific criterion for microcephaly is a head circumference that is more than two standard deviations below mean size. Some researchers classify severe microcephaly as head circumference that is more than three standard deviations below mean size.

Description

Microcephaly is an abnormally small sized skull and brain. The defect can be the result of hundreds of factors—genetic causes, exposure to alcohol or other drugs, maternal illness during pregnancy, and environment issues—that may affect brain development. Researchers now classify microcephaly as either congenital or postnatal.

Congenital microcephaly is also referred to as primary microcephaly. Other postnatal forms are considered secondary microcephaly.

Microcephaly is often diagnosed in children with cerebral palsy, epilepsy, cognitive impairments, and developmental delays.

Risk factors

Risk factors include maternal exposure to certain illnesses, radiation, or toxins during pregnancy. The condition may also be inherited in an autosomal recessive (carried by both parents) or autosomal dominant (carried by one parent) pattern. This means that a child may inherit it if one or both parents carry the chromosomal defect.

The specific causes of microcephaly are numerous, including:

- Chromosomal. Trisomies 13, 18, and 21
- Degenerative disorders of the mother. Tay-Sachs
- Familial genetics. Autosomal dominant pattern (only one parent carries the gene defect) or autosomal recessive pattern (both parents carry the gene defect)
- Malformations. Lissencephaly, schizencephaly

KEY TERMS

Circumference—The length around a circle.

Encephalitis—Inflammation of the brain.

Lissencephaly—A condition in which the brain lacks folds and is smooth.

Neuroimaging—Imaging studies of the brain, such as x-ray, computed tomography (CT) scans, or magnetic resonance imaging (MRI) scans.

Schizencephaly—A rare disorder caused by abnormal slits within the brain.

Trisomy—Three chromosomes in each cell, rather than two.

- Maternal nervous system infections during pregnancy. Bacterial meningitis (group B *Streptococcus*) or viral encephalitis, herpes virus
- Maternal infections during pregnancy. TORCH complex of maternal infections. TORCH is an acronym for toxoplasmosis, other infections, rubella, cytomegalovirus (CMV), and herpes simplex virus.
- Metabolic disorders of the mother. Phenylketonuria (PKU), maple syrup urine disease
- Placental insufficiency. Toxemia
- Radiation exposure
- Syndromes. Down (most common syndrome cause of microcephaly; 30% of Down syndrome babies have microcephaly), Rubinstein-Taybi, Angelman
- Toxin exposure. Fetal alcohol syndrome, possibly other drugs, such as anticonvulsant medication

In addition to the risk factors listed, scientists believe maternal tobacco smoking as well as uncontrolled or poorly controlled diabetes may cause congenital microcephaly during pregnancy. Older children may develop microcephaly due to lead poisoning or chronic renal failure. It is possible that nearly any chronic disease may contribute to microcephaly.

Genetic profile

Next generation sequencing coupled with whole genome sequencing capabilities have helped to identify genetic loci responsible for primary autosomal recessive microcephaly (MCPH). There have been 13 loci implicated, with mutations in the *ASPM* gene (also known as *MCPH5*) accounting for 25%–50% of diagnosed cases. The second most frequent mutation is in the *WDR62* gene. The identified genes encode for proteins that are essential in cell division and related cellular organelles

such as centrioles and centrosomes. Additionally, these genes encode for proteins involved in cell cycle checkpoints. Mutations in these genes cause improper neural cell division during the development of the cerebral cortex, leading to the reduced skull and brain size.

Demographics

The prevalence of all forms of microcephaly is unknown. The prevalence of all forms of primary microcephaly has been reported to range from 1 in 30,000 to 1 in 250,000 newborns worldwide. Research published in 2014 studying the largest cohort of children diagnosed with primary microcephaly included 680 patients. Of those patients included in the study, the majority were male at 59%, and 41% were female. It is thought that this difference in genders could be attributed to mutations in the X-chromosomal recessive genes, which primarily affect males.

Signs and symptoms

Symptoms of microcephaly include presence of an abnormally undersized skull and brain, usually accompanied by intellectual disability and a reduction in motor capabilities. Impaired muscle control can produce a range of effects from minor clumsiness to major loss of function in the arms and legs. Children can have mildly hyperactive behavior, varying levels of intellectual disability, and may develop seizures as they grow older.

Diagnosis

Examination

The head circumference of a baby is measured at birth. Follow-up measurements are performed during the first three to five years of life. If microcephaly is to be found after birth, most frequently the diagnosis is made by the time the child is two to three years of age.

Head circumference is measured with a measuring tape that is flexible but cannot be stretched. It is placed tightly around the largest portion of the back of the head (occiput) and gently but firmly wrapped around to the front of the head. If the measurement is two standard deviations below normal for the child's age, the measurement's accuracy should be verified, and its plot on the growth chart rechecked.

Tests

If microcephaly is found, imaging studies and genetic testing are performed to attempt to determine the cause. Since children with microcephaly face higher risk for disorders such as cerebral palsy and epilepsy, testing for these conditions should be performed as well.

QUESTIONS TO ASK YOUR DOCTOR

- How small is my baby's head circumference compared to normal size for his or her age?
- What supportive measures can I take to ensure my baby has the best chance for development?
- Is my baby's microcephaly considered congenital or developed?
- What do you think caused my baby to have microcephaly?
- What is my risk for giving birth to another child with microcephaly?

Procedures

Microcephaly may be diagnosed prior to birth, during a sonography (ultrasound) procedure in the latter stages of pregnancy.

Babies may undergo magnetic resonance imaging (MRI) studies to determine brain size and check for abnormalities in the brain.

Treatment and management

Treatment for primary microcephaly is supportive. Neuroimaging is important in treating babies with microcephaly to help determine the extent of the disorder. In secondary or postnatal microcephaly there may be the option to surgically open parts of the skull that have closed prematurely to allow continued growth of the brain tissue. Microcephaly may develop if the fetus is exposed to a number of infections or toxic substances. Avoiding alcohol, recreational drugs, and possibly certain medications, as well as maintaining optimum health during pregnancy are steps that a mother can take to lower her chances of giving birth to a child with microcephaly. Infections also play a role, and it is important for the pregnant woman to take steps to minimize her chance of acquiring infection. For example, toxoplasmosis is one potential cause of microcephaly, and may be transmitted in feline feces; therefore, pregnant women should not clean feline litter boxes.

If it is suspected that the gene may be present in either the mother or the father, genetic counseling is recommended.

Proper prenatal health care is essential to ensuring that, if health problems arise, they will be appropriately managed.

Prognosis

About 20%–30% of infants with severe microcephaly will die. Those who survive have a prognosis that includes intellectual deficiency, developmental delays, neurological disorders such as epilepsy, and intellectual disability. Treatment is supportive. Those patients that are candidates for surgical correction of the skull typically have a better prognosis.

Genetic counseling is recommended for families who have a case of microcephaly within the family.

Resources

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ORGANIZATIONS

- Birth Defect Research for Children, 976 Lake Baldwin Lane, Suite 104, Orlando, FL 32814, (407) 895-0802, staff@birthdefects.org, <http://birthdefects.org>
- March of Dimes, 1275 Mamaroneck Ave., White Plains, NY 10605, (914) 997-4488, <http://www.marchofdimes.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <https://rarediseases.org>

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Microcephaly and hypomyelination

Definition

Microcephaly can be congenital or can develop over the first two years of life. Microcephaly also can be a component of different conditions that cause brain growth defects.

Hypomyelination is a neurological disorder that is present at birth and is characterized by a loss of the fatty insulation around neurons.

Both conditions may be present as additional symptoms of other developmental or neurological syndromes.

Description

Microcephaly

Microcephaly means “small head” and is a neurodevelopmental disorder defined by a head circumference that is two to three standard deviations below the mean for age and gender. There are two types of microcephaly based on its onset:

- Congenital microcephaly—present before birth
- Postnatal microcephaly—develops after birth

Both forms of the disease result from the brain not developing normally, either in utero or after birth. There are genetic and environmental factors that contribute to the causes of microcephaly. A small head characterizes the disorder, but the facial features continue to develop normally, giving the individual disproportionate features. During infancy the bones of the skull can fuse too early and limit the size and shape of the skull; this can have an impact on brain development, as the smaller skull doesn't grow along with the brain. Individuals with microcephaly are often short in stature and have limited or low intelligence.

In the nineteenth and twentieth centuries in North America and Europe, people with microcephaly were sold to freak shows and circuses, where they were known as “pin heads” and sometimes presented as different species.

Hypomyelination/CHN

Hypomyelination is an inherited disease that affects the nervous system and sometimes also affects the eyes. Congenital hypomyelination neuropathy (CHN) presents at birth and involves defects in white matter in the brain, where the nerves lose or lack the myelin sheathing from around the axons. This leads to a breakdown in nerve impulses, causing lost or impaired feeling and movement, muscle weakness, and respiratory difficulties.

Genetic profile

Microcephaly

Congenital microcephaly develops before birth and can be inherited several different ways; it can be a familial autosomal recessive or dominant inherited trait, it can be X-linked, or it can be due to chromosomal balanced rearrangements. These are considered isolated events of

KEY TERMS

Cataracts—A cloudy disruption of the eye lens that affects sight due to protein deposits in the lens.

Chromosomal abnormality—When chromosomes are missing or extra chromosomes are present.

Congenital—Occurring at or before birth.

Craniosynostosis—A rare skull abnormality that causes the bones of the skull to be deformed or not develop normally.

Leukocephalopathies—Defects in the white matter of the brain.

Myelin—The fatty protein that insulates the axons of nerve cells and helps maintain the fidelity of nerve impulses.

White matter—Part of the central nervous system found in the brain and superficial spinal cord. It is made mostly of myelin-covered nerve cells that send signals from one region of the cerebrum to another. The name comes from the myelinated nerve cells, which are white in color.

the disorder. Non-genetic events that can contribute to acquired forms of the disorder are caused by disruptive injuries like stroke or congenital infections like rubella. Microcephaly is also sometimes seen in infants born with fetal alcohol syndrome. Maternal malnutrition can also contribute to microcephaly development in children.

In postnatal onset of microcephaly, metabolic disorders can cause abnormal development after birth. Mitochondrial and peroxisomal disorders are common examples of metabolic defects that lead to microcephaly.

The microcephalin gene (*MCPH1*) causes primary microcephaly when the mutation is homozygous. *MCPH1* is expressed in the brain and can affect the development of several different regions during fetus growth.

Hypomyelination/CHN

CHN is a congenital autosomal recessive disease that can present mild to severe phenotypes and is characterized by the recurrent loss and repair of myelin due to mutations in genes required for myelin formation. The exact cause of CHN is not well described, and the loss of myelin is not understood. Along with the inability to make myelin, CHN patients are also often born with cataracts.

Children born with CHN usually develop normally in their first year of life and then slowly start losing their ability to move on their own.

The *FAM126A* gene has been implicated in CHN. *FAM126A* encodes the protein hyccin, which is thought to function in myelin production. It is expressed in the cells of the nervous system and the cornea of the eye. Severity of CHN might depend on the type of mutation in *FAM126A* and whether the protein function is only partially or completely lost.

Recently, mutations in the gene *PYCR2* (pyrroline-5-carboxylate reductase 2) were shown to cause both microcephaly and hypomyelination. *PYCR2* is involved in proline biosynthesis, and the mutation displays a unique syndrome that includes both congenital microcephaly and reduced white matter in the brain due to hypomyelination.

Demographics

In most cases of microcephaly and CHN, both female and male children are affected equally. CHN is exceptionally rare, but can affect both sexes.

Signs and symptoms

Microcephaly

In newborns, neurological defects and seizures are common, as well as intellectual developmental delays. In some cases, infants can be born with normal or reduced head size, but then their head fails to grow as the rest of their body develops. As the child grows, the smallness of the skull will become more pronounced. This can lead to a receding forehead and loose scalp as the face continues to grow at a normal rate. Some individuals will also be short in stature, their motor function and speech can be delayed, and hyperactivity and mental disability are common to varying degrees.

Depending on the cause and the extent of the additional symptoms associated with microcephaly, the overall presentation of the disorder can vary. Some people develop normally with normal levels of intelligence; others can be mentally and physically disabled.

Hypomyelination/CHN

Signs and symptoms may vary depending on the extent of the effects of the disease. Major symptoms include delayed motor development, weakened muscles, impaired coordination, and difficulties breathing and swallowing.

Diagnosis

Microcephaly

Family histories can be taken to determine the chances of a child being born with microcephaly or one

QUESTIONS TO ASK YOUR DOCTOR

- What is the most likely cause of these syndromes?
- What additional testing or special treatments are available for my specific case?
- What are the chances that my other children will develop these syndromes?

of the other syndromes that include microcephaly as a symptom. Physical exams and head circumference measurements can be made at birth and during development to track the progression of the disorder. CT and MRI scans and blood tests can be used to better understand other underlying causes.

Hypomyelination/CHN

To test for CHN, an electromyogram can be used to measure the speed of electrical impulses produced by muscle, which will give some information about the function of neurons. Poorly myelinated neurons will have slower impulse measurements than those that are well insulated. Nerve and muscle biopsies can be taken to observe the physiology of the cells on a histological level.

Treatment and management

Microcephaly

In some cases of craniosynostosis, surgery can be used to separate the bones of the skull and make room for the brain to grow. In most cases, speech and occupational therapies are used to improve quality of life for patients.

Hypomyelination/CHN

There are no good treatment plans for individuals with CHN. Most treatment is supportive and seeks to improve the quality of life in CHN patients.

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ORGANIZATIONS

The Arc, 1825 K St. NW, Suite 1200, Washington, DC 20006, (202) 534-3700 or (800) 433-5255, (202) 534-3731, <http://www.thearc.org>

Birth Defect Research for Children, Inc., 976 Lake Baldwin Lane, Suite 104, Orlando, FL 32814, (407) 895-0802, staff@birthdefects.org, <http://www.birthdefects.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

United Leukodystrophy Foundation, 224 N. 2nd St., Suite 2, DeKalb, IL 60115, (815) 748-3211 or (800) 728-5483, (815) 748-0844, office@ulf.org, <http://www.ulf.org>

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Microcephaly with spastic diplegia

Definition

Microcephaly with spastic diplegia, also known as Paine syndrome, is a rare genetic condition that is present at birth. Characterized by an undersized head and related abnormalities in the brain, the disease results in severe intellectual disability and physical retardation, movement disorders, and vision problems. Most infants with microcephaly with spastic diplegia do not survive their first year of life.

Description

The cerebellum (Latin for “little brain”) is the part of the brain that controls involuntary movements, such as maintaining balance and coordinating muscles during physical activity. When shaking hands, for example, the cerebellum plays a primary role in coordinating the dozens of muscles involved in this seemingly simple task. Microcephaly with spastic diplegia interferes with the proper growth of the cerebellum and other parts of the brain while the fetus is still in the womb. Though this syndrome is considered a single entity, it actually includes several disorders that emerge together. The result is a variety of debilitating effects.

Microcephaly, which is characterized by an abnormally small head, is a neurological disease that is associated with several conditions. The head of an infant with

KEY TERMS

Amino acids—Organic compounds that form the building blocks of protein. There are 20 types of amino acids (8 are “essential amino acids” that the body cannot make that and must be obtained from food).

Congenital—Refers to a disorder that is present at birth.

Gavage—Administration of food via a feeding tube to the stomach.

Neurological—Relating to the brain and central nervous system.

microcephaly is smaller than average when compared to other babies of the same age and gender. This decreased skull size is an indication that the brain did not grow properly during fetal development. The form of microcephaly associated with microcephaly with spastic diplegia causes physical retardation and intellectual disability. Aside from a small head, infants with microcephaly with spastic diplegia may have undersized bodies. Motor skills, language abilities, and other aspects of normal development are impaired. Babies with microcephaly with spastic diplegia, for example, may require a gavage due to feeding difficulties or trouble swallowing. Unlike most infants, they may seem disinterested in the world around them.

Microcephaly with spastic diplegia also produces specific problems related to movement. Infants affected by the disease develop spasticity. This nervous system disorder, in which muscles do not relax properly after being stretched, can cause muscle stiffness, pain, or physical deformity. It can also lead to repetitive spasms by a particular muscle or group of muscles (these spasms are known as myoclonic jerks). Aside from spasticity, an infant with microcephaly with spastic diplegia may experience generalized seizures.

Vision can also be affected, resulting in optic atrophy. This eye disorder causes a degeneration of the nerves carrying information from the eyes to the brain. Optic atrophy can lead to blurry vision or other visual disturbances.

The underlying cause of microcephaly with spastic diplegia is unknown. The effects of the disease are thought to stem from the limited growth of the cerebellum and other areas of the brain. Autopsies of affected children have revealed underdevelopment of this region, as well as abnormalities in the cerebrum and other brain structures.

QUESTIONS TO ASK YOUR DOCTOR

- What physical conditions make microcephaly with spastic diplegia such a serious medical disorder?
- What information and advice can a genetic counselor provide about the possibility of our child's being born with microcephaly with spastic diplegia?
- Are there prenatal tests available for microcephaly with spastic diplegia?

Microcephaly with spastic diplegia is considered very similar to another genetic, congenital disease known as Seemanova syndrome. Both diseases have a number of symptoms in common, although Seemanova syndrome lacks certain characteristics of the former (such as an underdeveloped cerebellum). Some doctors view both conditions as variations of a more broadly defined disorder called Paine-Seemanova syndrome.

Genetic profile

The gene responsible for microcephaly with spastic diplegia has not been identified, but it is believed to lie on the X chromosome. For this reason, the disease is referred to as an X-linked genetic condition. Only males are affected. Females do not usually develop the symptoms of microcephaly with spastic diplegia, but they may be carriers of the gene associated with the disease. This is because women have two X chromosomes, while men only possess one. Even if a woman possesses the gene for microcephaly with spastic diplegia on one of her X chromosomes, she still has a second X chromosome that is free of the faulty gene. This second X chromosome is what protects her from developing symptoms of microcephaly with spastic diplegia, although she may be able to transmit the disease to her children.

Demographics

Microcephaly with spastic diplegia is a rare, congenital disease that only affects males. Most children born with it do not survive infancy.

Signs and symptoms

The most visible symptom of microcephaly with spastic diplegia is often the size of the head, which is smaller than normal. Affected infants may experience feeding difficulties or swallowing problems. They may

not appear to be growing properly, or they may seem disinterested in their environment. The development of motor skills and speech is delayed.

In simple terms, microcephaly with spastic diplegia causes structural abnormalities in the cerebellum, cerebrum, and other parts of the brain. The skull itself is abnormally small due to the fact that its size is dictated by brain growth. Damage to the optic nerve may also occur. In addition, microcephaly with spastic diplegia produces elevated amino acid levels in the urine and cerebrospinal fluid.

Diagnosis

Microcephaly with spastic diplegia is often diagnosed at birth when the size of the head is measured, although a small head circumference may be identified later during a routine exam if it is not detected shortly after delivery. Imaging procedures (such as an x-ray, CT scan, or MRI) are used to identify the structural abnormalities of the brain and skull. Analyses of blood and urine are also performed. An electroencephalogram (EEG), a non-invasive test that measures the electrical activity of the brain, may be recommended to help assess developmental problems or detect relevant brain or nervous system abnormalities.

Treatment and management

There is no cure for microcephaly with spastic diplegia. The changes in brain structure associated with the disease cannot be reversed. When possible, treatment focuses on alleviating symptoms. Anticonvulsants, for example, can be used to help control seizures; dextroamphetamine may also be prescribed to ease symptoms. In addition to drugs, orthopedic surgery is sometimes necessary. Family education and genetic counseling for parents is also recommended.

Prognosis

Due to its debilitating effects on the brain and nervous system, microcephaly with spastic diplegia is usually fatal within one year after birth.

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ORGANIZATIONS

Cortical Foundation, PO Box 340894, Austin, TX 78734, (512) 256-3855, info@cortfoundation.org, <http://cortfoundation.org/cms>

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Microdeletion and microdeletion syndromes

Definitions

Microdeletions are losses of genetic material from chromosomes that are too small to detect by karyotyping, which remains the standard cytogenetic procedure for identifying the complete set of chromosomes in an individual organism and detecting any abnormalities in the number or structure of the chromosomes. In regard to chromosomal deletions, karyotyping generally cannot detect deletions smaller than 5 mega bases (5 million base pairs). These smaller deletions (usually of several contiguous genes) are called microdeletions.

The significance of microdeletions for human health is that while some of these aberrations have no known effects on growth or development, others cause genetic disorders collectively known as microdeletion syndromes. Microdeletions on the long arm of the Y chromosome are associated with infertility in about 20% of men diagnosed with low sperm count.

A similar abnormality in which a small segment of a chromosome is doubled is called a microduplication. The significance of microduplication syndromes is less well defined as of 2021 than for microdeletion syndromes, partly because the symptoms of microduplication syndromes are less severe in most cases. Although both types of syndromes are sometimes called contiguous gene syndromes or CGSs, researchers prefer to refer to the two types separately.

Both microdeletions and microduplications are examples of copy number variations or CNVs. Microdeletions represent copy number losses, and microduplications represent copy number gains.



Fluorescence in situ hybridization (FISH) micrograph of human chromosomes showing Williams syndrome, a genetic disorder is caused by the deletion of a gene on chromosome 7. The chromosome marked 7 at lower right shows four dots (genes) at the corners of its lower half (green). The chromosome marked del(7) at upper left shows only one such green area. (Addenbrookes Hospital/Science Source)

Description

The basic cause of microdeletions as well as of other chromosome abnormalities is the instability of the human genome itself. There are a large number of repetitive elements in the genome that can be either lost or duplicated during the process of cell division or the recombination of chromosomes that occurs during meiosis. Most microdeletions occur during the formation of gametes (sperm or eggs). The loss of genetic material that characterizes microdeletions can occur as a result of unequal crossover between a pair of chromosomes or as a result of chromosomes breaking apart without rejoining.

Unlike some other chromosomal aberrations, microdeletions do not have any known connection to maternal age, which means that younger women can give birth to children with microdeletion syndromes. Microdeletions are thought to be sporadic (random) occurrences known as *de novo* mutations. In some cases, however, the discovery of a microdeletion syndrome in a child may lead to the parents being tested and found to have the same microdeletion but with milder effects.

Genetic profiles

The number of identified microdeletion syndromes continues to increase with the advent of sophisticated diagnostic assays and next-generation sequencing (NGS) technology, which allow researchers to focus on very small segments of chromosomal DNA throughout the human genome. The Genetic and Rare Diseases Information

Center (GARD) of the National Institutes of Health lists 62 microdeletion syndromes; the National Organization for Rare Disorders (NORD) lists 41; a paper published in 2012 lists no fewer than 211 microdeletion syndromes, and the number has risen to over 300 as of 2021. The following is a list of the better-known microdeletion syndromes and their genetic profiles:

- Alagille syndrome: microdeletion at chromosome 20p12, causing a loss of the *JAG1* gene.
- Angelman syndrome: microdeletion at 15q11 on the mother's chromosome 15, causing a loss of the *UBE3A* gene.
- DiGeorge syndrome: microdeletion at 22q11.2, causing the loss of 30 to 40 genes.
- Langer-Giedion syndrome: microdeletion at 8q24.1, causing the loss of the *TRPS1* and *EXT1* genes.
- Miller-Dieker syndrome: microdeletion at 17p13.3, causing the loss of the *PAFAH1B1* and *YWHAE* genes.
- Prader-Willi syndrome: microdeletion at 15q11 on the father's chromosome 15.
- Rubinstein-Taybi syndrome: microdeletion at 16p13.3, leading to the loss of either the *CREBBP* or the *EP300* gene.
- Smith-Magenis syndrome: microdeletion at 17p11.2, leading to the loss of the *RAI1* gene.
- Williams syndrome (also called Williams-Beuren syndrome): microdeletion at 7q11.23, causing the loss of more than 25 genes.

Demographics

The prevalence of microdeletion syndromes vary widely; some are extremely rare:

- Alagille syndrome: 1 in every 30,000 to 1 in every 40,000 persons.
- Angelman syndrome: 1 in 12,000 to 1 in 20,000 persons.
- DiGeorge syndrome: 1 person in 4,000.
- Langer-Giedion syndrome: very rare; about 60 cases reported worldwide, with males affected three times as often as females.
- Miller-Dieker syndrome: fewer than 1 person in every 100,000.
- Prader-Willi syndrome: 1 in 10,000 to 1 in 30,000 persons.
- Rubinstein-Taybi syndrome: 1 in 250,000 to 1 in 300,000 persons.
- Smith-Magenis syndrome: 1 in 15,000 to 1 in 25,000 persons.
- Williams syndrome: 1 in 7,500 to 1 in 20,000 persons.

Signs and symptoms

- Alagille syndrome: liver problems leading to eventual liver failure; failure to thrive; structural abnormalities of the heart; skeletal abnormalities; abnormal band within the cornea of the eye.
- Angelman syndrome: small head with characteristic facial features; severe intellectual disability, movement problems, seizures, and sleep disorders.
- DiGeorge syndrome: heart problems, characteristic facial features, developmental delays, cleft palate, learning difficulties, and psychiatric issues.
- Langer-Giedion syndrome: Sparse scalp hair, hearing loss, intellectual disability, short stature, and skeletal abnormalities.
- Miller-Dieker syndrome: lissencephaly (smooth brain without the usual grooves and ridges); short upturned nose, small jaw, widely spaced eyes; growth retardation, intellectual disability, epilepsy, feeding difficulties.
- Prader-Willi syndrome: weak muscles, mild intellectual impairment; ravenous appetite leading to obesity and type 2 diabetes; inability to have children.
- Rubinstein-Taybi syndrome: short stature, small head, broad thumbs and broad first toes; learning difficulties; delayed bone growth.
- Smith-Magenis syndrome: intellectual disability; abnormal facial features; behavioral problems including self-harm and temper tantrums; sleeping difficulties.
- Williams syndrome: mild-to-moderate intellectual disability; dental problems; heart defects; high levels of blood calcium.

Diagnosis

Some microdeletions can be detected by prenatal testing, but others—particularly the rare types—are identified after the child is born and develops the symptoms of a microdeletion syndrome. As standard karyotyping will not identify microdeletions, several techniques have been introduced since the early 2000s to assist in diagnosing microdeletion syndromes.

A noninvasive prenatal screening test known as NIPS or NIPT uses cell-free fetal DNA (cffDNA) that is released from cells in the placenta and circulates in the expectant mother's blood after the ninth or tenth week of pregnancy. The test is considered noninvasive, because it requires only a simple blood draw from a vein in the arm and poses no risk to the pregnancy. NIPT is designed to screen for some of the more common chromosomal disorders, including trisomies, abnormalities of the sex chromosomes, and several microdeletion syndromes (Angelman, DiGeorge, and Prader-Willi syndromes). NIPT is not a diagnostic test in the strict sense and must

be followed up by invasive tests like amniocentesis or chorionic villus sampling if the screening test indicates the presence of a chromosomal abnormality.

Cytogenetic techniques that have been developed to identify microdeletions in a person's genome include:

- **Fluorescence in situ hybridization (FISH).** FISH is a technique for detecting and identifying a specific sequence of DNA on a chromosome. The researcher designs a probe, which is a small DNA sequence that contains a fluorescent molecule. The probe then binds to its corresponding sequence on the chromosome being tested. FISH is now considered an older method for identifying microdeletions.
- **Array-based comparative genomic hybridization (array CGH).** Also called chromosomal microarray analysis or CMA, this test was introduced in 2005 and is most often used to identify microdeletion syndromes associated with developmental delays. The researcher takes a DNA sample from the blood of the affected person and a reference blood sample from a healthy subject. The DNA samples are then labeled with two different fluorescent substances, usually red for the control (normal) DNA and green for the DNA to be tested. The labeled DNA samples are mixed and allowed to bind (hybridize) to short fragments of synthetic DNA known as probes on the surface of the array (a glass or plastic chip). If the test DNA contains the microdeletion of interest, it will not bind correctly to the probes on the chip that represent the normal DNA sequence; it will instead bind to the sequence on the chip that represents the mutated DNA.
- **BACs-on-beads (BoBs)** is a newer assay used since 2014 to identify microdeletions during pregnancy. The BoBs assay is a bead-based multiplex assay using polystyrene beads impregnated with two different infrared fluorochromes (fluorescent chemical compounds). The DNA to be tested is derived from amniotic fluid or chorionic villus material taken from the expectant mother. The test DNA and reference DNA from a healthy subject are then hybridized onto the polystyrene beads. After washing, the beads are scanned with a microarray scanner to generate images for analysis. The BoBs assay can be used to identify Williams-Beuren, Miller-Dieker, Smith-Magenis, and Langer-Giedion microdeletion syndromes as well as DiGeorge, Angelman, and Prader-Willi syndromes.

Treatment and management

Treatment and management of microdeletion syndromes vary widely, depending on the patient's symptoms and their severity.

- **Alagille syndrome:** symptoms vary greatly in severity, ranging from minor digestive complaints to the need for heart or liver transplants. Some people with the syndrome may need treatment from a variety of specialists, including cardiologists, gastroenterologists, nephrologists, and ophthalmologists; others may not need any specialized treatment.
- **Angelman syndrome:** There is no cure for the syndrome; treatment is primarily supportive, with antiseizure medications and physical therapy.
- **DiGeorge syndrome:** Symptoms vary considerably in type and severity, even among members of the same family.
- **Langer-Giedion syndrome:** Some treatments are available for the hearing loss and facial abnormalities.
- **Miller-Dieker syndrome:** There are no effective treatments for the lissencephaly; few patients live past age 2.
- **Prader-Willi syndrome:** A strict diet and exercise program is needed to control weight; growth hormone is usually beneficial; counseling and medications are required for the behavioral issues. People with Prader-Willi syndrome typically need to live in group homes in adult life.
- **Rubinstein-Taybi syndrome:** There is no treatment that can reverse or cure the syndrome. Patients are usually referred to specialists for treatment of their specific symptoms.
- **Smith-Magenis syndrome:** Supportive treatment, including physical therapy, occupational therapy, and behavioral therapy, is required throughout the patient's lifetime. Medications may be needed to control the psychiatric symptoms.
- **Williams syndrome:** There is no cure for this syndrome, although avoiding extra calcium and vitamin D, and treating high blood calcium levels are helpful. Children and adolescents also benefit from social skills training and behavioral therapy.

Prognosis

- **Alagille syndrome:** Affected persons with severe heart or liver problems have a shortened lifespan, rarely reaching 40 years of age. Those who are less severely affected have a normal life expectancy.
- **Angelman syndrome:** In many patients, the symptoms improve with age; however, life expectancy is usually shortened by 10 to 15 years.
- **DiGeorge syndrome:** Life expectancy is shortened in patients with severe heart defects and/or severe immune system problems. In addition, patients have an increased risk of developing schizophrenia.

KEY TERMS

Aneuploidy—An abnormal number of chromosomes in a cell, whether extra or missing chromosomes.

Assay—A laboratory test designed to identify and measure the amount of a specific substance.

Autosome—Any chromosome that is not a sex chromosome. The human genome has 22 pairs of autosomes.

Base pair (bp)—Any of the complementary nucleotide bases (adenine-thymine and cytosine-guanine in DNA; adenine-uracil and cytosine-guanine in RNA) held together by weak hydrogen bonds. Base pairs form links between the two strands of DNA.

Carrier—In genetics, a person who has a genetic mutation associated with a disease and is capable of passing it on. A carrier may or may not display the symptoms of the disease.

Chromosome aberrations—A general term for abnormalities in either the number or the structure of chromosomes.

Contiguous gene syndrome (CGS)—An older term for microdeletion syndromes in which several genes lying closely together on the chromosome are lost as a group.

Copy number variation (CNV)—A difference in the number of copies of a gene (normally two) or of a specific segment of DNA.

Cytogenetics—The branch of genetics that studies the components of a cell associated with heredity, particularly the chromosomes.

De novo mutation—A genetic variant that occurs in a child but is not present in either parent.

Fluorescence in situ hybridization (FISH)—A laboratory technique for detecting and identifying a specific sequence of DNA on a chromosome. The researcher designs a probe, which is a small DNA sequence that contains a fluorescent molecule. The probe then binds to its corresponding sequence on the chromosome.

Genome—The total amount of genetic information within an organism's chromosomes, including its genes and DNA sequences.

Karyotype—The complete set of chromosomes in a species or individual organism. The term can also

refer to the laboratory technique used to produce an image of an individual's chromosomes.

Mega base pairs (Mbp)—A million base pairs.

Meiosis (pronounced my-OH-sis)—The process of cell division during the production of ova and sperm, in which the material in the chromosomes undergoes recombination (first-stage meiosis), and the chromosomes are reduced to a single set of 23 instead of the normal number of 23 pairs (second-stage meiosis).

Microdeletion—A chromosome deletion that is too small to be detected by standard karyotyping methods. Microdeletions are typically 1 to 3 mega bases in length (1 to 3 million base pairs), whereas standard deletions are 5 mega bases or longer.

Microduplication—The abnormal doubling of a small segment of a chromosome that is too small to be detected by standard karyotyping.

Next-generation sequencing—A general term for massively parallel sequencing of large portions of DNA base pairs, performed by first fragmenting the DNA, reading the individual fragments in parallel, and then reassembling the reads to obtain the sequence of the entire genome.

Noninvasive prenatal testing (NIPT)—A blood test administered to a pregnant woman to screen for an abnormal number of chromosomes (aneuploidy) in the developing fetus. It is also known as noninvasive prenatal screening or NIPS.

Single nucleotide polymorphism (SNP)—A germline substitution of a single nucleotide (any of a group of molecules that form the building blocks of DNA or RNA) at a specific position in a person's genome.

Trisomy—A type of aneuploidy in which there are three copies of a specific chromosome in cells instead of the normal two. Genetic disorders caused by trisomies include Down syndrome (trisomy 21) and Edwards syndrome (trisomy 18).

Y chromosome—The sex chromosome (allosome) that is found together with an X chromosome in normal human males. Microdeletions in the Y chromosome can affect a man's fertility in adult life.

QUESTIONS TO ASK YOUR DOCTOR

- Have you ever treated a patient with a microdeletion syndrome?
 - If so, how was the disorder diagnosed?
 - Because younger women can give birth to children with microdeletion syndromes, would you advise such women to undergo prenatal screening or testing for these disorders?
 - Have you ever referred a patient for FISH or CMA testing?
- Langer-Giedion syndrome: People with Langer-Giedion syndrome usually have a normal life expectancy.
 - Miller-Dieker syndrome: Death in childhood is the most common outcome; the oldest known individual with this syndrome died at the age of 17.
 - Prader-Willi syndrome: Patients usually have a normal life expectancy, provided they do not become extremely obese.
 - Rubinstein-Taybi syndrome: Life expectancy is usually not affected except in patients with severe heart defects. Patients are, however, at increased risk of developing cancer in adult life.
 - Smith-Magenis syndrome: Affected people usually have a normal life expectancy.
 - Williams syndrome: Patients suffer from high blood pressure throughout life; life expectancy is shortened by the increased risk of heart disease.

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ORGANIZATIONS

American College of Medical Genetics and Genomics (ACMG),
7101 Wisconsin Avenue, Suite 1101, Bethesda, MD 20814,
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American College of Obstetricians and Gynecologists (ACOG),
409 12th Street, SW, Washington, DC 20024-2188, (800)
673-8444, (202) 638-5577, <https://www.acog.org/>

Chromosome Disorder Outreach, Inc., P.O. Box 724, Boca
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Genetic and Rare Diseases Information Center (GARD), P.O.
Box 8126, Gaithersburg, MD 20898-8126, (888) 205-2311,
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National Human Genome Research Institute (NHGRI), Building
31, Room 4B09, 31 Center Drive, MSC 2152, 9000
Rockville Pike, Bethesda, MD 20892-2152, (301)
402-0911, <https://www.genome.gov/about-nhgri/Contact>,
<https://www.genome.gov/>

National Organization for Rare Disorders (NORD), 55 Kenosia
Avenue, Danbury, CT 06810, (203) 744-0100, (203)
263-9938, <https://rarediseases.org/contact-us/>, <https://rarediseases.org>

National Society of Genetic Counselors (NSGC), 330 North
Wabash Avenue, Suite 2000, Chicago, IL 60611, (312)
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Rebecca J. Frey, PhD

Microphthalmia with linear skin defects

Definition

Microphthalmia with linear skin defects (MLS) is a rare genetic disorder that causes abnormalities of the eyes and skin. This disorder was first recognized as a distinct genetic condition in 1990.

Description

MLS is a rare disorder that is observed only in females because males with the disease do not survive to birth. This disorder is also called MIDAS (microphthalmia, dermal aplasia, and sclerocornea) syndrome. People affected by MLS have the following:

- small sunken eyes (microphthalmia)
- irregular red streaks of skin on the head and neck (skin erythema)
- abnormal development of the sclera and cornea of the eye

The eye is composed of three layers: the sclera, the choroid, and the retina. The sclera is the tough white outer coat of the eyeball. As this coat passes over the lens,

KEY TERMS

Cornea—The transparent structure of the eye over the lens that is continuous with the sclera in forming the outermost, protective layer of the eye.

De novo mutation—A genetic mutation that is seen for the first time in the affected person, not inherited from the parents.

Microphthalmia—Small or underdeveloped eyes.

Orbital cysts—Small fluid-filled sacs that abnormally develop inside the bony cavity of the skull that holds the eyeball.

Sclera—The tough white membrane that forms the outer layer of the eyeball.

Septum pellucidum—A membrane between two of the normal cavities of the brain that prevents electrical signals from passing between different portions of the brain.

Skin erythema—Irregular red streaks of skin.

Terminal deletion—The abnormal early termination of a chromosome caused by the deletion of one of its ends.

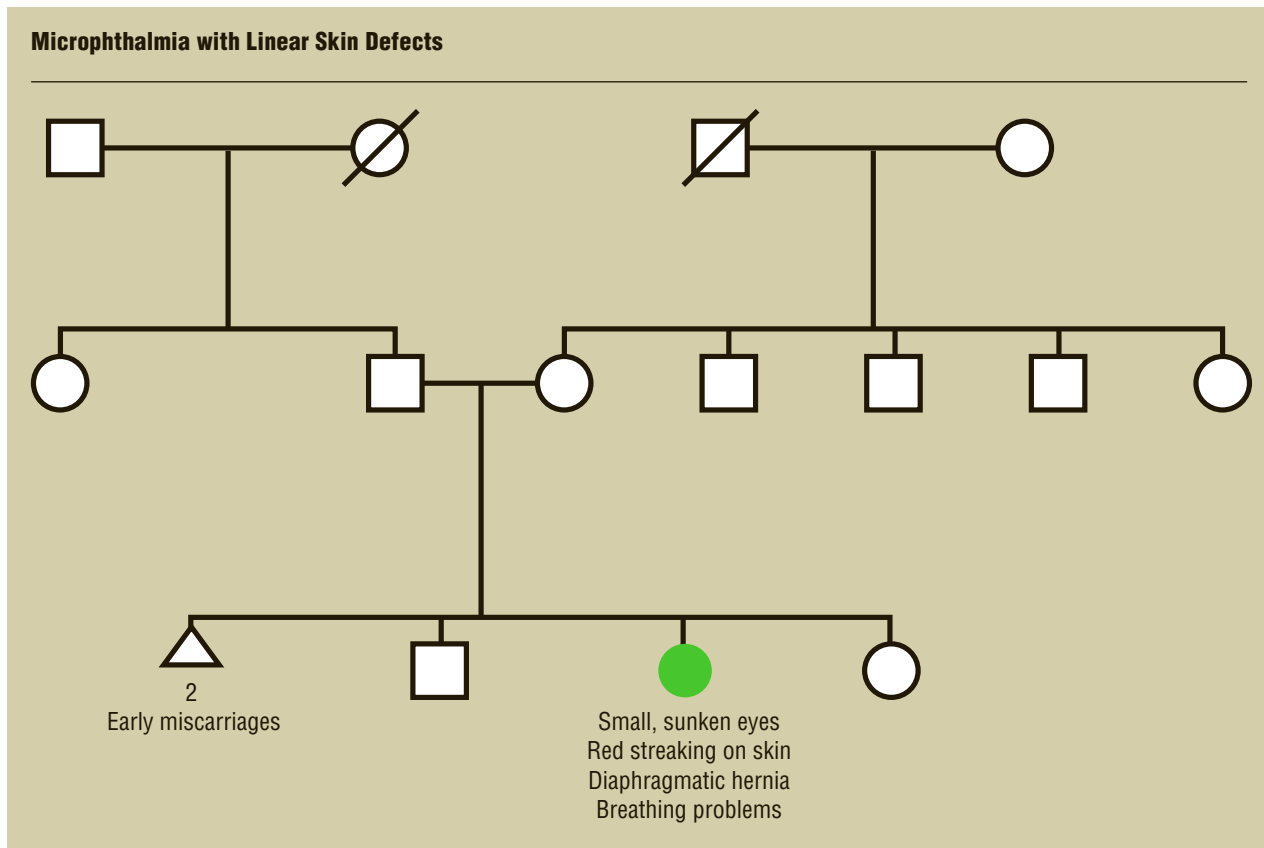
it normally becomes clear. This clear portion of the sclera is the cornea. Both the sclera and the cornea are affected by MLS.

The choroid is the middle layer of the eye. It serves to nourish the retina and absorb scattered light. The retina is the inner, light-sensitive layer of the eye. The retina receives the image transmitted by the lens, and it contains the rods and cones that are responsible for color vision and vision in dim light. Both the choroid and the retina are unaffected by MLS.

Genetic profile

The gene responsible for the signs and symptoms of MLS has been localized to a portion of the short arm (p) of the X chromosome Xp22.3. The specific symptoms of MLS are believed to result from a *de novo* premature cutoff (terminal deletion) of an X chromosome, which, in most cases, deletes the *HCCS* gene, the *MID1* gene, and a portion of the *ARHGAP6* gene, all of which play a role in the development of the eye. People with MLS do not have the portion of the short arm of the X chromosome beyond the Xp22.2 location.

The *HCCS* gene deletion is the primary gene deletion known to cause the signs and symptoms of the condition. This gene encodes for an enzyme known as holocytochrome c-type synthase enzyme, which functions in the



Microphthalmia with linear skin defects: pedigree analysis chart (Gale)

developing embryo within the mitochondria of cells, which are the energy-producing organelles of the cell. Damage to the mitochondria typically leads to cell death or at least moderate to severe cell impairment.

Nearly all of the cases of MLS are believed to result from *de novo* mutations, since parents of affected individuals do not carry the MLS mutation in their chromosomes. A *de novo* mutation is caused by a problem with the chromosomes of the parental egg or sperm cells. The remainder of the chromosomes in the parents is not affected. As the sex cells of one of the parents reproduce, an error occurs. This leads to the transmission of a new mutation from that parent to his or her child. This mutation is expressed for the first time in the child of that parent.

A typical female has two X chromosomes. A typical male has one X chromosome and one Y chromosome. Because no XY male has ever been diagnosed with MLS, it is assumed that MLS is dominant and X-linked with 100% fetal mortality in males. This type of genetic disorder is also called an X-linked male-lethal trait.

There have been a few reported cases of males affected with MLS. These individuals presumably

survived because they were XXY males (genetically female with ambiguous or male sex organs), rather than the typical male with XY chromosomes. This condition (XXY) is called Klinefelter syndrome.

Demographics

Approximately 300 individuals, all without a Y chromosome, have been diagnosed with MLS worldwide. MLS is not associated with any particular sub-populations. It appears with equal frequency in all races and across all geographies. Because it is an X-linked male-lethal trait, it is observed exclusively in females or, in a few cases, in XXY males.

Signs and symptoms

MLS is characterized by the following:

- small, sunken eyes (microphthalmia)
- defects of the sclera and cornea portions of the eye
- linear red streaking of the skin on the upper body, primarily the head and neck
- abnormal protrusion of the abdominal contents upward through an opening in the diaphragm (diaphragmatic

QUESTIONS TO ASK YOUR DOCTOR

- How often should I be examined for visual changes?
- What are my treatment options?
- What are the chances my future children will inherit this disease?
- Should my family members be tested for carrying the disorder?

hernia), which causes difficulty with breathing (respiratory distress)

- a lack of the transparent membrane (septum pellucidum) in the brain that forms a wall between two of the normal cavities (the lateral ventricles) of the brain
- a condition in which the heart is located on the right side rather than the left side of the chest (dextrocardia)

In individuals affected with MLS, the bony cavity that contains the eyeball (orbit) often contains small fluid-filled sacs (orbital cysts). The sclera is often not fully or properly formed, and the cornea generally has areas that are opaque rather than transparent. This corneal opacity causes blurring of vision and may result in blindness. Corneal opacities should not be confused with cataracts, which are opacities of the lens of the eye, not of the cornea.

Difficulty in breathing (respiratory distress) is seen at birth in some patients with MLS. This is caused by a hole in the muscle beneath the lungs (diaphragm) that is responsible for the flow of air into and out of the lungs. This condition will rapidly lead to death if it is not surgically repaired.

Seizures and intellectual disability have been observed in some MLS patients. It is believed that these individuals do not have a septum pellucidum. The absence of this membrane may allow electrical transmissions between parts of the brain that are usually isolated from each other. These inadvertent electrical signals may cause the seizures and the intellectual disability. Developmental symptoms that may be present in patients with MLS include growth delay and/or retardation, heart defects, hernias, auricular malformations, and/or genitourinary malformations.

Diagnosis

MLS is generally diagnosed by the presence of the characteristic red striping of the skin on the head and

neck accompanied by small eyes (microphthalmia) and opaque patches on the corneas.

MLS is differentiated from Goltz syndrome, which has a similar gene locus, in that the patient with MLS has skin irregularities only on the upper half of the body, most typically only on the head and neck. Goltz syndrome results in skin irregularities across the entire body. Also, patients with MLS do not have the abnormal fatty tissue deposits seen under the skin of Goltz syndrome patients. Finally, MLS does not have the clefting of the hands or feet (syndactyly) or incomplete formation of certain structures of the eyes (coloboma) seen in Goltz syndrome.

Identification of the gene responsible for MLS makes genetic testing for this dominant trait potentially possible.

Treatment and management

The treatment and management of MLS is directed toward the symptoms seen in each patient. All those affected with MLS will need eye care, including surgeries, to potentially repair damaged areas of the cornea and sclera. Some individuals may require skin care treatments depending on the severity of the skin abnormalities.

In cases of patients with a diaphragmatic hernia, emergency surgery shortly after birth may be necessary to attempt to repair the damaged area. Unfortunately, most cases of this type of hernia cannot be surgically corrected, and the patient will die.

In cases of patients with a lack of the septum pellucidum in the brain, anti-seizure medication may be necessary to control the seizures.

Genetic testing is currently available for family members, particularly to detect carrier frequency for at-risk females while pregnant.

Prognosis

MLS is lethal in males prior to birth. In females, a full life expectancy is possible if the complications are not severe and if medical treatment is followed.

Most problems of the cornea and sclera of the eye associated with MLS can be treated with corrective lenses or potentially surgically repaired with corneal implants or laser surgery.

Seizures, if present, can generally be controlled by anti-seizure medications.

Developmental delays in growth, motor ability, speech, and intellect occur in some, but not all, cases of MLS. The amount of delay that is observed is directly related to the severity of seizure activity in the brain caused by the malformation, or lack, of the septum pellucidum.

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ORGANIZATIONS

- National Foundation of the Blind, 200 E. Wells St., Baltimore, MD 21230, (410) 659-9314, (410) 685-5653, <http://www.nfb.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06813, (203) 744-0100, (203) 798.2291, <http://www.rarediseases.org>

Paul A. Johnson
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Micro syndrome

Definition

Micro syndrome is a rare genetic disorder. Children born with this condition may experience intellectual disability, seizures, visual impairment, difficulty eating, weakness, numbness, and/or abnormal sensations in the limbs.

Alternate names associated with micro syndrome are Warburg micro syndrome, WARBM, and Warburg Sjo Fledelius syndrome.

Description

Researchers described and named micro syndrome in 1993, but others had reported patients with what was probably the same malady as early as 1949. In the 1993

Symptoms of Micro syndrome

Mental retardation
Seizures
A small head (microcephaly)
Slow development of the external reproductive organs
Abnormally small eyes
Visual impairment
Cloudiness of the eye lenses (cataracts)
Drooping eyelid (ptosis)
Difficulty swallowing and therefore feeding
An undersized jaw (micrognathia)
A beaked nose
Decreased muscle tone (hypotonia)
Weakness and numbness in the limbs
Abnormal sensations in the limbs
Inability of the limbs to fully extend (joint contracture)
Delayed puberty

(Gale)

description, the researchers noted the symptoms of a Pakistani brother and sister and their male cousin. The symptoms included a small head and eyes, cataracts and near blindness, intellectual disability, excessive facial hair, decreased muscle tone (hypotonia), and incontinence.

Micro syndrome is an inherited disorder resulting from mutations in a gene that carries instructions for a membrane-associated Rab3 protein. This protein is important in the secretion of various substances from cells. These substances include neurotransmitters (chemicals that transmit nerve impulses) and hormones. The mutated gene produces faulty proteins, which in turn inhibit the proper flow of neurotransmitters and/or hormones and can lead to a wide range of symptoms.

Genetic profile

Located on chromosome 2, the *RAB3GAP* gene carries the blueprint for making the Rab3 protein, which actually comes in two forms. This gene is important in several normal functions, which include the following:

- Transmission of signals between nerve cells and between other cells and nerve cells. This function allows nerve impulses to travel properly, so that the body may move and function correctly.
- Release of hormones from cells. Hormones travel in the bloodstream to other areas of the body, where they can have an effect on such body processes as growth and development, sexual function and reproduction, and metabolism.

Mutations in the *RAB3GAP* gene are believed to lead to defects in both the transmission of nerve impulses and the secretion of hormones from cells. A study from 2015

KEY TERMS

Agenesis/hypoplasia of the corpus callosum—Birth defect in which the two halves of the brain are not properly separated.

Cataracts—Cloudiness of the eye lenses.

Hypogenitalism—Retarded development of the external reproductive organs.

Hypotonia—Decreased muscle tone.

Joint contracture—Inability of the limbs to fully extend.

Microcephaly—Small head.

Micrognathia—Undersized jaw.

Neurotransmitters—Chemicals that transmit nerve impulses.

Paresthesia—Presence of abnormal sensations in the limbs.

Ptosis—Drooping eyelid.

- abnormally small eyes
- visual impairment
- cloudiness of the eye lenses (cataracts)
- drooping eyelid (ptosis)
- difficulty swallowing and therefore feeding
- undersized jaw (micrognathia)
- beaked nose
- decreased muscle tone (hypotonia)
- weakness and numbness in the limbs
- abnormal sensations in the limbs, such as burning or tingling (paresthesia)
- muscle spasms
- inability of the limbs to fully extend (joint contracture)
- delayed puberty

Diagnosis

Examination

Doctors may focus primarily on the eyes to make a preliminary diagnosis of micro syndrome. Individuals with the disorder have congenital cataracts, small eyes, and visual impairment. The diagnosis is made more solid when the infant also shows other symptoms such as severe intellectual disability and movement problems.

Tests

The doctor may order cell samples be examined for the mutated *RAB3GAP* gene.

Procedures

The doctor may order an MRI (magnetic resonance imaging) scan to check the patient for malformations of the brain. Patients with micro syndrome typically show agenesis/hypoplasia of the corpus callosum, in which the two halves of the brain are not properly separated. An MRI can detect this abnormality.

Treatment and management

No treatment exists for micro syndrome, but some help is available to ease some of the symptoms.

Traditional

A common treatment for cataracts is surgery to remove or dissolve the affected lens. Doctors often recommend physical therapy to help improve muscle tone, to promote full extension of the limbs, and to counter muscle spasms. They may also suggest occupational therapy and speech therapy.

provided evidence that micro syndrome can also be caused by *RAB18* deficiency or dysregulation.

Demographics

Micro syndrome is very rare, and only a few dozen cases have been reported in the literature since its initial description in 1993.

Signs and symptoms

Micro syndrome is an autosomal recessive disorder. It occurs when individuals inherit a mutated *RAB3GAP* gene from each parent. The parents may not have the condition themselves but may be carriers. Carriers are individuals who do not develop the disorder themselves but may pass the gene for the disorder onto their children. If both parents are carriers, each of their children has a 50% chance of being a carrier and a 25% chance of acquiring the disorder. If both parents have micro syndrome, all of their children will acquire the disorder.

Many symptoms of micro syndrome are present at birth, but others will become evident as time goes on. Symptoms may include the following:

- intellectual disability
- seizures
- small head (microcephaly)
- hypogenitalism (retarded development of the external reproductive organs)

QUESTIONS TO ASK YOUR DOCTOR

- My baby has just been diagnosed with micro syndrome. What type of care is available to help with my child's mental development, and how much improvement should I expect?
- I do not feel equipped to care for my child on my own. What resources are available in my area?
- My spouse and I are carriers and would like to have a child. Is prenatal testing available to determine whether a baby has micro syndrome? Is there a way, perhaps through preimplantation genetic diagnosis, to ensure that we have a baby that does not have the disorder?

Drugs

For recurring seizures, doctors may prescribe anti-seizure medication.

Prognosis

Individuals with micro syndrome are of normal weight at birth, but soon show signs of slowed growth. Other symptoms such as evidence of intellectual disability, decreased muscle tone, and movement impairment may also soon begin appearing. By the first birthday, the baby typically has experienced muscle spasms. Children with this disorder can speak few if any words by the time they are ten years old. Many experience incontinence, and some may be unable to walk or even sit up on their own. Puberty is delayed. Vision may decline over time.

Resources

BOOKS

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ORGANIZATIONS

Genetic Alliance, 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008-2369, (202) 966-5557, (202) 966-8553, info@geneticalliance.org, <http://www.geneticalliance.org>

Genetic Disease Foundation, 1425 Madison Ave., Box 1498, New York, NY 10029, (212) 659-6704, <http://www.geneticdiseasefoundation.org>

Leslie A. Mertz, PhD

MIDAS syndrome see **Microphthalmia with linear skin defects**

Mild hypophosphatasin see **Hypophosphatasia**

Miller-Dieker syndrome

Definition

Miller-Dieker syndrome (MDS) is a rare genetic disorder. Its signs and symptoms include severe abnormalities in brain development as well as characteristic facial features. Additional birth defects may also be present.

Description

MDS was named for the two physicians, J. Miller and H. Dieker, who independently described the condition in the 1960s. The hallmark of MDS is lissencephaly (smooth brain), a condition in which the outer layer of the brain, the cerebral cortex, is abnormally thick and lacks the normal convolutions (gyri). In some areas of the brain, gyri are fewer in number but wider than normal (pachygyri). Other areas lack gyri entirely (agyri). Normally, during the third and fourth months of pregnancy, the brain cells in the baby multiply and move to the surface of the brain to form the cortex. Lissencephaly is caused by a failure of this nerve cell migration. MDS is often called Miller-Dieker lissencephaly syndrome.

Genetic profile

When MDS was first described, geneticists thought it followed an autosomal recessive pattern of inheritance. However, in the early 1990s, several patients with MDS

were found to be missing a small portion of the short arm of chromosome 17 (17p13.3). This is called a partial deletion of chromosome 17. MDS is now classified as a “micro-deletion syndrome” because it is the result of the absence of genes that are normally located in this region of chromosome 17. In 1993, research scientists identified one of the genes in this region. They named it *LIS1* for “first lissencephaly gene” because it appeared to be important in normal brain formation. The main evidence for this was that the *LIS1* gene was missing in a number of individuals with isolated lissencephaly; that is, lissencephaly without the additional characteristics found in MDS. In 2003, researchers identified 12 additional genes consistently deleted in patients with MDS. From these recently identified genes the *YWHAE* gene is believed to play a large role in the MDS phenotype and the *CRK* gene is thought to cause the symptom of growth restriction. Because the full breadth of this syndrome’s phenotype requires the deletion of multiple genes located near each other, MDS has also been described as a contiguous gene syndrome.

Most genes, including all genes on the autosomes (non-sex chromosomes), are normally present in pairs. Individuals with MDS who have a micro-deletion of a small region of the short arm of one copy of their chromosome 17 still have one normal copy of this chromosome region on their other chromosome 17. For this reason, MDS is said to be due to “haploinsufficiency,” the term for a genetic condition caused by the lack of function of only one of the two copies of a gene. As with other haploinsufficiency syndromes, MDS has also been described as having an autosomal dominant pattern of inheritance.

Individuals with MDS usually die in infancy. Because they do not live to the age where they can reproduce, they cannot transmit MDS to their offspring. Eighty percent of individuals with MDS have it as the result of a new (*de novo*) deletion of a small part of the short arm of one chromosome 17 in just the one egg or sperm that formed that individual. The parents of these affected individuals have normal chromosomes without deletions. This means that their risk of having another child with MDS is very low (probably less than 1%). The other 20% of those with MDS have the syndrome because one of their parents carries a rearrangement of one copy of their own chromosome 17. The rearrangement can be an inversion or a balanced translocation between chromosome 17 and one of the other chromosomes. Since the rearrangement is balanced, that is, all the chromosome material is present but in a rearranged form, the parent is normal. However, when that parent produces an egg or a sperm, the balanced chromosome rearrangement can go through a further rearrangement. This results in a portion of the short arm of chromosome

17 being deleted. The individual who develops from that egg or sperm will have MDS.

Demographics

MDS is present in fewer than 1 in 100,000 births. There is no information to suggest that the syndrome is more common in any particular ethnic or racial group.

Signs and symptoms

Infants with MDS are usually small at birth. Characteristic facial features may include a high forehead with furrows and vertical ridges; indentation of the temples; a small, upturned nose; up-slanting eyes; a small mouth; a thick, broad upper lip with a thin border; low-set ears; and occasionally, a cleft palate. Some infants with MDS also have birth defects involving the heart and kidneys. Signs and symptoms can vary among MDS patients. This may relate to the actual size or exact location of the chromosome 17 deletion in that individual.

MDS infants have a very limited capacity for development due to the lissencephaly and associated brain abnormalities. Intellectual disability is severe to profound. Infants with MDS may be able to do little more than roll over. Convulsions (seizures) develop within a few weeks of birth and can be severe. Most newborns with MDS have low muscle tone (hypotonia), but later develop stiffness (spasticity) and an arching of the body (opisthotonos). Poor feeding leads to a failure to thrive and increases the risk of pneumonia because the infants can accidentally inhale baby formula into their lungs. Head size is usually in the normal range at birth, but poor brain growth means that, by the age of one year, the children have a smaller-than-normal head size (microcephaly).

Diagnosis

MDS is not the only disorder associated with lissencephaly. Autosomal dominant, autosomal recessive, and X-linked patterns of inheritance have been described among the more than two dozen genetic syndromes featuring this brain abnormality. Less commonly, lissencephaly can be the result of fetal infections such as prenatal cytomegalovirus (CMV). An accurate diagnosis of MDS is important not only because it can provide a prognosis for the affected child, but because it can give parents an estimate of their risk for having another child with MDS.

MDS may be suspected in the newborn period if an infant has the characteristic facial features along with low muscle tone. Studies of the infant’s brain by CAT scan or MRI will show the smooth brain surface. After the diagnosis of MDS is made on the basis of these signs

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman’s abdomen into her uterus to draw out a small sample of the amniotic fluid from around the fetus. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Cerebral cortex—The outer surface of the cerebrum made up of gray matter and involved in higher thought processes.

Chorionic villus biopsy—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother’s vagina or abdominal wall and a sample of cells is collected from around the early fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Contiguous gene syndrome—A genetic syndrome caused by the deletion of two or more genes located next to each other.

FISH (fluorescence in situ hybridization)—Technique used to detect small deletions or rearrangements in chromosomes by attempting to attach a fluorescent (glowing) piece of a chromosome to a sample of cells obtained from a patient.

Haploinsufficiency—The lack of one of the two normal copies of a gene. Haploinsufficiency can result in a genetic disorder if normal function requires both copies of the gene. Haploinsufficiency is one explanation for a dominant pattern of inheritance.

Hypotonia—Reduced or diminished muscle tone.

Inversion—A type of chromosomal defect in which a broken segment of a chromosome attaches to the same chromosome, but in reverse position.

Lissencephaly—A condition in which the brain has a smooth appearance because the normal convolutions (gyri) failed to develop.

Micro-deletion syndrome—A collection of signs and symptoms caused by a deletion of a gene or genes that is too small to be seen through the microscope.

Microcephaly—An abnormally small head.

Opisthotonos—An arched position of the body in which only the head and feet touch the floor or bed when the patient is lying on their back.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosome material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

X-linked—Located on the X chromosome, one of the sex chromosomes. X-linked genes follow a characteristic pattern of inheritance from one generation to the next.

and symptoms, it is very important to study the infant’s chromosomes to check for the characteristic chromosome 17 deletion. This is done by sending a small sample of the infant’s blood to a cytogenetics laboratory. Trained laboratory personnel (cytogeneticists) first examine the infant’s chromosomes through the microscope using traditional techniques. If no deletion or other chromosome rearrangement is detected in this step, newer methods can be used to search for deletions that are too small to see by ordinary means (micro-deletions). A special technique called FISH (fluorescent in situ hybridization) can detect chromosome regions where very small pieces of DNA are missing. This test is usually done on the same blood sample.

Carrier detection

When a chromosome deletion is found in an infant, both parents’ chromosomes should also be studied to determine if one of them carries a chromosome rearrangement such as a balanced translocation. Although most parents of infants with MDS have normal chromosomes, in approximately 20% of children, one parent will have a chromosome rearrangement, which can increase the risk for having another child with MDS. Other family members should also be offered chromosome studies because these balanced chromosome rearrangements can be passed down through a family undetected, and thus, other family members may be carriers. The first step in studying other family members is for a geneticist or

QUESTIONS TO ASK YOUR DOCTOR

- What genetic and/or chromosomal changes are responsible for Miller-Dieker syndrome?
- What are the most prominent physical and mental manifestations of this disorder?
- Can Miller-Dieker syndrome be diagnosed prenatally, and if so, how?
- What lifespan should we anticipate for a child born with this disorder?

genetic counselor to obtain a detailed family history and construct a pedigree (family tree) to determine which family members should be offered testing.

Prenatal diagnosis

If a couple has had one child with MDS, they can be offered prenatal diagnosis in future pregnancies. This option is particularly important for the 20% of MDS families where one parent carries a balanced chromosome rearrangement. The risk for these couples of having another affected child depends on the exact type of chromosome rearrangement present and may be as high as 25%–33%. For families in which both parents' chromosomes are normal, the risk of having another child with MDS is low (1% or less). Either chorionic villus sampling (CVS) or amniocentesis can be used early in a pregnancy to obtain a small sample of cells from the developing embryo for chromosome studies. Early prenatal diagnosis by ultrasound is not reliable because the brain is normally smooth until later in pregnancy. Couples who are considering prenatal diagnosis should discuss the risks and benefits of this type of testing with a geneticist or genetic counselor.

Treatment and management

There is no cure for MDS, and treatment is usually directed toward comfort measures. Because of the feeding problems and risk of pneumonia, surgeons often place a tube between the stomach and the outside of the abdomen (gastrostomy tube). Feedings can be made through the tube. Seizures are often difficult to control even with medication.

Prognosis

Death often occurs in the first three months of life, and most infants with MDS die by two years of age, although there have been reports of individuals living for several years.

Resources

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"Miller-Dieker Syndrome." ScienceDirect. <https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/miller-dieker-syndrome> (accessed June 14, 2021).

ORGANIZATIONS

Genetic Alliance, 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008-2369, (202) 966-5557, (202) 966-8553, info@geneticalliance.org, <http://www.geneticalliance.org>

Genetic Disease Foundation, 1425 Madison Ave., Box 1498, New York, NY 10029, (212) 659-6704, <http://www.geneticdiseasefoundation.org>

Sallie Boineau Freeman, PhD
and Sherrill Lathrop Macura, PhD

Mirhosseini-Holmes-Walton syndrome see
Cohen syndrome

Mitochondrial disease

Definition

Mitochondrial disease is a group of disorders in which organelles (structures) inside the cell, called mitochondria, do not function properly. Mitochondria produce most of the energy used by a cell and, in turn, by the body. When they malfunction, the cell dies. When enough cells die, the entire body is at risk for death. This lack of energy and cellular death cause the muscle weakness and other symptoms of mitochondrial disease.

Description

Mitochondria are organelles that play a crucial role in providing energy to a cell by creating a substance called adenosine triphosphate (ATP) that helps transfer

energy. Mitochondria have their own DNA consisting of 37 genes called mitochondrial DNA (mtDNA). Mitochondrial disease occurs when one or more of these 37 genes or others that support them mutate, causing the mitochondria to malfunction. Researchers have identified hundreds of different mitochondrial disorders with individual genetic causes.

Mitochondrial disease may be primary or secondary. Primary mitochondrial disease is caused by a mutation of any gene that produces protein used directly by mitochondria. Secondary disease is caused by mutations in a gene that does not directly produce protein or is not directly involved in energy production. These mutations may, however, eventually result in reduced energy production. Secondary mitochondrial disease is often seen in people with Alzheimer's and Parkinson's disease.

Some of the more common types of mitochondrial disease are the following:

- Alpers' progressive sclerosing poliodystrophy (Alpers' disease)
- Barth syndrome
- Chronic progressive external ophthalmoplegia (CPEO)
- Dominant optic atrophy
- Friedreich's ataxia
- Hereditary paraganglioma
- Hereditary spastic paraplegia
- Kearns-Sayre syndrome
- Leber optic neuropathy
- Leigh and Leigh-like syndrome
- Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)
- Myoclonic epilepsy with ragged red fibers (MERRF)
- Neuropathy, ataxia, and retinitis pigmentosa (NARP)
- Pearson syndrome
- Wolfram syndrome

Genetic profile

Mitochondria contain 37 genes; however, that is not the full expression of genes that is necessary to make mitochondria or for them to function properly. According to geneticists, it takes more than 3,000 genes to produce a mitochondrion; of those, only 37 originate from mitochondria. The majority of the genes are created in the cell nucleus and transported, via proteins, to the mitochondria. Of the thousands of genes used to produce and maintain mitochondria, only 3%, or about 100 genes, are used to produce the ATP involved in energy production; the remaining 97% of the genetic material is used for other purposes. These genes are used in processes such as fetal development to help immature cells

differentiate into the cells needed to grow and mature. As a person ages, these genes become essential for building and maintaining cells. A cell cannot create RNA or DNA without mitochondria. Every organ in the body needs mitochondria to perform the functions necessary for life. The exact genetic mutations determine which form of mitochondrial disease is present and which organs are affected. These mutations may be either spontaneous or inherited and may involve mtDNA or nDNA. This variation and the large number of possible genes involved is why there are hundreds of different mitochondrial diseases and why, even among individuals with similar genetic mutations, there is such a diverse spectrum of symptoms. It is a common clinical finding that individuals with the same mtDNA mutation do not have the same disease.

Because of the vast number of possible mutations that can cause mitochondrial disease, diagnosis has been difficult. In the past, genetic testing was time consuming and costly and might not identify the correct mutation. With the development of next-generation sequencing (NGS), a genetic testing process that allows a person's entire genome to be sequenced in one day, it has become much easier to identify specific mutations and to identify the best treatment options. In January 2015, the Mitochondrial Medicine Society issued their next-generation sequencing statement in support of NGS as the preferred diagnostic method, stating, "NGS is the most appropriate test given the complexity of symptoms and the genetic heterogeneity of mitochondrial disease and is medically important for most patients in order to guide treatment."

NGS is also called high-throughput sequencing. There are several different genetic sequencing technologies that may be used when performing NGS, such as Illumina (Solexa) sequencing, ion torrent: proton/PGM sequencing, Roche 454 sequencing, or SOLiD sequencing. These new technologies and others in development are causing NGS to become more affordable and more important as a diagnostic tool for many diseases.

Demographics

The exact number of people with mitochondrial disease is not known. It is estimated that every year there are between 1,000 and 4,000 children born with mitochondrial disease in the United States. However, there is no way to know the exact number because of the wide spectrum of symptoms and many types of mitochondrial disease. Because of this, many people are misdiagnosed. According to the United Mitochondrial Disease Foundation, mitochondrial disease is approaching childhood cancer in numbers of children affected. It affects males and females and people of all races.

Signs and symptoms

Mitochondrial disease affects multiple organ systems in the body. The main symptoms include muscle weakness; neurological problems such as seizures and ataxia; vision and hearing impairment; cardiac, liver, or respiratory disease; developmental delay; poor growth; diabetes; and increased susceptibility to infection. The presence of three or more of these symptoms is an indicator for mitochondrial disease, especially if symptoms involve more than one organ system.

More specific symptoms affecting individual organ systems vary depending on which type of mitochondrial disease is present and which genes have been mutated. The following are symptoms of mitochondrial disease by body system.

Brain

- Atypical cerebral palsy
- Autistic features
- Dementia
- Developmental delays
- Intellectual impairment
- Migraines
- Neurological disturbances
- Psychiatric disorders
- Seizures
- Strokes

Eyes and ears

- Hearing loss and deafness
- Ophthalmoplegia
- Optic atrophy
- Ptosis
- Retinitis pigmentosa
- Strabismus
- Visual impairment and blindness

Heart, liver, and kidneys

- Heart block (cardiac conduction defects)
- Liver failure
- Renal tubular acidosis or wasting

Muscles

- Cramping
- Diarrhea or constipation
- Dysmotility
- Gastrointestinal problems such as reflux and IBS
- Hypotonia
- Muscle pain
- Weakness

KEY TERMS

Apoenzyme—An enzyme that cannot function without assistance from other molecules called cofactors.

ATP—Adenosine triphosphate. The molecule used by the cells of the body for energy.

Autosomal recessive disorder—A disorder where two copies of a dysfunctional gene must be inherited for the trait to present. The gene is present on the non-sex chromosomes.

Cofactor—A substance that is required by an enzyme to perform its function.

Ketosis—An abnormal build-up of compounds called ketones in the blood. This condition usually indicates a problem with blood sugar regulation.

Metabolic acidosis—High acidity (low pH) in the body due to abnormal metabolism, excessive acid intake, or retention in the kidneys.

Methylmalonic acid—An intermediate product formed when certain substances are metabolized.

Sudden infant death syndrome (SIDS)—The unexpected, sudden death of a child under one year of age. Often called “crib death.”

TCA cycle—Formerly known as the Krebs cycle, this is the process by which glucose and other compounds are broken down into forms that are directly useable as energy in the cells.

Nerves

- Absent reflexes
- Fainting
- Neuropathic pain
- Weakness—intermittent or constant

Pancreas and other glands

- Diabetes
- Exocrine pancreatic failure (inability to make digestive enzymes)
- Parathyroid failure (low calcium)

Systemic

- Fatigue
- Poor weight gain
- Respiratory problems
- Short stature

- Vomiting

Diagnosis

Because there are so many possible genetic causes for mitochondrial disease and such a wide variation of symptoms, there is no one reliable diagnostic test. If an individual has three or more of the main symptoms, then mitochondrial disease is suspected. It is important to find a physician who specializes in the diagnosis and treatment of mitochondrial disease. The first step of diagnosis is to collect a detailed medical and family history. Next, a physical and neurological examination will be performed. A muscle biopsy may be performed. During muscle biopsy a small piece of muscle is removed and examined for abnormal muscle structure, in particular “ragged red fibers,” which indicate a specific type of mitochondrial disease. Muscle biopsy as a diagnostic tool has several limiting factors. It is invasive and painful, and children usually require general anesthesia for it to be performed. There can be false positive results, and—particularly in patients with secondary mitochondrial disease—the results may be normal even in the presence of the disease.

There are multiple laboratory blood tests used in the process of diagnosing mitochondrial disease, such as blood enzyme tests; several types of lactate tests; glucose, ammonia, amino, and organic acid tests; BUN; and CBC.

Genetic testing, including NGS, has become the most accurate and preferred method for diagnosing mitochondrial disease. While NGS is the preferred method of the Mitochondrial Medicine Society, there are other genetic tests that may be used. However, they are limited to use when specific types of the disease are suspected because they test only a few genes at a time. Other genetic tests include Mitochondrial DNA Point Mutations and Mitochondrial DNA Southern Blot.

Other testing procedures may be performed to assess specific symptoms and specific organ systems, such as magnetic resonance imaging (MRI) of the brain, retinal exams, EKG and echocardiograms (ECHO), thyroid function test, and audiograms.

Treatment and management

Treatment for mitochondrial disease is generally used to improve quality of life, reduce symptoms, and slow the progression of the disease. There is no cure.

There are standard treatments for many symptoms, such as physical therapy for individuals with muscle weakness and physical limitations and anticonvulsants for those with seizures. Supplements such as riboflavin, coenzyme Q, and carnitine (a specialized amino acid) may be used to help increase energy level and stamina

QUESTIONS TO ASK YOUR DOCTOR

- What type of mitochondrial disease do I have (does my child have)?
- Is there a special diet I should follow?
- Should I take vitamins, and if so, which ones?
- Do I need more testing? If so, what type?
- If I have mitochondrial disease, will my children have it, too?

for those who are experiencing fatigue, and there are many medications available to treat other symptoms such as nausea, infection, and pain.

There are dietary recommendations for individuals with metabolic diseases such as mitochondrial disease. It is recommended to avoid fasting, eat at regular intervals during the day and night, monitor fat intake and eat more or less fat depending on the type of mitochondrial disease present, avoid access iron in the diet, and avoid toxins such as cigarette smoke and alcohol.

Prognosis

The prognosis for patients with mitochondrial disease varies greatly, depending on the type of disease. Some individuals will have mild symptoms, while others will continue to worsen. In the most serious cases, the disease will lead to death.

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“Mitochondrial diseases.” MedlinePlus. March 18, 2021. <https://medlineplus.gov/mitochondrialdiseases.html> (accessed July 9, 2021).

ORGANIZATIONS

MitoAction, 14 Pembroke St., Medford, MA 02155, (888) 648-6411, <http://www.mitoaction.org>

Muscular Dystrophy Association, 222 S. Riverside Plaza, Suite 1500, Chicago, IL 60606, (800) 572-1717, <http://www.mda.org>

United Mitochondrial Disease Foundation, 8085 Saltsburg Rd., Suite 201, Pittsburgh, PA 15239, (412) 793-8077 or (888) 317-8633, (412) 793-6477, info@umdf.org, <http://www.umdf.org>

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Mitochondrial replacement therapy (MRT)

Definition

Mitochondrial replacement therapy, also known as mitochondrial replacement technique (MRT) or mitochondrial donation, is the only approach known as of 2021 to prevent a mitochondrial disease in human offspring. Given the lack of treatments for these severe diseases and the limitations of prenatal diagnosis, researchers have focused on preventing the transmission of mitochondrial diseases through germline gene replacement therapy. MRT is used during in vitro fertilization (IVF) to replace mitochondria with harmful mutations within a female oocyte (a cell that develops into an ovum by meiosis). The healthy replacement mitochondria are obtained from a donated oocyte. Because children born as a result of MRT and IVF have genetic material derived from two women and one man, they have been referred to in the popular press as three-parent babies.

Description

Mitochondrial diseases

Some background information about mitochondrial diseases is necessary in order to understand both the significance of MRT and the controversies surrounding it. Mitochondrial diseases are a group of metabolic disorders in which defective mitochondria within the affected person's cells fail to produce enough energy to meet the body's needs. Mitochondria are microscopic organelles found within all cells of the human body except red blood cells. Sometimes called the powerhouses of the cell, mitochondria convert energy derived from food into adenosine triphosphate (ATP), an organic molecule necessary for most cell functions. But because mitochondria perform a wide range of functions within different body tissues and organs, the symptoms of mitochondrial diseases vary widely in location and severity, ranging from muscular weakness, loss of balance, nausea, vomiting, developmental delays and dementia, to pain, kidney or liver failure, vision loss, and difficulty breathing. Most mitochondrial

diseases appear in humans before 20 years of age; some affect infants and are often fatal.

The website of the United Mitochondrial Disease Foundation (UMDF) contains detailed descriptions of 43 different mitochondrial diseases, but researchers estimate that there are at least several hundred disorders in this category. The exact number of people affected by mitochondrial diseases is not known, because these disorders are often misdiagnosed. Most mitochondrial diseases are genetic disorders. They may be caused either by mutations in the nuclear DNA in the cell or by mutations in the mitochondrial DNA (abbreviated as mtDNA). Most mitochondrial function is encoded by the DNA in the cell nucleus, which in humans is inherited from both parents. In contrast, mtDNA is inherited only from the mother; it contains only 37 genes and encodes 13 proteins. Another difference is that while there are only two copies of DNA in a human cell nucleus, each mitochondrion contains between two and ten copies of mtDNA.

As there are about 500 mitochondria in an average human cell (although liver and muscle cells may contain thousands), the difference in the number of DNA copies means that mutations occur at a much higher rate in mtDNA than in nuclear DNA. When mitochondria multiply during the normal process of cell division, they can accumulate random mutations, a condition called heteroplasmy. In some people, only a few mitochondria are affected by these mutations. In others, however, the number of mutant mitochondria increases over time until the mutant organelles dominate the pool of mtDNA. When this threshold is reached, typically in adolescence or early adult life, the person will begin to show symptoms of a mitochondrial disease. About 0.5% of the population carries mtDNA mutations, and about one person in every 5,000 (0.02%) is at risk of developing a mitochondrial disease.

In vitro fertilization

MRT is a recent specialized form of in vitro fertilization, or IVF, which has helped couples with fertility difficulties have children since 1978. About eight million children around the world have been born through IVF as of 2021. The basic IVF technique involves the administration of hormone therapy to the intended mother to stimulate the release of multiple eggs into the uterus. The eggs are retrieved, selected for health and maturity, and either mixed with sperm or fertilized by the injection of a single sperm into an egg.

The resultant embryos are allowed to mature for a short period of time and then subjected to genetic testing to screen for genetic disorders, abnormal chromosomes, or defective mitochondrial DNA. The embryos that pass

screening are returned to the intended mother's uterus, where it is hoped that at least one will implant and produce a successful pregnancy.

Types of MRT

Four major types of MRT have been used since the 1990s, one of which is no longer used as of 2021.

Ooplasmic/cytoplasmic transfer

Ooplasmic/cytoplasmic transfer is the oldest form of MRT, which was introduced in the 1990s to assist older women who were having difficulty conceiving. In this form of transfer, ooplasm containing proteins, mRNA, mitochondria, and other organelles was taken from a donor's egg, combined with a single sperm from the patient's husband, and injected into the intended mother's egg. A baby girl was born in a New Jersey hospital in 1997 following this type of MRT; another 30 babies were born as a result of cytoplasmic transfer between 1997 and 2001, even though the FDA banned the procedure in 1998 after three of the earliest children born through the use of the technique were found to have developmental disorders (two cases of Turner's syndrome and one of autism spectrum disorder).

Maternal spindle transfer

Maternal spindle transfer (MST) has been used when the intended mother's eggs indicate the presence of mutant mtDNA. The term *spindle* in this context refers to a microscopic network of microtubules (sometimes called spindle fibers) that forms during cell division to pull chromosomes to the poles of the cell during the phase of cell division called metaphase. To perform MST, an oocyte is first removed from the intended mother. When it reaches the metaphase stage of cell division, the spindle-chromosome complex is removed from the intended mother's oocyte, which is then discarded. The spindle complex is then transferred to a donated oocyte that has had its nuclear DNA removed. The result is a mature egg that contains a selection of the mother's haploid DNA along with healthy mitochondria from the donor. The egg is then fertilized with the father's sperm.

After fertilization, the embryo is allowed to grow until it forms a blastocyst, which is an early pre-implantation stage of the embryo consisting of a hollow sphere of 16 to 40 cells. The blastocyst can then be investigated with pre-implantation genetic testing for the presence of mtDNA mutations. If no mutations are found, the blastocyst can be implanted in the intended mother's uterus.

The spindle transfer technique has been performed only rarely since its first use in 2014, as the number of births among women at risk of transmitting diseases

caused by defective mtDNA is estimated to be quite small—about 150 per year in the United Kingdom and 800 per year in the United States.

Pronuclear transfer

In pronuclear transfer (PNT), the oocyte from the mother and the oocyte from the donor are both fertilized with sperm from the same person. The male and female pronuclei (the nucleus of an ovum or sperm before these have united to form the definitive nucleus of an impregnated ovum) are removed from each fertilized egg prior to their fusing, and the pronuclei from the recipient's fertilized egg are inserted into the fertilized egg from the donor. As with MST, the fertilized egg is then allowed to form a blastocyst, which can be subjected to pre-implantation genetic testing before it is implanted in the mother's uterus.

Polar body transfer

In polar body transfer (PBT), a polar body, which is a small cell with very little cytoplasm created when an oocyte divides, is taken from the intended mother and used in its entirety instead of using material extracted from the normal egg. The advantage of PBT is that there is a greatly reduced chance of transmitting defective mitochondria from the intended mother, because polar bodies contain very few mitochondria.

Limitations, risks, and controversies

The most important limitation of MRT is that its long-term risks and benefits are unknown as of 2021, because so few children have been born as a result of its use. The parents of an American child born in Mexico in 2016 have refused to allow ongoing testing of the child's mtDNA. This refusal means that the success of the first use of the maternal spindle transfer technique cannot be fully evaluated. In the United Kingdom, 14 women were given permission to undergo MRT after it was legalized in 2015, but it is not known as of 2021 how many children have been born from these procedures, because of the parents' wishes for privacy.

MRT has a number of known risks, mostly related to the number of different laboratory procedures involved. It requires pre-implantation genetic screening of the mother; pre-implantation genetic diagnosis of the fertilized egg (which carries its own risk of disrupting the development of the embryo); and in vitro fertilization. In addition, all current MRT techniques involve physical disruption of oocytes, which may cause unexpected damage. Moreover, the need to perform precisely timed actions during the development and fertilization of the eggs may result in the eggs either maturing abnormally

KEY TERMS

Adenosine triphosphate (ATP)—An organic molecule found in all living organisms, involved in energy production for metabolic processes and RNA synthesis.

Cytoplasm—All of the material within a cell enclosed by the cell membrane, excluding the nucleus. The cytoplasm includes cytosol, organelles (including mitochondria), and various inclusions.

Diploid—Referring to a cell or nucleus that contains two copies of genetic material, or a complete set of chromosomes.

Gamete—A sex cell (sperm or ovum) containing the haploid number of chromosomes, and capable of fusing with a gamete of the opposite sex to form a zygote.

Genetic drift—Variations in gene frequency within a population due to chance rather than mutation or natural selection.

Genome—The total amount of genetic information within an organism's chromosomes, including its genes and DNA sequences.

Germline—The population of a complex organism's cells that pass on genetic information to offspring.

Germline cells include eggs, sperm, and fertilized eggs.

Haploid—Referring to cells that have only one chromosome of each type and therefore have only one complete set of genes.

Heteroplasmy—The presence of two or more sources of mitochondrial DNA within a cell, person, or mitochondrion. It is an important factor in determining the likelihood or severity of a mitochondrial disease.

In vitro fertilization (IVF)—A form of assisted reproduction technology in which a human ovum (egg) is combined with sperm outside the body in a laboratory container ("in vitro" means "in a glass").

Leigh syndrome—A rare genetic disease associated with mutations in either mitochondrial DNA or nuclear DNA, and characterized by degeneration of the central nervous system. It is named for Archibald Denis Leigh, a British psychiatrist who first described the syndrome in 1951.

Meiosis (pronounced my-OH-sis)—The process of cell division during the production of ova and sperm, in which the material in the chromosomes undergoes recombination (first-stage meiosis), and

or normal fertilization failing to occur. Last, some of the intended mother's mtDNA will be carried over into the donated egg. Studies of both animal and donated human embryos indicate that the carryover of pathogenic DNA is about 2%, which some researchers consider unlikely to cause disease in the offspring. On the other hand, a group of Japanese researchers reported in 2020 that some embryonic stem cell lines showed evidence of genetic drift, or the reversion of healthy donated mtDNA to pathogenic mtDNA.

MRT is the subject of a number of controversies as of 2021:

- Whether the techniques involved in MRT have been adequately tested from the standpoint of the safety of the resultant offspring. A team of Dutch and Belgian researchers argued in 2020 that scientific innovation has been generally been favored over safety concerns.
- Whether MRT is a form of germline gene therapy or heritable genetic modification; or whether it simply involves donated intact mitochondria that do not affect the DNA in the cell nucleus—which would constitute alteration of the offspring's genome.
- Whether having a child genetically related to oneself should take precedence over all other ways of becoming a parent. A British and a Portuguese researcher noted that PNT and MST have both tended to increase couples' focus on the importance of a genetic link to a desired child without considering the low likelihood of success with these technologies. They suggest fertility counseling that presents couples with a balanced discussion of other options.
- Whether MRT is ready for "prime time" as a form of assisted reproductive technology (ART) or whether its routine use in present circumstances would be premature. Most researchers think that the proposed benefits of MRT to infertile couples are more theoretical than actual as of 2021.
- Whether women who desire genetically related children should have the ultimate say about using MRT. Two American researchers maintain that women in the United States have a constitutional right to reproductive autonomy and that denying them the right to MRT amounts to a violation of "a parental right to genetic affinity."
- Whether MRT is a step down a "slippery slope" of unwarranted experimental procedures driven by

the chromosomes are reduced to a single set of 23 instead of the normal number of 23 pairs (second-stage meiosis).

Metaphase—A stage in the cycle of cell division in which the cell's genetic material condenses into chromosomes, which become visible and line up in the center of the dividing cell.

Mitochondria (singular, mitochondrion)—Organelles in the cytoplasm of cells that contain genetic material and enzymes responsible for converting food to usable energy.

Mitochondrial replacement therapy (MRT)—A technique to prevent or treat certain genetic diseases by replacing the mitochondria in one or more cells. It is also called mitochondrial donation.

Oocyte (pronounced OH-eh-site)—A diploid cell in females from which an egg or ovum develops by meiosis.

Organelle—A specialized structure found within a cell that performs a specific function or carries out a specific life process. Mitochondria are organelles.

Polar body—Either of two small cells produced during the two meiotic divisions in the production of

an oocyte. Polar bodies contain only small amounts of cytoplasm and eventually disintegrate.

Pronuclear transfer—A mitochondrial replacement technique in which the mother's egg is first fertilized by the father's sperm; then the two pronuclei are inserted into a donor egg that has been fertilized and has had its own nucleus removed.

Pronucleus (plural, pronuclei)—The nucleus of a sperm or egg cell during the process of fertilization.

Three-parent baby—A term used in the mass media to describe a baby produced from the genetic material of one man and two women through the use of mitochondrial replacement technologies and three-person in vitro fertilization (IVF). It is not a scientific term.

Turner syndrome—A chromosomal disorder with a 45,X or 45,X0 karyotype that affects only females, in which one of the X chromosomes is either partially or completely missing. Most women with Turner syndrome are infertile because of a lack of ovarian function.

Zygote—A fertilized egg cell that results from the union of two gametes, a female egg and a male sperm.

commercial interests rather than patients' needs. The assisted reproductive technology market in the United States is largely unconstrained by government agencies, insurance companies, or research universities, and it is undergoing consolidation into a few large chains of consumer-oriented ART centers. An American researcher noted that the now-abandoned cytoplasmic transfer method of MRT was encouraged by several commercial firms before the FDA banned the procedure.

Legal and regulatory status of MRT

Because MRT is controversial, its legal and regulatory status varies from country to country as of 2021. To date, the United Kingdom is the only country in which MRT is legally permissible.

United Kingdom

As of 2021, MRT is allowed in the United Kingdom, but is permitted only within clinics approved by the country's Human Fertilization and Embryology Authority (HFEA), and only for patients approved by the HFEA. To date, only women at high risk of transmitting a severe

mitochondrial disease to offspring and for whom pre-implantation genetic testing is not an alternative have been approved for MRT. These approved patients must sign an informed consent form stating that they understand that the risks and benefits of MRT are not yet well understood.

Canada

According to MitoCanada, MRT is illegal in Canada under the provisions of the *Assisted Human Reproduction Act* (AHRA) of 2004, "and research on these techniques is illegal even if the resulting embryo will never be implanted in a uterus." As of late 2019, Canadian health agencies had not formally reviewed the newer techniques of MRT.

United States

MRT has not been approved by the U.S. Food and Drug Authority (FDA) for use in the United States as of mid-2021. The agency states that its "jurisdiction includes human cells used in therapy involving the transfer of genetic material by means other than the union of gamete nuclei." In 2014, the FDA convened a meeting of an advisory committee "to discuss oocyte modification in

QUESTIONS TO ASK YOUR DOCTOR

- Do you think there should be limits to the types of assisted reproductive technology allowed?
- Should the FDA approve the use of MRT in the United States? If so, should it approve all forms of MRT in current use or only one?
- What do you consider the most significant risks of mitochondrial replacement therapy?
- Have you ever treated a patient at high risk of bearing a child with a mitochondrial disease? If so, what advice did you offer?

assisted reproduction for the prevention of mitochondrial disease or treatment of infertility.”

The meeting was followed in 2015 by a request from the FDA to the Institute of Medicine (IOM; now called the National Academy of Medicine or NAM) to produce a report on the social and ethical issues involved in mitochondrial replacement therapy. The IOM’s report concluded that MRT is ethically permissible provided that two conditions are met: 1) treatment should be limited to women at risk of transmitting a severe mitochondrial disease; and 2) research should be limited at least initially to male embryos, because female embryos produced by MRT would result in heritable genetic modifications. Paternal mtDNA is not transmitted to offspring, and thus changes made to mtDNA in the male germline are not heritable.

The FDA posted its most recent statement on MRT on March 16, 2018, to the effect that “Congress has included provisions in annual federal appropriations laws [since 2015] that prohibit FDA from accepting applications for clinical research using MRT. Therefore, clinical research using MRT in humans cannot legally proceed in the United States. The FDA maintains the authority to investigate and take enforcement action in the event that it becomes aware of noncompliance with the laws and regulations administered by FDA.”

Because of the FDA’s refusal to allow the use of MRT within the United States, the sole American child born as a result of MRT was delivered in a Mexican hospital in 2016. The baby boy’s mother has Leigh syndrome, a rare neurological disorder caused by a mutation in her mtDNA. The physician, John Zhang, runs the New Hope Fertility Center in New York City. Other American women who are interested in MRT to prevent mitochondrial disease in their offspring must travel to

foreign clinics as of 2021. Zhang is currently offering the maternal spindle transfer technique in such clinics at a cost of \$80,000 to \$100,000 per patient—which places the procedure beyond the reach of most patients.

Other countries

China banned MRT after a trial of the pronuclear transfer method resulted in the death of two fetuses. Singapore considered legalizing MRT in 2018 during a process that included consulting the general public as well as bioethicists and lawyers, but no legislation has been passed officially as of 2021. Countries in which children have been born following the use of MRT include Greece, the Ukraine, and Spain.

Clinical trials

There are no clinical trials of any form of mitochondrial replacement therapy registered with the NIH as of mid-2021.

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American College of Medical Genetics and Genomics (ACMG), 7101 Wisconsin Avenue, Suite 1101, Bethesda, MD 20814, (301) 718-9603, (301) 718-9604, acmg@acmg.net, <https://www.acmg.net/>

MitoAction, P.O. Box 310, Novi, MI 48376, (888) 648-6228, info@mitoaction.org, <https://www.mitoaction.org/>

MitoCanada, 30052-478 Dundas Street West, Oakville, Ontario, Canada L6H 7L8, (877) 708-MITO (6486), info@mitocanada.org, <https://mitocanada.org/>

National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, <https://www.genome.gov/about-nhgri/Contact>, <https://www.genome.gov/>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 263-9938, <https://rarediseases.org/contact-us/>, <https://rarediseases.org/>

National Society of Genetic Counselors (NSGC), 330 North Wabash Avenue, Suite 2000, Chicago, IL 60611, (312) 321-6834, nsgc@nsgc.org, <https://www.nsgc.org>

United Mitochondrial Disease Foundation (UMDF), 8085 Saltsburg Road, Suite 201, Pittsburgh, PA 15239, (888) 317-UMDF (8633), info@umdf.org, <https://www.umdf.org/>

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) 463-6332, <https://www.fda.gov/>

Rebecca J. Frey, PhD

Moebius syndrome

Definition

Moebius (möbius) syndrome is a condition in which the facial nerve is underdeveloped, causing paralysis or weakness of the muscles of the face. Other nerves to the facial structures may also be underdeveloped.

Description

Moebius syndrome has been called "life without a smile" because the paralysis of the facial muscles, the most constant feature, leads to the physical inability to form a smile even when happy feelings are experienced. The facial nerve is one of a group of 12 nerves known as the cranial nerves because they originate in the brain. The facial nerve is also known as the seventh cranial nerve. The sixth cranial nerve, also called the abducens, controls blinking and back-and-forth eye movement and is the second most commonly affected cranial nerve in Moebius syndrome. Additional cranial nerves affected in

some patients control other eye movements and other functions such as hearing, balance, speech, and feeding.

During pregnancy, certain exposures, such as to the drugs misoprostol or thalidomide, appear to increase the risk of Moebius syndrome. Moebius syndrome cannot be prevented since its cause is unknown. Pregnant women should avoid any kind of illegal drugs, especially cocaine or methamphetamines, as well as misoprostol or thalidomide.

Individuals with Moebius syndrome may also have abnormalities of their limbs, chest muscles, and tongue. The chance of intellectual disability appears to be increased in people with Moebius syndrome, but most people with the disorder have normal intelligence.

Genetic profile

Most cases of Moebius syndrome are isolated and do not appear to be genetic, but occurrence in multiple individuals within some families indicates that there are multiple genetic forms.

Chromosomes 13, 3, and 10 appear to contain genes causing forms of Moebius syndrome, now named, respectively, types 1, 2, and 3.

One family was reported in which two brothers and their male cousin, who were the sons of sisters, all had Moebius syndrome along with other physical abnormalities and intellectual disability. Boys only have one X chromosome and can inherit an X-linked disease from their unaffected mothers, who have two X chromosomes. The pattern of affected children in this family is typical of X-linked inheritance, so it is suggested that there may be a gene involved in Moebius syndrome on the X chromosome as well. If this is the case, the son of a woman with an altered Moebius gene on one X chromosome would have a 50% chance of inheriting the gene and having the condition. A man with this type of Moebius syndrome would be unlikely to have affected children since his daughters would likely have one normal X chromosome from their mother and his sons would receive his Y chromosome, not his X chromosome. In another family, a brother and sister with unaffected parents had Moebius syndrome, suggesting autosomal recessive inheritance, in which two altered copies of a gene are required to have the disorder. In an autosomal recessive disorder, a couple in which each parent carries one altered copy of the disease gene has a 25% chance of having a child with the condition with each pregnancy.

Demographics

Moebius syndrome is extremely rare and does not seem to affect any particular ethnic group more than

QUESTIONS TO ASK YOUR DOCTOR

- What are the treatment options for Moebius syndrome?
- Is surgery required?
- How will Moebius syndrome affect my child?

others. The families in which genes on chromosomes 3 and 10 were mapped were Dutch.

Signs and symptoms

The first sign of Moebius syndrome in newborns is an inability to suck, sometimes accompanied by excessive drooling and strabismus (crossed eyes). Also seen at birth in some patients are abnormalities of the limbs, tongue, and jaw. Children often have low muscle tone, particularly in the upper body. The lack of facial expression and inability to smile become apparent as children get older.

When cranial nerve palsy is associated with limb reduction abnormalities and the absence of the pectoralis muscles, the condition is known as Poland-Moebius or Möbius-Poland syndrome. Common limb abnormalities are missing or webbed fingers and clubfoot.

The prevalence of intellectual disability in Moebius syndrome is uncertain. It has been estimated in the past to be between 10% and 50%, but these numbers are thought to be overestimates resulting from the lack of facial expression and drooling seen in people with Moebius syndrome. In one study of familial cases of Moebius syndrome, 3% were reported to be intellectually disabled.

Diagnosis

Diagnosis of Moebius syndrome is made on the basis of clinical symptoms, especially the lack of facial expression. Since exact genes involved in Moebius syndrome had not yet been identified as of 2015, molecular genetic testing was not available at this time.

Treatment and management

The ability to smile has been restored in some cases of Moebius syndrome by surgery that transfers nerve and muscle from the thigh to the face. Other surgeries can be used to treat eye, limb, and jaw problems. In children with feeding problems, special bottles or feeding tubes are used. Physical and speech therapy are used when necessary to improve control over coordination, speech, and eating.

Prognosis

Moebius syndrome does not appear to affect lifespan, and individuals who are treated for their symptoms can lead normal lives.

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ORGANIZATIONS

Birth Defect Research for Children, 976 Lake Baldwin Ave., Suite 104, Orlando, FL 32814, (407) 895-0802, staff@birthdefects.org, <http://www.birthdefects.org>

FACES: The National Craniofacial Association, PO Box 11082, Chattanooga, TN 37401, (423) 266-1632 or (800) 322-2373, faces@faces-cranio.org, <http://www.faces-cranio.org>

Moebius Syndrome Foundation, PO Box 147, EH32, Pilot Grove, MO 65276, (660) 834-3406, vicki@moebiussyndrome.com, <http://www.moebiussyndrome.com/index.cfm>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, <http://www.rarediseases.org>

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Mohr syndrome see **Oral-facial-digital syndrome**

Monosomy 1p36 syndrome

Definition

Monosomy 1p36 syndrome is a genetic disorder caused by the deletion of critical DNA on the chromosome pair 1. Children affected by this disorder have facial abnormalities, intellectual disability, and developmental delays. Monosomy refers to the deletion occurring on

only one of the chromosomes of the pair. The code 1p36 refers to the exact location on chromosome 1 where the deletion takes place. This location is at the terminal point of the chromosome. A syndrome is a collection of characteristics that tend to occur together in a disorder. Although it is a rare condition, monosomy 1p36 syndrome is the most common terminal deletion disorder.

Description

Monosomy 1p36 syndrome is a rare disorder. The severity of symptoms is diverse; however, most individuals experiencing this disorder have severe symptoms. The most notable symptoms are the facial features. Almost all children with this disorder have some level of intellectual disability. They also experience developmental delays. When they grow into adulthood, most require supportive living such as a group home with special services.

Risk factors

The cause of this disorder is the terminal deletion on chromosome 1, which is the largest human chromosome. Most cases of monosomy 1p36 syndrome appear to be from a spontaneous mutation. However, most spontaneous mutations take place on genes inherited from the mother. Evidence from research in 2009 suggested that the tendency for the deletion to occur is inherited as an autosomal dominant trait.

The facial characteristics of a person affected by monosomy 1p36 syndrome include deep-set eyes and flat nose bridge. Most individuals have a small head and ears that are disproportionate to one another. Another common characteristic is a pointed chin. Almost 65% of those affected are born with a cleft lip. Almost all children have low muscle tone leading to awkward motor skills.

Those affected with this disorder are born with some form of abnormality in the brain structure. In addition, most experience heart and hearing problems. Delays in language development and structural problems contribute to a lack of verbal communication.

There is no cure for the underlying condition, although genetic research is investigating ways to resolve similar conditions. Most treatment involves solving the individual symptoms and constant monitoring for further complications. Early intervention and life-long education is designed to help the affected person adapt to as independent a lifestyle as possible.

Genetic profile

The cause of this syndrome is a deletion of the continuous DNA on chromosome 1, which is responsible

for neurological functioning and normal development. The deletion is usually at the terminal point of the corrupted chromosome; however, in a few cases the deletion takes place in the middle of the strand. The rate of maternal chromosomes affected is slightly higher than paternal chromosomes affected with 60% of affected chromosomes coming from the mother's side. There are no notable differences in characteristics marking the differences in chromosomal differences.

Demographics

As of 2015, the estimate of this disorder's occurrence was between 1 in 5,000 and 1 in 10,000 newborns. Twice as many females are affected as males. No racial or ethnic ratios have been established.

Signs and symptoms

The most observable characteristics are the distinct facial features of an affected person. These include a prominent forehead and an underdeveloped midface. Included in the underdeveloped midface are the characteristics of a flat nose and flat nasal bridge. The eyes are deep set, and the openings are unusually small. Most people affected have microcephaly and brachycephaly. Microcephaly is a condition in which the circumference of the head is abnormally small for age and gender. Brachycephaly is a condition contributing to a flat head, in which the head is disproportionately wide but the front to back ratio is abnormally short. The ears are small, low set, and unaligned with each other. People with monosomy 1p36 syndrome have short stature in comparison to others of the same age and gender.

Developmental and intellectual disabilities are almost universal among those with this syndrome. Measures of intelligence are often below the standard for moderate intellectual disability; although some may be more severe. Language and speech development are often severely delayed. All measures of developmental milestones are later than observed in children from a normal population. Behavioral problems related to these delays are common with a greater than expected rate of self-injury.

The most serious and common congenital disorder is the heart malformation. This problem can be manifested as patent ductus arteriosus (failure of a prenatal bypass to close at birth) or cardiomyopathy (a congenital weakness of the heart muscle). Other serious congenital problems are associated with brain malformation. The related conditions include cerebral atrophy (loss of brain cells) and cerebral ventricular dilatation (condition where the amount of blood coming into the brain is greater than what can be accommodated by the blood vessels taking

blood away from the brain). Other congenital disorders include visual disability to some degree. Many individuals experience problems of the esophagus interfering with normal swallowing. Sensitivity in hearing is reduced to some degree in most affected people due to problems with the ear structure or to the nerve, but complete hearing loss is no greater than in the normal population.

Diagnosis

Many characteristics of monosomy 1p36 syndrome are observable from birth. Certainly the distinct facial characteristics can be identified as good evidence of the presence of monosomy 1p36 syndrome. There are no known cases of a diagnosis based on the observable features alone.

Examination

An examination of the newborn suspected of having this syndrome begins with noting the usual observable features, including a prominent forehead; a flat nose and nasal bridge; deep set eyes; abnormally small, flat head; and small, low set, unaligned ears. In addition to these easily observed features, most children with monosomy 1p36 syndrome have problems with the little finger on one or both hands. This fifth finger may be unusually short or pointed. Oftentimes the fifth finger is either curving toward the other fingers or is inflexible. In newborns, the anterior fontanelle (the soft spot of the head) is either unusually large or is unusually late in closing. Quite a few affected people experience seizures; therefore, it is appropriate to note in the clinical examination whether the child has had seizures.

Tests

Tests should be conducted for the expected congenital disorders, including problems of the heart and brain. Tests of reflexes and reaction can be conducted with a newborn to determine intellectual functioning. In early childhood, developmental tests can demonstrate the rate of developmental growth in comparison with normally developing children. However, a diagnosis of monosomy 1p36 syndrome cannot be definite without a test detecting the chromosome 1 deletion.

The main test for recognizing chromosomal disorders is fluorescence in-situ hybridization (FISH). This method of analyzing the structures of human genetics relies on fluorescent probes designed to link to specific genetic particles such as proteins, genes, or chromosomal material. If the correlating probe cannot link to the material for which it is designed, then the result is accepted as an absence of the material. In testing for monosomy 1p36 syndrome, the probes specific to a continuous pattern on

chromosome 1 would be injected into genetic material from the patient. If examination of the probes does not detect a continuous pattern, then it is confirmation that the person has monosomy 1p36 syndrome.

The condition can also be detected prenatally through amniocentesis.

Treatment and management

Treatment is focused on relieving discomfort caused by the secondary characteristics. Depending on what the characteristics are and how severe they are, there may be an effort to reverse the individual symptoms. However, there is little effort to find a cure for the underlying cause of the disorder.

One of the most important sources for treatment for the child diagnosed with monosomy 1p36 syndrome is early intervention for intellectual disability. Early intervention can assist the child in overcoming the challenges of developmental delay. As the child grows, the individual will require special services in school and rehabilitative services in adult life. Involving the child in early intervention can assist in making these later services more effective. The agency providing the early intervention can help educate and prepare the parents for the challenges that the child will face over the years. The best intervention is based in a day-care setting with the child living at home, unless the developmental disabilities are too severe. In that case, the child might be recommended to a residential facility.

The severity of any congenital physical problems has to be met appropriately from birth. Doing so requires constant observation and medical diagnosis. If the condition is not severe, it may not be dangerous to postpone treatment until later in life; however, diagnosis of the condition and its progress has to be constantly monitored over time.

Since most children with monosomy 1p36 syndrome have some level of a hearing disability, lessons in American Sign Language are often recommended. The children often have speech problems; therefore, learning sign language can improve their communication skills. Constant assessment of all symptomatic conditions, including language, intellectual functioning, heart condition, seizures, and hearing, is necessary throughout life.

There is no prevention for monosomy 1p36 syndrome. Genetic counseling and prenatal testing is available but is usually only conducted when one of the parents is suspected of being a carrier. Genetic counseling can help prospective parents recognize the risks of conceiving a child with this syndrome. If the risk is high, the parents might have the option of in vitro fertilization. With in vitro fertilization, the genetic diagnosis, done before implantation, can detect which available zygote has the least chance for the syndrome. The advantage of

QUESTIONS TO ASK YOUR DOCTOR

- What specific congenital disorders does my child have?
- How can we as parents monitor the many conditions of our child?
- What are the chances for my child to grow up to be independent?
- How can we determine what social services are available for our child at all stages of life?
- What can we as parents do to help our child better adapt?
- Where can we find out about trial treatments available now or in the future?

early detection through prenatal testing is that the necessary accommodations and interventions can be ready immediately after birth. The necessary tests for genetic counseling and prenatal assessment are not usually conducted unless there is a known family risk. Therefore, it is important to investigate one's family history. Furthermore, when there is a known risk, it is important to communicate that to all concerned.

Prognosis

There is no cure for monosomy 1p36 syndrome. The prognosis of this syndrome is related to the severity of the condition and the nature of the symptoms. There is a correlation between the extent of the deletion on chromosome 1 and the severity of the conditions of the syndrome. However, the deletion of chromosome 1p36 is never seen as a contributing factor in a fatality. The resulting congenital disorders are more often referred to as contributing to death of a person. Statistics on life expectancy are usually given in relation to those collected for the congenital disorders.

The prognosis for adapting to living conditions and for quality of life is related to the effectiveness and appropriateness of recommended treatments. Family members and advocates have to be constantly aware of the availability of necessary social services for those with developmental disabilities.

Resources

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ORGANIZATIONS

American Association on Intellectual and Developmental Disabilities (AAIDD), 501 3rd St. NW, Suite 200, Washington, DC 20001, (202) 387-1968, (202) 387-2193, <http://www.aamr.org>

Ray F. Brogan, PhD

Morquio syndrome (MPS IV) see **Mucopolysaccharidoses**

Mowat-Wilson syndrome

Definition

Mowat-Wilson syndrome is a rare genetic disorder characterized by moderate to severe mental impairment, distinctive physical features, and a collection of intestinal problems known as Hirschsprung's disease.

An alternate name associated with Mowat-Wilson syndrome is Hirschsprung Disease-Mental Retardation syndrome. A similar condition, called Goldberg-Shprintzen syndrome, is sometimes confused with Mowat-Wilson syndrome, but appears to have a different genetic basis.

Description

Mowat-Wilson syndrome is named for clinical geneticists David Mowat and Meredith J. Wilson, who, along with their research team, described the disorder in a 1998 issue of the *Journal of Medical Genetics*. In the article, they provided details about six children, five from New South Wales, Australia, and one from Manchester, England. The children were unrelated. Four of the six children had the following combination of primary symptoms:

- distinctive facial appearance, including large, uplifted earlobes
- intellectual disability

KEY TERMS

Agenesis/hypoplasia of the corpus callosum—Birth defect in which the two halves of the brain are not properly separated.

Cataracts—Cloudiness of the eye lenses.

Hypogenitalism—Retarded development of the external reproductive organs.

Hypotonia—Decreased muscle tone.

Joint contracture—Inability of the limbs to fully extend.

Microcephaly—Small head.

Micrognathia—Undersized jaw.

Neurotransmitters—Chemicals that transmit nerve impulses.

Paresthesia—Presence of abnormal sensations in the limbs.

Ptosis—Drooping eyelid.

- small head
- short stature
- severe constipation, intestinal blockage, and enlargement of the colon, a collection of symptoms known as Hirschsprung's disease, which first appeared when these patients were newborns

The remaining two patients had similar symptoms, but one did not develop Hirschsprung's disease until the age of three, and the other did not have Hirschsprung's disease but did experience chronic constipation. The researchers also noted that all six patients had "a generally happy, smiling affect," often with an open-mouthed expression.

Mowat and Wilson suggested that the cause of the disorder was a genetic mutation or the loss of a miniscule bit of a chromosome (known as a microdeletion). The researchers continued to collect evidence and review other patients with the same suite of symptoms and, in 2003, published their findings that the disorder, by then named Mowat-Wilson syndrome, resulted from the mutation of a specific gene, and this mutation need only affect one of the two copies of the gene in a cell to have an effect.

Genetic profile

The *ZEB2* gene is located on the long arm of chromosome 2. It carries the blueprint for the *ZEB2* protein, which is a transcription factor. Transcription factors

attach to DNA and regulate the expression of genes. In other words, they control whether certain genes' instructions are read. The *ZEB2* protein regulates those genes that have roles in early growth and development. In particular, the *ZEB2* protein is vital to the development of embryonic tissue called the neural crest, which later transforms into more specific tissues that are critical to a well-functioning nervous system, heart, and other systems and organs. This protein is also crucial in the development of a properly formed face and skull.

Individuals who have the mutated *ZEB2* gene cannot make enough properly functioning *ZEB2* protein, which causes the neural crest to suffer, and associated organs and tissues do not develop as they should.

Scientists know of more than 180 different mutations in the *ZEB2* gene that can lead to Mowat-Wilson syndrome. Usually, the mutation either completely deletes one copy of the gene or affects its instructions such that it makes shortened and nonfunctional *ZEB2* protein.

Demographics

Mowat-Wilson syndrome is a rare genetic disorder that affects individuals worldwide and appears to have no preference for gender, ethnicity, or geographic area. Information about its prevalence was not available as of 2015. There have been more than 200 reported cases of Mowat-Wilson syndrome globally.

Signs and symptoms

Mowat-Wilson syndrome results from a mutation in a gene that carries the instructions for making the protein called zinc finger E-box binding homeobox 2 (*ZEB2*). When a mutation of this gene, which is generally called the *ZEB2* gene, occurs, individuals cannot make a sufficient amount of the functioning *ZEB2* protein, and in some cases, they cannot make any at all. This protein is involved in the prenatal development of the nervous, gastrointestinal, cardiovascular, and other systems and tissues in the body. When it is lacking, a wide range of symptoms can arise.

Although this disorder has a genetic component, patients typically do not have a family history of it. Instead, Mowat-Wilson syndrome usually arises spontaneously, which means that it is not passed from one generation to the next, nor is it more likely in brothers or sisters of an affected individual. Mowat-Wilson syndrome is considered an autosomal dominant disorder, because individuals only need to have one copy of the mutated gene to develop the disorder.

Symptoms

Individuals with Mowat-Wilson syndrome have a wide range of symptoms, including characteristic facial features, some of which may be evident at birth, and moderate to severe mental impairment. Symptoms may include the following:

- small head (microcephaly)
- heavy eyebrows
- mental impairments that may be severe
- impaired, late-developing speech, or absent speech
- motor-skill delays, including late development of walking
- severe constipation, intestinal blockage, and enlargement of the colon (collectively known as Hirschsprung's disease)
- chronic constipation, even in the absence of Hirschsprung's disease
- short stature
- heart defects
- urinary tract/genital defects, such as the abnormally placed opening of the urethra or undescended testicles among males
- seizures
- improper separation of the two halves of the brain (agenesis/hypoplasia of the corpus callosum)

Facial features common to infants include:

- widely spaced, deep-set, large eyes
- square-shaped face
- broad nasal bridge, and an overall flat, or so-called saddle nose or boxer's nose with a rounded tip
- open, frequently smiling mouth
- full lower lip
- narrow, strongly pointed chin
- cup-shaped ears with large earlobes and a dimple in the middle of each lobe
- thick and horizontal (rather than arched) eyebrows

As the child ages, the facial features typically change in the following ways:

- chin becomes stronger
- rounded tip of the nose becomes more evident
- upper lip becomes narrow at the center point and outer edges, but full elsewhere
- continued smiling, open-mouthed expression
- blue-eyed children with black patches in their irises

Facial features continue to develop into adulthood, and patients generally have a long face with protruding jaw (prognathism); a long, pointed chin; very thick,

QUESTIONS TO ASK YOUR DOCTOR

- What can I do to help my child learn to walk?
- What specialists are available to help my child begin talking?
- Do seizure medications have any side effects?
- Should we consider prenatal genetic testing to make sure our next child does not have this disorder as well?

horizontal eyebrows; and a long nose that dips down toward the top of the upper lip.

Diagnosis

Examination

Notable facial features (which become more prominent as the affected individual ages), developmental delays, and intellectual disabilities aid in a preliminary diagnosis of Mowat-Wilson syndrome.

Tests

Genetic testing is used to detect *ZEB2* gene mutations that are indicative of the disorder.

Treatment and management

No cure is available. Individuals with this disorder are typically treated by a range of specialists that focus on various symptoms.

There is no way to prevent Mowat-Wilson syndrome. It is a genetic disorder that usually results from a mutation that occurs spontaneously.

Traditional

Depending on the severity of symptoms, the doctor may refer a patient to an orthodontist, ophthalmologist, urologist, cardiologist, or other specialist for additional symptom diagnosis and treatment. For instance, individuals may undergo an electroencephalogram (EEG) or magnetic resonance imaging (MRI) to check for the potential of neurologic problems, such as seizures.

Drugs

A doctor may prescribe anti-epileptic drugs to treat seizures. Additional medication may be of help in treating specific symptoms.

Prognosis

Initial symptoms, including characteristic facial features, are often seen soon after birth, and mental abilities become evident shortly thereafter. Toddlers generally have poor muscle tone and begin walking late (at about four years of age) or never develop this ability. Seizures may develop in infancy or in later childhood, but in about 10% of patients, seizures do not develop. Nearly one-half of patients develop congenital heart disease, and about 60% develop Hirschsprung's disease. Those without Hirschsprung's disease usually have chronic constipation.

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Mowat-Wilson Syndrome Foundation, 4009 Tyler William Ln., Las Vegas, NV 89130-2628, (702) 658-5391, <https://mowat-wilson.org/about/contact/>, <http://www.mowat-wilson.org>

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Moyamoya

Definition

Moyamoya is a progressive syndrome characterized by narrowing of the blood vessels in the brain. Moyamoya is the Japanese term for "cloud of smoke drifting in the air."

Description

The term "moyamoya" is used to describe how the arteries in the brain look in this syndrome, which was first described in the 1950s. There is no clear cause for this

disease. It can be caused genetically but can also occur as a result of other diseases. Moyamoya is seen in patients with a variety of diseases, including neurofibromatosis, trisomy 21 (Down syndrome), sickle cell disease, chronic meningitis, and as a side effect of irradiation.

Moyamoya is a disease of the blood vessels in the brain. The carotid arteries are two of the large arteries that allow blood to flow into the brain. The external carotid artery allows blood to reach areas within the neck, while the internal carotid artery travels to the brain and branches off into smaller vessels to reach all areas of the brain. In patients with moyamoya, there is a symmetric thinning of the width of the internal carotid arteries. The brain responds to this thinning by making the smaller blood vessels bigger, trying to get blood to the areas of the brain that are not getting enough. When dye is injected into the arteries of the brain (a cerebral angiogram), a characteristic pattern is seen. On the angiogram, this looks like a cloud of smoke.

Genetic profile

The primary form of moyamoya is seen most often in Japan. Studies have found the familial form to account for 7%–10% of the cases. A recent study focused on 16 families in order to find the genetic marker for the disease. The gene locus was found to be present on the short arm of chromosome 3, specifically 3p26–p24.2. Other studies have found possible involvement of genes on chromosomes 6 and 17 as well.

Demographics

Although the disease seems to occur most often in Japanese people, patients have been found throughout the world. It is thought that one in a million people are affected each year. The age of onset of the disease has two peaks, the first being in children under 10 years old, and the second in adults in their 20s–40s. Fifty percent of moyamoya cases are found in patients younger than ten years of age. Females seem to have moyamoya more often than males. The female-to-male ratio is 3:2.

Signs and symptoms

The first signs and symptoms of moyamoya tend to be different in children and adults. Children most often present with a sudden seizure or a stroke. Strokes can cause weakness on one side of the body. These are often brought on with exercise or fast breathing. Less severe strokes, called transient ischemic attacks (TIAs), can occur very often. During these TIAs, the weakness in the body is temporary and will not last more than a few hours. Over a period of years, strokes and TIAs leave patients with permanent weakness on both sides of the body, seizure disorders, and intellectual disabilities.

KEY TERMS

Angiography—Injecting dye into blood vessels so they can be seen on a radiograph or picture.

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Stroke—A sudden neurological condition related to a block of blood flow in part of the brain, which can lead to a variety of problems, including paralysis, difficulty speaking, difficulty understanding others, or problems with balance.

While children will present with seizures or strokes, adults tend to present with intracerebral hemorrhage (bleeding within the brain). Depending on where the bleeding or strokes occur, there can be a variety of chronic symptoms, including speech disturbance, visual disturbance, headaches, difficulties with sensation, and involuntary movements (moving parts of the body when you do not intend to).

Diagnosis

Cerebral angiography is the main method of diagnosis. This is the best way to see the arteries in the brain and to assess their level of occlusion (blockage). Other methods of imaging have been used in an attempt to diagnose moyamoya. High-resolution imaging such as computed tomography scans (CT scans) do not show findings specific to this syndrome. However, areas of old strokes or bleeding can be seen. Magnetic resonance imaging (MRI) is also very sensitive at looking for old areas of stroke but cannot show which blood vessels may be blocked as compared with angiography. These non-invasive imaging techniques may, however, provide clues for the diagnosis. The doctor would then recommend angiography to confirm the diagnosis.

Treatment and management

There is no one best treatment for moyamoya. Medical therapy consists of drugs that prevent blood clot formation, such as aspirin. Drugs that help dilate the narrowed blood vessels, such as calcium channel blockers, are also used. Calcium channel blockers that have been successful include nicardipine and verapamil. These calcium channel blockers may also help with the

headaches that some patients may get during the course of their illness.

Many different surgical approaches have been used to help improve blood flow in these patients. It is not known what the long-term outcomes of these procedures are. The most popular operations are: encephaloduroarteriosynangiosis (EDAS), encephalomyosynangiosis (EMS), and superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis.

In EDAS, an artery that sits under the scalp called the superficial temporal artery is separated from the skin. A small opening in the skull is then made. The artery from the scalp is then sewn into the surface of the brain. The piece of skull that was removed is then put back in place to protect the new connection. This procedure has also been termed pial syngiosis.

In the EMS procedure, a muscle overlying the temple region of the forehead, called the temporalis muscle, is detached. Once again, an opening in the skull is made and the muscle is placed on the surface of the brain.

In the STA-MCA operation, the scalp artery is connected directly to an artery in the brain. All of these surgical procedures attempt to provide blood to areas of the brain that are not getting enough. Although symptoms may be improved soon after surgery, it usually takes months for the new blood vessels to form.

Prognosis

The long-term risks due to complications in people with moyamoya disease are unknown. A study published in 2000 looked at 334 patients with moyamoya disease diagnosed between 1976 and 1994. Approximately 60% of the adults who had moyamoya had a cerebral hemorrhage at some point. Approximately 60% of the children who had moyamoya had a stroke or TIA at some point. Cerebral hemorrhage was found to be the most important factor that predicted a poor outcome. The overall effect of medical and surgical treatment on long-term outcomes was unknown as of 2015.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06180, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

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mRNA vaccine technology

Messenger ribonucleic acid (mRNA) is one of a variety of nucleic acids found in cells. It has a chemical composition similar to, but distinguishable from, DNA. Like DNA, it is capable of carrying the genetic code that translates to the amino acid sequence of proteins. Unlike DNA, mRNA works in the cytoplasm, or body of the cell separate from the chromosomes in the nucleus. In the cytoplasm, ribosomes read the genetic code of mRNA, and the ribosomes add amino acids to the growing protein according to the genetic code.

mRNA vaccine technology uses mRNA custom-made to direct the production of a protein. When a protein from a virus is desired, a custom-made mRNA molecule is delivered to the cytoplasm of cells with instructions for production of the desired viral protein. No live or attenuated virus is needed.

History of mRNA in Medical Research

mRNA has been in use for decades in experimental cancer treatments. Experimental Zika virus, rabies virus, and influenza virus vaccines have been developed and tested in animals. Notably, for influenza, the goal of an mRNA vaccine is to develop immunity with a vaccine that is easily manufactured and can be administered in one or two injections and does not require annual flu shots. Research focus shifted rapidly to SARS-CoV-2 early in the pandemic that began in 2019.

Emergence of SARS-CoV-2

SARS CoV-2 is a respiratory disease-causing virus newly introduced into the human population. The coronaviruses are a large viral family found throughout nature. They infect animals, including humans. Many common colds are caused by coronaviruses. A far more serious respiratory infection, COVID-19, caused by SARS-CoV-2, was

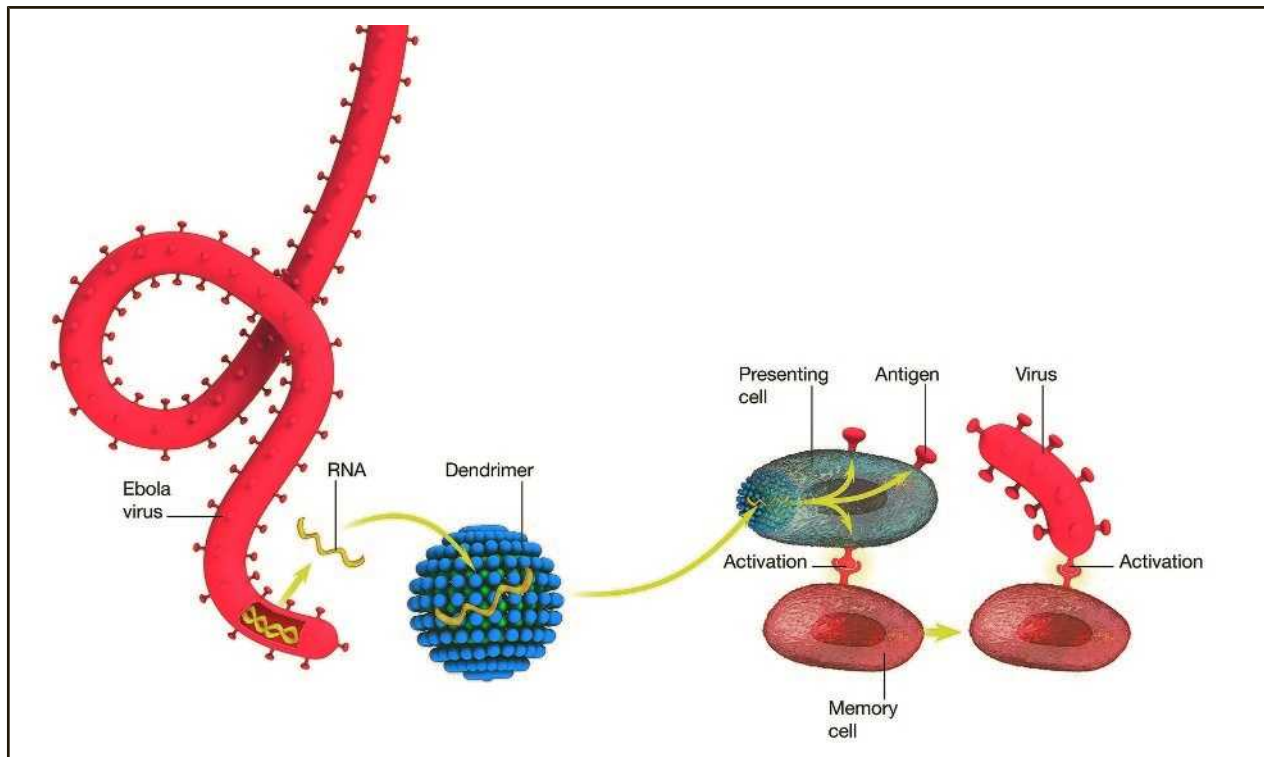


Illustration of an mRNA Ebola vaccine that uses replicon mRNA (messenger ribonucleic acid), a self-replicating nucleic acid, to prime a recipient's immune system. mRNA (yellow) that encodes ebola virus glycoprotein is extracted from an Ebola virus (left) and packaged in a dendrimer nanoparticle (blue). The dendrimer protects the mRNA from degradation when injected into the host and helps with delivery to a host cell. Once inside the host cell the mRNA produces Ebola virus glycoproteins, but not the virus itself. This foreign antigen activates the body's immune system (red cells) to produce antibodies that protect against future infections with the actual virus (far right). (Mikkel Juul Jensen/Science Source)

responsible for an outbreak near Wuhan China late in 2019 that spread globally.

Vaccination for disease prevention

Prevention of viral disease through vaccination requires that a sample of the virus be made available to the body to teach the immune system how to destroy the virus before infection is established and symptoms develop. COVID-19 mRNA vaccines deliver their genetic code to the interior of cells so that the cellular machinery can be used to make new viral proteins. Whether infected by the virus naturally or immunized, the spike protein becomes exposed on the outer surface of human cells. The immune system gets an example of the composition of the virus and mounts a response that prevents infection from closely related coronavirus.

The immune response is twofold: there are cellular and antibody components. The response destroys free viral particles after binding their spike protein with antibody. Infected cells are destroyed by white blood cells to stop them from producing virus particles. Then, through a cascade of events, cells able to produce mass

quantities of protective antibodies and white blood cells that can destroy infected human cells develop. Immunological memory resides in those antibody-producing and other white blood cells. A rapid and protective response is launched upon re-exposure to the virus or vaccine-derived spike protein, and infection is diminished in severity or prevented completely.

The vaccine mRNA must contain the genetic sequence of protein from the virus. Several research teams chose spike protein for vaccine research because it is accessible on the surfaces of infected cells and on free virus particles. The immune system has easy access to spike so that antibodies and cells can act on it. In addition to coding for the spike protein, the vaccine mRNA must contain code serving as instructions for the cell to correctly use the mRNA to make the protein.

Delivery of the vaccine to the interior of the cell

The gene gun is a device that works through the skin to "shoot" vaccine into cells. It has been used for mRNA delivery and vaccination in mice. Lipid or polymer-based

nanoparticles can be used to carry the mRNA and “melt” into the cell surface, delivering the mRNA to the cells’ interior. Vector-delivered mRNA is inserted into an unrelated virus that is unable to infect or cause disease. The virus vector enters cells and delivers the mRNA so that the spike protein can be made. Nanoparticle or vector delivery is used in the three COVID-19 vaccines used under an emergency use authorization in 2021.

COVID-19 Vaccine Safety

mRNA is a non-infectious platform. There is no risk of infection or mutations to human genes. Additionally, mRNA is degraded by normal cellular processes at a rate that can be controlled, so foreign substances do not remain in cells. The COVID-19 mRNA vaccines have high potency, ease of rapid development, and the potential for low-cost manufacture and safe administration.

Effectiveness of COVID-19 Vaccinations

All COVID-19 vaccines currently available in the United States have been shown to be safe and effective at preventing COVID-19. Between 85% and 95% of fully vaccinated people develop protective immunity to the virus. Vaccination is also likely to reduce the spread of virus to other people and limit its opportunities to reproduce and mutate into variants that vaccines are less effective at preventing. The duration of protective immunity is at least a few months, but remains to be seen.

Side effects of vaccination

Coronavirus vaccination may cause pain, redness, and swelling of the arm where the shot is given. Other typical and mild side effects are fatigue, headache, muscle pain, chills, fever, or nausea. Side effects after the second shot may be more intense than the ones experienced after the first shot. These side effects are normal signs that the body is building protection, and they should go away within a few days. Rarely reported side effects include allergic reactions. All people who get a COVID-19 vaccine should be monitored on site for 15 minutes for any developing side effects. Fewer than one in 1,000,000 patients develop serious blood clots weeks to months after vaccination. The rarity of serious side effects and the lethal nature of COVID-19 make the risk of vaccination worthwhile for most people.

Advantages of mRNA Vaccine Technology

These vaccines do not require the use of easily contaminated tissue culture or infectious virus. The process does not produce spike protein in a lab that must then be characterized or preserved before vaccination, because the spike protein is made in the cells of the person

receiving the vaccine. mRNA vaccines are potent, the technology has the capacity for rapid development, as with COVID-19 vaccines, and they have potential for low-cost manufacturing and safe administration.

Challenges of mRNA technology

COVID-19 vaccine production was easily scaled up under federal and international regulations meant to ensure purity, consistency, safety, and potency. Since viruses mutate while in circulation, an extensive system for monitoring infectious strains globally for newly emerging variants must alert public health authorities if the new variants require vaccine reformulation to mimic the variants.

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Mucopolipidosis

Definition

Mucopolipidosis (ML) is a group of rare, inherited disorders that are characterized by the accumulation of complex fats, called mucolipids, in the cells of the body. The symptoms range from skeletal abnormalities and vision problems to physical retardation and intellectual disability.

Description

Types of mucopolipidosis

There are three major types of mucopolipidosis. Mucopolipidosis II (ML II, ML2), or ML disorder type II, is known as I-cell disease (ICD). Sometimes it is called Leroy disease, after Jules Leroy, who described the disorder in 1969. ML II is also known as N-acetylglucosamine-1-phosphotransferase (GNPTA) deficiency. GNPTA is the enzyme that is defective in ML II.

Mucopolipidosis III (ML III, ML3), or ML disorder III, is a milder form of ML II. In ML III, the enzyme GNPTA has reduced activity, whereas it has no activity in ML II. ML III was first described in 1966. It is often called pseudo-Hurler polydystrophy because its symptoms resemble a mild form of the mucopolysaccharide disorder known as Hurler syndrome. It is a polydystrophy because several systems of the body are affected.

In the past, ML II and ML III were classified as mucopolysaccharidoses (MPS II and MPS III, respectively). MPS is a condition in which complex sugars called mucopolysaccharides accumulate in the cells of the body. Although this may occur in ML, excess amounts of mucopolysaccharides are not excreted in the urine, as they are in MPS.

Mucopolipidosis IV (ML IV, ML4) was first described in 1974. It also is called ML disorder IV, Berman syndrome, or sialolipidosis. Recently the gene *TRMPL1*, a widely expressed cation channel protein expressed in lysosomes and late endosomes, has been implicated in ML IV.

Neuraminidase deficiency originally was classified as mucopolipidosis I (ML I). However, neuraminidase deficiency does not involve the accumulation of mucolipids.

Lipids

Lipids are large, complex biomolecules that are very important components of cell membranes. They also are used to store energy and are present in mucus secretions. Lipids are continually broken down and replaced. This breakdown of lipids occurs in a membrane-bound compartment or organelle within cells, called the

lysosome. The lysosome contains many enzymes that break down the lipids. These enzymes are produced outside of the lysosome and have to be transported into the organelle. The enzyme GNPTA attaches a signal to these enzymes that directs them to the lysosome.

Lysosomal storage diseases

MLs are classified as lysosomal storage diseases because the lysosomes accumulate lipids that cannot be broken down. Eventually, the lysosomes become so filled with lipids that the cells form structures called inclusion bodies to contain the lipids. Inclusion bodies give the cells a characteristic appearance. The name “I-cell disease” refers to these inclusion bodies.

Individuals with ML II or ML III have little or no GNPTA enzyme activity. Thus, the lysosomal enzymes cannot reach the lysosome to help break down lipids. ML II and ML III are caused by mutations, or changes, in one of the genes that encodes a part of GNPTA. A disorder called mucopolipidosis III, variant form, or complementation group C, is caused by a mutation in a gene that encodes a different part of GNPTA. The symptoms of this form of ML III are very similar to those of the more common type of ML III.

ML IV is caused by a mutation in the gene encoding a protein called mucolipin-1. In ML IV, membrane lipids and mucopolysaccharides accumulate in the lysosomes of cells throughout the body. Apparently, in the absence of mucolipin-1, these substances are transported to the lysosome rather than recycled to the cell membrane.

Genetic profile

All of the MLs are inherited as autosomal recessive traits. They are autosomal because the genes that are responsible for these disorders are located on autosomal chromosomes, rather than on the X or Y sex chromosomes. The traits are recessive because they are only expressed in individuals who have inherited two copies of the gene that causes the disorder, one copy from each parent.

Individuals with only one copy of a gene that causes ML are called carriers. They usually do not have symptoms of ML. The offspring of two carriers of an ML gene have a 25% chance of inheriting both genes and developing ML.

Demographics

MLs are very rare disorders that often have been misdiagnosed. Thus, the frequency of ML is not clear. Since MLs are recessive disorders that only develop when both parents are carriers of one of the ML genes, the condition most often occurs in the offspring of closely related

individuals, such as first cousins. These disorders are much more prevalent in small, isolated populations. For example, among French-Canadians in one region of Quebec province, it is estimated that 1 out of every 39 people carries a gene for ML II and 1 out of 6,184 infants has the disorder. In contrast, over a ten-year-period, only 35 infants with ML II or ML III were born in Great Britain. In the Republic of Ireland the carrier rate is 1 in 512, and in Northern Ireland the frequency is 1 in 15. In Portugal the frequency of ML II is 1 in 123,500 births, in Japan the incidence is 1 in 252,500 births, and in the Netherlands it is 1 in 625,000 births. The global carrier prevalence has been estimated to be between 1 in 158 and 1 in 316.

Although ML IV can occur in any nationality or ethnic group, more than 80% of all known cases are Jews of Eastern European descent (Ashkenazim). It is estimated that 1 out of 50 individuals of Ashkenazi descent is a carrier of ML IV. Worldwide, there are about 100 known cases of the disorder. However, it is thought that there are many more undiagnosed or misdiagnosed cases.

Signs and symptoms

The symptoms and the age of onset of ML II vary greatly, even within families. Some signs of ML II can be congenital, or present at birth. These may include the following:

- multiple abnormalities in bone formation, particularly in the hip
- limited mobility of the joints
- multiple abnormalities of the skull and face
- a fold of skin extending from the inner corner of the eyelid, called an epicanthal fold

ML II and ML III are progressive conditions. Infants may show few symptoms of the disorder until lipids begin to accumulate and damage cells. Additional symptoms of ML II may include the following:

- dwarfism
- delayed mental and physical development
- hearing loss
- heart disease in the aortic valve
- swollen liver and spleen

The symptoms of ML III are similar to those of ML II, but they are usually less severe. Additional signs of ML III may include the following:

- acne
- clouding of the cornea, the clear portion of the eye through which light passes
- enlarged tongue

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are needed to display the trait or disease.

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Carrier—An individual who possesses an unexpressed abnormal gene of a recessive genetic disorder.

Epicanthal fold—A wrinkle in the skin extending from the nose up to the eyebrow; it is sometimes associated with genetic anomalies.

Hydrolase—An enzyme that uses water to break down substances.

Inclusion body—An abnormal storage compartment inside a cell.

Lipid—Large, complex biomolecule, such as a fatty acid, that will not dissolve in water. A major constituent of membranes.

Lysosome—A membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

Mucolipid—A lipid that accumulates in cells in mucopolipidosis disorders.

Mucolipin-1—A protein in the cell membrane, probably a calcium ion channel, involved in recycling membrane lipids and deficient in mucopolipidosis IV.

Mucopolysaccharide—A complex molecule made of smaller sugar molecules strung together to form a chain. Found in mucous secretions and intercellular spaces.

N-acetylglucosamine-1-phosphotransferase (GNPTA)—Enzyme that attaches a signal to other enzymes and directs those enzymes to the lysosome; deficient in mucopolipidoses II and III.

ML IV is characterized by intellectual disability, physical retardation, and eye disorders. Many individuals with ML IV do not develop beyond the skill level of a one-year-old. However, some individuals with ML IV have very mild symptoms.

Infants with ML IV appear normal at birth. However, signs of the disorder usually become apparent during the first year. Often, clouding or opacity of the cornea is the first symptom, and vision problems may develop before

the age of one. The physical retardation and intellectual disability may be mild at first, but they often become severe as the disorder slowly progresses. Most individuals with ML IV never walk. Other signs of ML IV may include the following:

- delayed growth
- poor muscle tone
- crossed eyes
- puffy eyelids
- aversion to light
- degeneration of the retina, eventually leading to blindness

Diagnosis

In ML I, there is a high level of urinary glycosaminoglycans (GAGs), which is normal in ML II, allowing for a differential diagnosis between ML I and ML II.

ML II and ML III may be diagnosed by high levels of lysosomal enzymes, called hydrolases, in the blood. The following hydrolases are found to be 5- to 20-fold higher in plasma, leading to a differential diagnosis: β -D-hexosaminidase, β -D-glucuronidase, β -D-galactosidase, and α -L-fucosidase.

The absence of mucopolysaccharides in the urine indicates that the disorder is not a mucopolysaccharidosis. However, the urinary excretion of oligosaccharides is high.

The microscopic examination of various cells reveals inclusion bodies.

X-rays are used to detect skeletal abnormalities.

The initial diagnosis of ML IV usually results from a biopsy. A small piece from the skin or from the membrane underneath the eyelid is removed and examined under a microscope for the accumulation of lipids and mucopolysaccharides in storage bodies.

Treatment and management

There is no cure for ML. Management of symptoms, close medical monitoring, and supportive care are the primary treatments.

Surgery can remove the thin layer of cells that causes the corneal cloudiness that is characteristic of ML IV. However, the layer of cells will grow back. Physical, occupational, and speech therapy can improve the functioning of children with ML IV.

Prognosis

The life expectancy for individuals with ML is not known, although many do not survive childhood.

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National MPS Society, PO Box 14686, Durham, NC 27709-4686, (919) 806-0101 or (800) MPS-1001, info@mpssociety.org, <http://www.mpssociety.org>

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Mucopolysaccharidoses

Definition

Mucopolysaccharidoses (MPS) is a general term for a number of inherited diseases that are caused by the accumulation of mucopolysaccharides, resulting in problems with an individual's development. With each condition, mucopolysaccharides accumulate in the cells and tissues of the body because of a deficiency of a specific enzyme. The specific enzyme that is deficient or absent is what distinguishes one type of MPS from another. Before these enzymes were identified, the MPS disorders were diagnosed by the signs and symptoms that an individual expressed. The discovery of these enzymes resulted in a reclassification of some of the MPS disorders. These conditions are often referred to as MPS I, MPS II, MPS III, MPS IV, MPS VI, MPS VII, and MPS IX. These conditions are also referred to by their original names, which are Hurler, Hurler-Scheie, Scheie (all MPS I), Hunter (MPS II), Sanfilippo (MPS III), Morquio (MPS IV), Maroteaux-Lamy (MPS VI), Sly (MPS VII), and Hyaluronidase deficiency (MPS IX).

Description

Mucopolysaccharides are long chains of sugar molecules that are essential for building the bones, cartilage, skin, tendons, and other tissues in the body. Normally, the human body continuously breaks down and builds mucopolysaccharides. Another name for mucopolysaccharides is glycosaminoglycans (GAGs). There are many different types of GAGs, and specific GAGs are unable to be broken down in each of the MPS conditions. There are several enzymes involved in breaking down each GAG, and a deficiency or absence of any of the essential enzymes can cause the GAG to not be broken down completely and results in its accumulation in the tissues and organs in the body. In some MPS conditions, in addition to the GAG being stored in the body, some of the incompletely broken down GAGs can leave the body via the urine. When too much GAG is stored, organs and tissues can be damaged or function improperly.

Genetic profile

Except for MPS II, the MPS conditions are inherited in an autosomal recessive manner. MPS conditions occur when both of an individual's genes that produce the specific enzyme contain a mutation causing them to not work properly. When both genes do not work properly, either none or a reduced amount of the enzyme is produced. An individual with an autosomal recessive condition inherits one nonworking gene from each parent. These parents are called carriers of the condition. When two people are known carriers for an autosomal recessive condition, they have a 25% chance with each pregnancy to have a child affected with the disease. Some individuals with MPS do have children of their own. Children of parents who have an autosomal recessive condition are all carriers of that condition. These children are not at risk to develop the condition unless the other parent is a carrier or affected with the same autosomal recessive condition.

Unlike the other MPS conditions, MPS II is inherited in an X-linked recessive manner. This means that the gene causing the condition is located on the X chromosome, one of the two sex chromosomes. Since a male has only one X chromosome, he will have the disease if the X chromosome—inherited from his mother—carries the defective gene. Females will be carriers of the condition if only one of their two X chromosomes has the gene that causes the condition.

Demographics

The National Institute for Neurological Disorders and Stroke (NINDS) estimates that 1 in every 25,000 babies born in the United States has some form of

mucopolysaccharidosis. Males and females are affected equally.

Signs and symptoms

Each type of MPS is caused by a deficiency of one of the enzymes involved in breaking down GAGs. It is the accumulation of the GAGs in the tissues and organs in the body that causes the wide array of symptoms characteristic of the MPS conditions. The accumulating material is stored in cellular structures called lysosomes, and these disorders are also known as lysosomal storage diseases.

MPS I

MPS I is caused by a deficiency of the enzyme alpha-L-iduronidase. Three conditions, Hurler, Hurler-Scheie, and Scheie syndromes, are all caused by a deficiency of this enzyme. Initially, these three conditions were believed to be separate because each was associated with different physical symptoms and prognoses. Once the underlying cause of these conditions was identified, it was realized that these three conditions were all variants of the same disorder. The gene involved with MPS I is alpha-L-iduronidase (*IDUA*), which is located on chromosome 4p16.3.

MPS I H (HURLER SYNDROME). It has been estimated that approximately 1 in 100,000 will be born with Hurler syndrome. Individuals with Hurler syndrome tend to have the most severe form of MPS I. Symptoms of Hurler syndrome are often evident within the first year or two after birth. These infants often begin to develop as expected, but then reach a point where they begin to lose the skills that they have learned. Many of these infants may initially grow faster than expected, but their growth slows and typically stops by age three. Facial features also begin to appear "coarse." They develop a short nose, flatter face, thicker skin, and a protruding tongue. Additionally, their heads become larger and they develop more hair on their bodies with the hair becoming coarser. Their bones are also affected, with these children usually developing joint contractures (stiff joints), kyphosis (a "hunchback" curve of the spine), and broad hands with short fingers. Many of these children experience breathing difficulties, and respiratory infections are common. Other common problems include heart valve dysfunction, thickening of the heart muscle (cardiomyopathy), enlarged spleen and liver, clouding of the cornea, hearing loss, and carpal tunnel syndrome. These children typically do not live past age 12.

MPS I H/S (HURLER-SCHIE SYNDROME). Hurler-Scheie syndrome is felt to be the intermediate form of MPS I, meaning that the symptoms are not as severe as those in individuals who have MPS I H but not as mild

as those in MPS I S. Approximately 1 in 115,000 will be born with Hurler-Scheie syndrome. These individuals tend to be shorter than expected, and they can have normal intelligence; however, some individuals with MPS I H/S will experience learning difficulties. These individuals may develop some of the same physical features as those with Hurler syndrome, but usually they are not as severe. The prognosis for children with MPS I H/S is variable with some individuals dying during childhood, while others live to adulthood.

MPS I S (SCHEIE SYNDROME). Scheie syndrome is considered the mildest form of MPS I. It is estimated that approximately 1 in 500,000 will be born with Scheie syndrome. Individuals with MPS I S usually have normal intelligence, but there have been some reports of individuals with MPS I S developing psychiatric problems. Common physical problems include corneal clouding, heart abnormalities, and orthopedic difficulties involving their hands and back. Individuals with MPS I S do not develop the facial features seen with MPS I H, and usually these individuals have a normal lifespan.

MPS II (Hunter syndrome)

Hunter syndrome is caused by a deficiency of the enzyme iduronate-2-sulphatase. Individuals with Hunter syndrome are primarily male, because the gene that encodes iduronate-2-sulphatase (IDS) is located on the X chromosome, specifically at location Xq28. However, there have been rare reported cases of females being diagnosed with MPS II. Like many MPS conditions, Hunter syndrome is divided into two groups, mild and severe. It has been estimated that approximately 1 in 110,000 males are born with Hunter syndrome, with the severe form being three times more common than the mild form. The severe form is felt to be associated with progressive intellectual disability and physical disability, with most individuals dying before age 15. In the milder form, most of these individuals live to adulthood and have normal intelligence or only mild mental impairments. Males with the mild form of Hunter syndrome develop physical differences similar to males with the severe form, but not as quickly. Men with mild Hunter syndrome can have a normal lifespan and some have had children. Most males with Hunter syndrome develop joint stiffness, chronic diarrhea, enlarged liver and spleen, heart valve problems, hearing loss, and kyphosis, and tend to be shorter than expected. These symptoms tend to progress at different rates depending on if an individual has a mild or severe form of MPS II.

MPS III (Sanfilippo syndrome)

MPS III, like the other MPS conditions, was initially diagnosed by the individual having certain physical

characteristics. It was later discovered that the physical symptoms associated with Sanfilippo syndrome could be caused by a deficiency in one of four enzymes. Each type of MPS III is now subdivided into four groups, labeled A–D, based on the specific enzyme that is deficient. All four of these enzymes are involved in breaking down the same GAG: heparan sulfate. Heparan sulfate is mainly found in the central nervous system and accumulates in the brain when it cannot be broken down because one of those four enzymes is deficient or missing. The overall incidence of all four types of MPS III is estimated to be 1 in 70,000 births.

MPS III is a variable condition with symptoms beginning to appear between two and six years of age. Because of the accumulation of heparan sulfate in the central nervous system, the central nervous system is severely affected. In MPS III, signs that the central nervous system is degenerating usually are evident in most individuals between ages six and ten. Many children with MPS III develop seizures, sleeplessness, thicker skin, joint contractures, enlarged tongues, cardiomyopathy, behavior problems, and intellectual disability. The life expectancy in MPS III is variable. On average, individuals with MPS III live until they are teenagers, with some living longer and others not surviving as long.

MPS IIIA (SANFILIPPO SYNDROME TYPE A). MPS IIIA is caused by a deficiency of the enzyme heparan N-sulfatase. Type IIIA is felt to be the most severe of the four types, in which symptoms appear and death occurs at an earlier age. A study in British Columbia estimated that 1 in 324,617 live births are born with MPS IIIA. MPS IIIA is the most common of the four types in Northwestern Europe. The gene that causes MPS IIIA is N-sulfoglucosamine sulfohydrolase (*SGSH*), located on the long arm of chromosome 17 (location 17q25.3).

MPS IIIB (SANFILIPPO SYNDROME TYPE B). MPS IIIB is due to a deficiency in N-acetyl-alpha-D-glucosaminidase (NAG). This type of MPS III is not felt to be as severe as Type IIIA and the characteristics vary. Type IIIB is the most common of the four in Southeastern Europe. The gene associated with MPS IIIB is N-acetylglucosaminidase, alpha (*NAGLU*), also located on the long arm of chromosome 17 (location 17q21).

MPS IIIC (SANFILIPPO SYNDROME TYPE C). A deficiency in the enzyme heparan-alpha-glucosaminidase N-acetyltransferase (HGSNAT) causes MPS IIIC. This is considered a rare form of MPS III. The gene involved in MPS IIIC is located on chromosome 8 (location 8p11.1).

MPS IIID (SANFILIPPO SYNDROME TYPE D). MPS IIID is caused by a deficiency in the enzyme N-acetylglucosamine-6-sulfatase. This form of MPS III

is also rare. The gene involved in MPS IIID is glucosamine (N-acetyl)-6-sulfatase (*GNS*) located on the long arm of chromosome 12 (location 12q14).

MPS IV (Morquio syndrome)

As with several of the MPS disorders, Morquio syndrome was diagnosed by the presence of particular signs and symptoms. However, it is now known that the deficiency of two different enzymes can cause the characteristics of MPS IV. These two types of MPS IV are called MPS IV A and MPS IV B. MPS IV is also variable in its severity. The intelligence of individuals with MPS IV is often completely normal. In individuals with a severe form, skeletal abnormalities can be extreme and include dwarfism, kyphosis (outward-curved spine), prominent breastbone, flat feet, and knock-knees. Usually, one of the earliest symptoms seen in this condition is a difference in the way a child walks. In individuals with a mild form of MPS IV, limb stiffness and joint pain are the primary symptoms. MPS IV is one of the rarest MPS disorders, with approximately 1 in 300,000 born with this condition.

MPS IV A (MORQUIO SYNDROME TYPE A). MPS IV A is the “classic” or the severe form of the condition and is caused by a deficiency in the enzyme galactosamine-6-sulphatase. The gene involved with MPS IV A is galactosamine (N-acetyl)-6-sulfatase (*GALNS*) located on the long arm of chromosome 16 (location 16q24.3).

MPS IV B (MORQUIO SYNDROME TYPE B). MPS IV B is considered the milder form of the condition. The enzyme, beta-galactosidase, is deficient in MPS IV B. The location of the gene encoding galactosidase, beta 1 (*GLB1*) is located on the short arm of chromosome 3 (location 3p21.33).

MPS VI (Maroteaux-Lamy syndrome)

MPS VI, which is another rare form of MPS, is caused by a deficiency of the enzyme N-acetylglucosamine-4-sulphatase. This condition is also variable; individuals may have a mild or severe form of the condition. Typically, the nervous system and intelligence of an individual with MPS VI are not affected. Individuals with a more severe form of MPS VI can have airway obstruction, develop hydrocephalus (extra fluid accumulating in the brain), and have bone changes. Additionally, individuals with a severe form of MPS VI are more likely to die while in their teens. With a milder form of the condition, individuals tend to be shorter than expected for their age, develop corneal clouding, and live longer. It is estimated that 1 in 215,000 births is affected with MPS VI. The gene involved in MPS VI is arylsulfatase B (*ARSB*) located on the long arm of chromosome 5 (location 5q14.1).

KEY TERMS

Cardiomyopathy—A thickening of the heart muscle.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Enzyme replacement therapy—Medical treatment replacing an enzyme in patients in whom that particular enzyme is deficient or absent.

Joint contractures—Stiffness of the joints that prevents full extension.

Kyphosis—An abnormal outward curvature of the spine, with a hump at the upper back.

Lysosome—Membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

Mucopolysaccharide—A complex molecule made of smaller sugar molecules strung together to form a chain. Found in mucous secretions and intercellular spaces.

Recessive gene—A type of gene that is not expressed as a trait unless inherited by both parents.

X-linked gene—A gene carried on the X chromosome, one of the two sex chromosomes.

MPS VII (Sly syndrome)

MPS VII is an extremely rare form of MPS, occurring only 1 in 250,000 births, and is caused by a deficiency of the enzyme beta-glucuronidase. It is also highly variable, but symptoms are generally similar to those seen in individuals with Hurler syndrome. The gene that causes MPS VII is designated glucuronidase, beta (*GUSB*), located on the long arm of chromosome 7 (location 7q21.11).

MPS IX (Hyaluronidase deficiency)

MPS IX is a condition that was first described in 1996 and has been grouped with the other MPS conditions by some researchers. MPS IX is caused by the deficiency of the enzyme hyaluronidase. In the few individuals described with this condition, the symptoms are variable, but some develop soft-tissue masses (growths under the skin). Also, these individuals are shorter than expected for their age. The gene involved in MPS IX is encoded by hyaluronoglucosaminidase 1 (*HYAL1*) located on the short arm of chromosome 3 (possibly 3p21.31).

Diagnosis

While a diagnosis for each type of MPS can be made on the basis of the physical signs described, several of the conditions have similar features. Therefore, enzyme analysis is used to determine the specific MPS disorder. Enzyme analysis usually cannot accurately determine if an individual is a carrier for an MPS condition. This is because the enzyme levels in individuals who are not carriers can be similar to enzyme levels seen in individuals who are carriers for MPS. In many of the MPS conditions, several potential symptom-causing mutations have been found in each associated gene. If the specific mutation is known in a family, DNA analysis may be possible.

Once a couple has had a child with an MPS condition, prenatal diagnosis is available to them to help determine if a fetus is affected with the same MPS as their other child. This can be accomplished through testing fluid samples using procedures such as an amniocentesis or chorionic villus sampling (CVS). Each of these procedures has its own risks, benefits, and limitations.

Treatment and management

There is no cure for mucopolysaccharidosis; however, several types of experimental therapies are being investigated. Typically, treatment involves trying to relieve some of the symptoms. Early diagnosis and treatment have been associated with the most favorable outcomes. Targeted drug therapies are available for specific MPS groups. The FDA has approved the drug treatments for MPS I (Aldurazyme, 2003), MPS II (Elaprase, 2006), MPS IVA (Vimizim, 2014), and MPS VI (Naglazyme, 2005). For multiple forms of MPS, the current gold standard of therapy is haematopoietic stem cell transplant, particularly if diagnosed before 2.5 years of age. For MPS I, II, and VI, enzyme replacement therapy is available. Enzyme replacement therapy has proven useful in reducing non-neurological symptoms and pain.

Many individuals with an MPS condition have problems with airway constriction. This constriction may be so serious as to create significant difficulties in administering general anesthesia. Therefore, it is recommended that surgical procedures be performed under local anesthesia whenever possible.

No specific preventive measures are available for genetic diseases of this type. For some of the MPS diseases, biochemical tests are available that will identify healthy individuals who are carriers of the defective gene, allowing them to make informed reproductive decisions. There is also the availability of prenatal diagnosis for all MPS disease to detect affected fetuses.

QUESTIONS TO ASK YOUR DOCTOR

- What are the most serious medical problems that arise because of mucopolysaccharidosis?
- What kinds of treatments or medications are available for the control of mucopolysaccharidosis?
- Are there clinical trials recruiting patients for the MPS that my child has been diagnosed with?
- Is it necessary to have periodic medical check-ups to monitor the progress of MPS in my child?

Clinical trials

Clinical trials on mucopolysaccharidoses are sponsored by the National Institutes of Health (NIH) and other agencies. As of 2015, NIH was reporting 115 ongoing and completed studies.

Examples include:

- The evaluation of the use of enzyme replacement therapy in mucopolysaccharidosis II (MPS II). (NCT00069641)
- A study evaluating the combined treatment using both enzyme replacement therapy and haematopoietic stem cell transplant (the current gold standard therapy) in patients with mucopolysaccharidosis I (MPS I). (NCT00176891)
- The development of a registry to provide information to better characterize the natural history and progression of MPS I as well as the clinical responses of patients receiving enzyme replacement therapy. (NCT00144794)

Clinical trial information is constantly updated by NIH, and the most recent information on mucopolysaccharidoses trials can be found at: <http://clinicaltrials.gov>.

Prognosis

Individuals affected with MPS are affected by many similar clinical features with different degrees of severity. While most undergo a time of normal development, this is followed by a decline in both physical and mental function. The specific syndrome affects the prognosis. For example, children affected with Hurler syndrome often do not live beyond age ten, while a child diagnosed with Scheie syndrome may live to adulthood, and an individual diagnosed with Hunter syndrome, which is a more mild type of MPS, may live into his or her 50s or beyond.

Resources

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ORGANIZATIONS

Canadian Society for Mucopolysaccharide & Related Diseases, 218-2055 Commercial Dr., Vancouver, BC Canada V5N 0C7, (604) 924-5130, (800) 667-1846, (604) 924-5131, info@mpssociety.ca, <http://www.mpssociety.ca>

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Mucoviscidosis see **Cystic fibrosis**

Muir-Torre syndrome

Definition

A syndrome is a condition in which a certain set of features is regularly seen. In Muir-Torre syndrome, the consistent features are skin tumors (sebaceous neoplasms) and internal organ cancers, most commonly colon cancer.

Description

Muir-Torre syndrome is named for two doctors who provided some of the earliest descriptions of the condition, E. G. Muir in 1967 and D. Torre in 1968. Originally thought to be separate conditions, it is now known that Muir-Torre syndrome is a phenotypic subtype of Lynch syndrome (also known as hereditary non-polyposis colon cancer [HNPCC]) and that disease occurs due to

Additional screening recommendations for females with Muir-Torrie syndrome

Test/Procedure	Age	Frequency
Breast exam	20 40	Every 3 years Annually
Pelvic exam	181 or sexually active	Annually
Pap smear	181 or sexually active	Annually
Mammogram	40 50	Every 1–2 years Annually
Endometrial biopsy	Menopause	Every 3–5 years after onset

(Gale)

alterations in the same genes. Some of the features of the conditions are the same, including increased risk of colorectal cancer (cancer of the colon and rectum) and cancer of other organs. Both conditions are hereditary cancer predisposition syndromes, meaning that the risk of cancer has been linked to an inherited tendency for the disease. A unique feature of Muir-Torre syndrome is the skin tumors. The most common skin tumors associated with Muir-Torre syndrome are benign (non-cancerous) or malignant (cancerous) tumors of the oil-secreting (sebaceous) glands of the skin. Another relatively common skin finding is the presence of growths called keratoacanthomas.

Genetic profile

HNPCC and Muir-Torre syndrome are allelic, meaning that they are due to changes in the same genes. Genes, the units of instruction for the body, can have changes or mutations that develop over time. Certain DNA sequence errors are repaired by the protein products of a class of

Screening recommendations for patients with Muir-Torrie syndrome

Test/Procedure	Age	Frequency
Physical exam	20+ 40+	Every 3 years Annually
Digital rectal exam	Any	Annually
Gualac of stool for occult blood	Any	Annually
Lab work-up	Any	Annually
Carcinoembryonic antigen		
Complete blood cell count with differential and platelet count		
Erythrocyte sedimentation rate		
Serum chemistries (SMA-20)		
Urinalysis		
Chest roentgenogram	Any	Every 3–5 years
Colonoscopy	Any If positive for polyps	Every 5 years Every 3 years

(Gale)

genes known as mismatch repair genes. When mutations in these genes occur, the resulting proteins are unable to function properly, and there is a higher chance of cancer due to the alterations that accumulate in the genetic material. Heritable mutations in at least five mismatch repair genes have been linked to HNPCC, although the majority, over 90%, are in the *MLH1* and *MSH2* genes. Mutations in *MLH1* and *MSH2* also have been reported in Muir-Torre syndrome, although most have been *MSH2* mutations. The location of the *MLH1* gene is on chromosome 3 at 3p21.3, while the location of *MSH2* is chromosome 2, 2p21. Genetic testing for *MLH1* and *MSH2* is available, but the detection rate for mismatch repair gene mutations is less than 100%. Therefore, diagnosis of Muir-Torre syndrome is based not only on genetic testing alone but also on the presence of the typical features of the disease.

Muir-Torre syndrome is inherited in an autosomal dominant fashion. Thus, both men and women can have Muir-Torre syndrome, and only one gene needs to be altered to have the syndrome. Children of individuals with Muir-Torre syndrome have a 50% chance of inheriting the gene alteration. The symptoms of the syndrome are variable, and not all individuals with the condition will develop all of the features.

Demographics

At least 250 cases of Muir-Torre syndrome have been reported. It is estimated that between 1 in 200 to 1 in 2,000 people in Western countries carry an alteration in the genes associated with HNPCC, but the rate of Muir-Torre syndrome itself has not been clarified. More males than females appear to exhibit the features of Muir-Torre syndrome. The average age at time of diagnosis of the syndrome is around 55 years.

Signs and symptoms

Skin findings

Sebaceous neoplasms typically appear as yellowish bumps on the skin of the head or neck but can be found on the trunk and other areas. The classification of the different types of sebaceous neoplasms can be difficult, so microscopic evaluation is usually required for the final diagnosis. Keratoacanthomas are skin-colored or reddish, firm skin nodules that are distinct from sebaceous neoplasms upon microscopic examination. The skin findings in Muir-Torre syndrome can either appear before, during, or after the development of the internal cancer.

Internal findings

Internal organ cancers are common in Muir-Torre syndrome. Several individuals with Muir-Torre syndrome

KEY TERMS

Allelic—Related to the same gene.

Benign—A non-cancerous tumor that does not spread and is not life-threatening.

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Colectomy—Surgical removal of the colon.

Colonoscopy—Procedure for viewing the large intestine (colon) by inserting an illuminated tube into the rectum and guiding it up the large intestine.

Colorectal—Of the colon and/or rectum.

Gene—A building block of inheritance that contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found at a precise location on a chromosome.

Genitourinary—Related to the reproductive and urinary systems of the body.

Hereditary non-polyposis colon cancer (HNPCC)—A genetic syndrome causing increased cancer risks, most notably colon cancer. Also called Lynch syndrome.

Keratoacanthoma—A firm nodule on the skin typically found in areas of sun exposure.

Lymph node—A bean-sized mass of tissue that is part of the immune system and is found in different areas of the body.

Lynch syndrome—A genetic syndrome causing increased cancer risks, most notably colon cancer. Also called hereditary non-polyposis colon cancer (HNPCC).

Malignant—A tumor growth that spreads to another part of the body, usually cancerous.

Mismatch repair—Repair of gene alterations due to mismatching.

Mutation—An inherited or *de novo* change in the DNA sequence of the genome.

Polyp—A mass of tissue bulging out from the normal surface of a mucous membrane.

Radiation—High-energy rays used in cancer treatment to kill or shrink cancer cells.

Sebaceous—Related to the glands of the skin that produce an oily substance.

Splenic flexure—The area of the large intestine at which the transverse colon meets the descending colon.

QUESTIONS TO ASK YOUR DOCTOR

- What are the most serious medical consequences associated with Muir-Torre syndrome?
- Are there medicines that can be taken to relieve the symptoms of Muir-Torre syndrome or to reduce their severity?
- What screening recommendations are usually made for individuals with Muir-Torre syndrome?
- What is the prognosis for a child born with this disorder, and on what factors is this prognosis based?

with multiple types of internal cancers have been reported. The most common internal organ cancer is colorectal cancer. Unlike colon cancers in the general population, the tumors due to Muir-Torre syndrome are more frequently seen around or closer to the right side of an area of the colon known as the splenic flexure. This tumor location, the meeting point of the transverse and the descending colon, is different than the usual location of colon cancer in the general population. Colon polyps (benign growths with the possibility of cancer development) have been reported in individuals with Muir-Torre syndrome; however, the number of polyps typically is limited.

Symptoms of colorectal cancer or polyps may include the following:

- red blood in stool
- weight loss
- pain or bloating in abdomen
- long-term constipation
- diarrhea
- decrease in stool size

The next most frequent cancer occurrences in Muir-Torre syndrome are those of the genitourinary system, including uterine cancer, ovarian cancer, and bladder cancer. Other cancers that have been seen with Muir-Torre syndrome include breast cancers, blood cancers, head and neck cancers, and cancers of the small intestine.

Diagnosis

Since not all families with the features of Muir-Torre syndrome have identifiable mismatch repair gene alterations, diagnosis is based mainly on the presence of the physical features of the disease. Muir-Torre syndrome is defined by the presence of certain types of sebaceous neoplasms (sebaceous adenomas, sebaceous epitheliomas, sebaceous

carcinomas, and keratoacanthomas with sebaceous differentiation) and at least one internal organ cancer in the same individual. Muir-Torre syndrome may also be diagnosed if an individual has multiple keratoacanthomas, multiple internal organ cancers, and a family history of Muir-Torre syndrome. Testing of the *MLH1* and *MSH2* genes is available and can be done to confirm a diagnosis or to assist in testing at-risk relatives prior to development of symptoms. Given the complexity of this disorder, genetic counseling may be considered before testing.

Screening recommendations have been proposed for individuals with Muir-Torre syndrome or at-risk relatives. In addition to regular screening for the skin findings, screening for internal cancers may be considered. The effectiveness of screening for individuals with or at risk for Muir-Torre syndrome has yet to be proven.

Treatment and management

While it is not possible to cure the genetic abnormality that results in Muir-Torre syndrome, it is possible to prevent and treat the symptoms of the syndrome. The skin tumors are removed by freezing or cutting. If lymph nodes, small bean-sized lumps of tissue that are part of the immune system, are involved, they must be removed also. Radiation (high energy rays) to the affected area can be beneficial. A medication, isotretinoin, may reduce the risk of skin tumors. Internal organ cancers are treated in the standard manner: removal by surgery and possible treatment with radiation or cancer-killing medication (chemotherapy). Removal of the colon (colectomy) before colon cancer develops is an option with HNPCC and may be considered for individuals with Muir-Torre syndrome.

Prognosis

The cancers associated with Muir-Torre syndrome are usually diagnosed at earlier ages than other cancers. For instance, the average age at diagnosis of colorectal cancer is ten years earlier than in the general population. Fortunately, the internal organ cancers seen in Muir-Torre syndrome appear less aggressive. Therefore, the prognosis may be better for a person with colon cancer due to Muir-Torre syndrome than colon cancer in the general population.

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American Society of Clinical Oncology (ASCO), 2318 Mill Rd., Suite 800, Alexandria, VA 22314, (571) 483-1780 or (888) 651-3038, (571) 366-9537, contactus@cancer.net, <http://www.cancer.net>

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Multifactorial inheritance

Definition

Many common congenital malformations and diseases are caused by a combination of genetic and environmental factors. The term “multifactorial inheritance” is used to describe conditions that occur due to these multiple factors. In contrast to dominantly or recessively inherited diseases, multifactorial traits do not follow any particular pattern of inheritance in families. Multifactorial conditions do tend to cluster in families, but pedigree analysis does not reveal a specific pattern of affected individuals. Some multifactorial conditions occur because of the interplay of many genetic factors and limited environmental factors. Others occur because of limited genetic factors and significant environmental factors. The number of genetic and environmental factors vary, as does the amount of impact of each factor on the presence or severity of disease. Often there are multiple susceptibility genes involved, each of which has an additive effect on outcome.

Examples of congenital malformations following a multifactorial pattern of inheritance include cleft lip and palate, neural tube defects, and heart defects. Adult onset diseases that follow multifactorial inheritance include diabetes, heart disease, epilepsy, and affective disorders like schizophrenia. Many normal traits in the general population follow multifactorial inheritance. For instance, height, intelligence, and blood pressure are all determined

in part by genetic factors but are influenced by environmental factors.

Continuous and discontinuous traits

Some multifactorial traits are considered continuous because there is a bell-shaped distribution of those traits in the population. These are quantitative traits such as height. Other traits are discontinuous because there is a cutoff or threshold of genetic and environmental risk that must be crossed in order for the trait to occur. An example would be a malformation like a cleft lip, in which the person is either affected or unaffected. In both cases, the genetic and environmental factors that are involved in the occurrence of the condition are referred to as liability.

Pyloric stenosis

An example of a discontinuous multifactorial trait that follows the threshold model is pyloric stenosis. Pyloric stenosis is a narrowing of the pylorus, the connection between the stomach and the intestine. Symptoms of pyloric stenosis include vomiting, constipation, and weight loss. Surgery is often needed for repair. An important genetic factor in the occurrence of pyloric stenosis is a person’s gender. The condition is five times more common in males. The liability is higher in women, such that more or stronger genetic and environmental factors are needed to cause the condition in women. Therefore, male first-degree relatives of a female who is affected with pyloric stenosis have a higher risk to be born with the condition than do female first-degree relatives of the same person. This is because the stronger genetic factors present in the family (represented by the affected female) are more likely to cross the lower liability threshold in male family members.

Recurrence risks

Recurrence risks for multifactorial traits are based on empiric data, or observations from other families with affected individuals. Most multifactorial traits have a recurrence risk to first-degree relatives of 2%–5%. However, empiric data for a specific condition may provide a more specific recurrence risk. Some general characteristics about the recurrence risk of multifactorial traits include the following:

- The recurrence risk to first-degree relatives is increased above the general population risk for the trait, but the risk drops off quickly for more distantly related individuals.
- The recurrence risk increases proportionately to the number of affected individuals in the family. A person with two affected relatives has a higher risk than someone with one affected relative.

- The recurrence risk is higher if the disorder is in the severe range of the possible outcomes. For instance, the risk to a relative of a person with a unilateral cleft lip is lower than if the affected person had bilateral cleft lip and a cleft palate.
- If the condition is more common in one sex, the recurrence risk for relatives is higher in the less affected sex. Pyloric stenosis is an example of this.
- Recurrence risks quoted are averages, and the true risk in a specific family may be higher or lower.

It is important to understand that recurrence risks for conditions may vary from one population to another. For instance, North Carolina, South Carolina, and Texas all have a higher incidence of neural tube defects than other states in the United States. Ireland has a higher incidence of neural tube defects than many other countries.

Examples of multifactorial traits

Neural tube defects

Neural tube defects are birth defects that result from the failure of part of the spinal column to close approximately 28 days after conception. If the anterior (top) portion of the neural tube fails to close, anencephaly, the most severe type of neural tube defect, results. Anencephaly is the absence of portions of the skull and brain and is a lethal defect. If a lower area of the spine fails to close, spina bifida occurs. People with spina bifida have varying degrees of paralysis, difficulty with bowel and bladder control, and extra fluid in the brain called hydrocephalus. The size and location of the neural tube opening determines the severity of symptoms. Surgery is needed to cover or close the open area of the spine. When hydrocephalus is present, surgery is needed for shunt placement.

Neural tube defects are believed to follow a multifactorial pattern of inheritance. Empiric data suggests that the risk to first-degree relatives of a person with a neural tube defect is increased 3%–5%. The risk to other more distantly related relatives decreases significantly. In addition, it is known that a form of vitamin B called folic acid can significantly reduce the chance for the occurrence of a neural tube defect. Studies have shown that when folic acid is taken at least three months prior to pregnancy and through the first trimester, the chance for a neural tube defect can be reduced by 50%–70%. This data suggest that one environmental factor in the occurrence of neural tube defects is maternal folate levels. However, some women who are not folate deficient have babies with open spine abnormalities. Other women who are folate deficient do not have babies with spinal openings. The exact interplay of genetic and environmental factors in the occurrence of neural tube defects is not yet clear.

Studies are currently underway to identify genes involved in the occurrence of neural tube defects.

Diabetes

There are two general types of diabetes. Type I is the juvenile-onset form that often begins in adolescence and requires insulin injections for control of blood sugar levels. Type II is the more common, later-onset form that does not usually require insulin therapy. Both are known to be influenced by environmental factors and show familial clustering. Important environmental factors involved in the occurrence of diabetes include diet, viral exposure in childhood, and certain drug exposures. It is clear that genetic factors are involved in the occurrence of type I diabetes since empiric data show that 10% of people with the condition have an affected sibling. An important susceptibility gene for type I diabetes has been discovered on chromosome 6. The gene is called *IDDM1*. Another gene on chromosome 11 has also been identified as a susceptibility gene. Studies in mice have indicated that there are probably 12–20 susceptibility genes for insulin-dependent diabetes. *IDDM1* is believed to have a strong effect and is modified by other susceptibility genes and environmental factors.

Analysis of multifactorial conditions

Genetic studies of multifactorial traits are usually more difficult than genetic studies of dominant or recessive traits. This is because it is difficult to determine the amount of genetic contribution to the multifactorial trait versus the amount of environmental contribution. For most multifactorial traits, it is not possible to perform a genetic test to determine if a person will be affected. Instead, studies involving multifactorial traits strive to determine the proportion of the phenotype due to genetic factors and to identify those genetic factors. The inherited portion of a multifactorial trait is called heritability.

Disease association studies

One method of studying the heritability of multifactorial traits is to determine if a candidate gene is more common in an affected population than in the general population.

Sibling pair studies

Another type of study involves gathering many pairs of siblings who are affected with a multifactorial trait. Researchers try to identify polymorphisms common in the sibling pairs. These polymorphisms can then be further analyzed. Researchers can also study candidate genes in these sibling pairs. Studying individuals who are at the extreme end of the affected range and are thought to have a

larger heritability for the trait can strengthen this type of study.

Twin studies

Another approach is to study a trait of interest in twins. Identical twins have 100% of their genes in common. Non-identical twins have 50% of their genes in common, just like any other siblings. In multifactorial traits, identical twins will be concordant for the trait significantly more often than non-identical twins. One way to control for the influence of a similar environment on twins is to study twins who are raised separately. However, situations in which one or both identical twins were adopted out and are available for study are rare.

Linkage analysis and animal studies are also used to study the heritability of conditions, although there are significant limitations to these approaches for multifactorial traits.

Ethical concerns of testing

One of the goals of studying the genetic factors involved in multifactorial traits is to be able to counsel those at highest genetic risk about ways to alter their environment to minimize risk of symptoms. However, genetic testing for multifactorial traits is limited by the lack of understanding about how other genes and environment interact with major susceptibility genes to cause disease. Testing is also limited by genetic heterogeneity for major susceptibility loci. Often the attention of the media to certain genetic tests increases demand for the test, even though the limitations of the test are not fully explained. Therefore, it is important for people to receive appropriate pre-test counseling before undergoing genetic testing. Patients should consider the emotional impact of both positive and negative test results. Patients should understand that insurance and employment discrimination might occur due to test results. In addition, there may not be any treatment or lifestyle modification available for many multifactorial traits for which a genetic test is available. The patient should consider the inability to alter their risk when deciding about knowing their susceptibility for the condition. When a person chooses to have testing, it is important to have accurate post-test counseling about the result and its meaning.

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- National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Dr., MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, .
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Sonja Rene Eubanks, MS

Multiplex ligation-dependent probe amplification

Definition

Multiplex ligation-dependent probe amplification (MLPA) is a technique used by laboratories to detect an abnormal number of chromosomes, gene deletions, gene duplications, and gene expansions.

Description

Multiplex ligation-dependent probe amplification (MLPA) was first described by Schouten and his colleagues in 2002. The technique is designed to detect genetic issues ranging from an abnormal number of chromosomes to the location of changes in the "spelling" of genes. The technique is a multiplex assay in that it allows simultaneous testing of multiple genetic sequences.

Chromosomes are the gene-containing structures found in all of the body's cells. In each cell, there are 46 chromosomes that come in 23 pairs. Bodies are so specific that the exact amount of genetic information contained in the 46 chromosomes is required to grow and

develop properly; having any more or any less genetic information causes abnormal physical and mental growth and development.

Genes are the blueprints that carry the instructions for making all of the proteins a cell needs and determine traits, such as hair and eye color. Genes contain the inherited information that is passed on from parents to children. Each gene has a specific spelling made of the base pairs, including C, G, A, and T. If the spelling of a gene is changed, or mutated, it can cause abnormalities in the way the gene functions. Missing genetic information from the loss of one normal base pair to the loss of most of a chromosome is referred to as a deletion. A copy of genetic information that results in a redundant piece of genetic information is known as a duplication. A gene expansion refers to a genetic abnormality caused by a sequence of base pairs that is repeated too many times in a section of a gene. Detection of chromosomal abnormalities, deletions, duplications, and expansions of genetic material is an important part of diagnosing genetic conditions and diseases.

The technique of MLPA uses the spelling of the base pairs to determine if portions of chromosomes or genes are changed or mutated. The technique begins with probes that attach to the base pairs of genes and chromosomes in a specific location. The probes are divided into halves that attach around a specific gene or chromosomal location and then attach to each other. This attachment to the area around a gene or chromosome is called hybridization, and the “glue” that attaches the two probe halves to each other is the enzyme ligase. In order to help count the number of probe halves present at the end of the procedure, the probes are made in a series of different lengths. If two probe halves have properly attached to their gene or chromosomal location and each other, they serve as a target for the next step. If the probes are attached to the wrong gene area or a mismatched probe half, they will not participate in the next part of the procedure.

In the next step, a technique called polymerase chain reaction (PCR) is used to make many copies of the correctly paired and attached probe halves. The PCR will not make copies of probes attached or paired incorrectly. Finally, the properly attached and matched probes of each size are separated by size and counted. The amount of each probe size provides the information whether a small area of the gene (called an exon) or the chromosome contains a deletion, duplication, or expansion. Since there are multiple probe sizes with different gene targets, 40 or more gene exons can be tested for abnormalities at the same time.

Indications

The technique of MLPA may be indicated when a genetic condition, disease, syndrome, or disorder

KEY TERMS

Chromosomes—The gene-containing structures found in all of the body’s cells; in each normal cell, there are 46 chromosomes that come in 23 pairs.

Deletion—A mutation resulting in the loss of normal base pair sequence; a deletion may be of any size from one base pair to most of a chromosome.

Duplication—Production of one or more copies of any piece of DNA, including a base pair, gene, or entire chromosome.

Exon—Segments of a gene that contain instruction for making a protein; in many genes, the exons are separated by intervening segments of DNA, known as introns, which do not code for proteins.

Expansion—A genetic abnormality caused by a sequence of nucleotides that is repeated too many times in a section of a gene.

Genes—The basic units of heredity that contain the blueprints for the processes crucial to growth and development.

Multiplex assay—A procedure that allows the testing of several gene samples simultaneously.

Polymerase chain reaction (PCR)—A laboratory process used to make a large number of copies of specific genetic information from small amounts of DNA.

involving a chromosome abnormality, gene deletion, gene duplication, or gene amplification is suspected. Possible testing options include chromosomal disorders, such as Down syndrome; conditions caused by rearrangements of a chromosome; genetic conditions caused by gene deletions and duplications, such as Duchenne muscular dystrophy; certain forms of inherited cancer predisposition; and diseases caused by gene amplification, such as fragile X syndrome.

Samples

MLPA can be run on many bodily fluids and tissues, including blood, human embryonic stem cells, amniocytes, chorionic villi, and formalin-fixed paraffin-embedded tissue. The MLPA method requires that DNA samples obtained from the fluids and tissues be samples of uniform quality, which reduces false positives.

Results

The MLPA test can provide information about chromosomal abnormalities and gene duplications, deletions, or

expansions. If a chromosome abnormality, gene duplication, deletion, or expansion is found, it may indicate predisposition for, diagnosis of, or carrier status for a specific genetic disorder or condition.

Benefits

MLPA is a quick technique that requires a smaller amount of DNA than other testing methods. The test exhibits good sensitivity and specificity when probes are made correctly and proper reaction conditions are used. Several genetic locations can be tested in the same procedure and, accordingly, large genes made of many exons can be tested in a quick and efficient manner. Data from the technique are reproducible. DNA degradation to small fragments does not influence results, and thus testing can be done on formalin-fixed paraffin-embedded tissue.

Limitations

MLPA requires the creation of labor-intensive probes for each new gene or chromosome to be examined before the test can be run. Kits of developed probes are sold, but were not certified by the U.S. Food and Drug Administration (FDA) for use in diagnostic procedures as of 2015. The probe kits are labeled for research purposes and to demonstrate the possibilities of the MLPA technique. Accordingly, results detected through MLPA should be verified with an independent method, such as G-banding chromosome analysis or Southern blots. Although MLPA can determine the approximate location of a genetic anomaly within an exon, unless special probes for specific mutations are designed, the test cannot determine the exact mutation of base pair or pairs.

Alternative tests

There are several testing methods that provide the same information as the MLPA technique. Standard chromosome analysis, comparative genomic hybridization (CGH), fluorescent in situ hybridization (FISH), BAC arrays, Southern blots, and loss of heterozygosity (LOH) assays are used to detect chromosomal abnormalities. Some genetic mutations and expansions can be detected with multiplex polymerase chain reaction (PCR) assays, fluorescent in situ hybridization (FISH), and/or Southern blotting.

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ORGANIZATIONS

- National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Dr., MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152,

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Multiple cartilaginous exostoses see **Hereditary multiple osteochondromas**

Multiple endocrine neoplasia

Definition

Multiple endocrine neoplasia (MEN) is a group of related disorders affecting the thyroid and other endocrine glands (glands that secrete hormones into the bloodstream) of the body. Mutations in three separate genes are associated with the development of MEN. MEN was previously known as familial endocrine adenomatosis.

All MEN disorders are associated with the development of neuroendocrine tumors. These tumorous cells have in common the fact that they produce hormones, or regulatory substances for the body's homeostasis. They come from the amine precursor and uptake decarboxylase (APUD) system, and they have to do with the cell apparatus and function to make these substances common to the cell line. Neuroendocrine tumors cause syndromes associated with each other by genetic predisposition.

Description

The three forms of MEN are MEN1 (Wermer's syndrome); MEN2, which includes three subgroups—MEN2A (Sipple syndrome), MEN2B (previously known as MEN3), and familial medullary thyroid carcinoma (FMTC); and MEN4. Each is an autosomal dominant genetic condition, and all except FMTC predispose to hyperplasia (excessive growth of cells) and tumor formation in a number of endocrine glands. FMTC predisposes only to this specific type of thyroid cancer.

Association of multiple endocrine neoplasias with other conditions

Form	Inheritance	Associated diseases/conditions	Affected gene
MEN 1 (Wermer's syndrome)	Autosomal dominant	Parathyroid hyperplasia Pancreatic islet cell carcinomas Pituitary hyperplasia Thymus, adrenal, carcinoid tumors (less common)	MEN 1
MEN 2A (Sipple syndrome)	Autosomal dominant	Medullary thyroid carcinoma Pheochromocytoma Parathyroid hyperplasia	RET
MEN 2B	Autosomal dominant	Medullary thyroid carcinoma Pheochromocytoma Parathyroid hyperplasia Swollen lips Tumors of mucous membranes (eyes, mouth, tongue, nasal cavities) Enlarged colon Skeletal problems such as spinal curving	RET
Familial medullary thyroid carcinoma	Autosomal dominant	Medullary thyroid carcinoma	RET

(Gale)

MEN1 predisposes affected individuals to more than 20 benign and malignant endocrine and non-endocrine neoplasias. Individuals with MEN1 experience hyperplasia (increased reproduction of cells that is often the first stage in the development of malignancies) of the parathyroid glands and may develop tumors of several endocrine glands, including the pancreas and pituitary. The most frequent symptom of MEN1 is hyperparathyroidism. Hyperparathyroidism results from overgrowth of the parathyroid glands, leading to excessive secretion of parathyroid hormone, which in turn leads to elevated blood calcium levels (hypercalcemia), kidney stones, weakened bones, fatigue, and weakness. Almost all individuals with MEN1 show parathyroid symptoms by age 50, with some individuals developing symptoms in childhood.

About 40% to 70% of individuals with MEN1 develop a pancreatic tumor, called a pancreatic islet cell carcinoma. These tumors tend to be benign, although occasionally they may become malignant and spread. The pancreatic tumors associated with MEN1 may be non-functional tumors (no increase in hormone production and, consequently, no symptoms) or functional tumors where hormone production is increased, resulting in symptoms; the symptoms depend upon the hormone produced. The most common functional tumor is gastrinoma, followed by insulinoma. Other less-frequent functional tumors are VIPoma and glucagonoma. Gastrinoma results in excessive secretion of gastrin (a hormone secreted into the stomach to aid in digestion), which in turn may cause upper gastrointestinal ulcers; this condition is sometimes referred to as Zollinger-Ellison syndrome. About one in three people with MEN1 develops a gastrinoma. Insulinoma causes an increase in insulin levels, which in turn causes glucose levels to decrease.

This tumor causes symptoms consistent with low glucose levels (hypoglycemia, low blood sugar), which include anxiety, confusion, tremor, and seizure during periods of fasting. The pituitary may also be affected, resulting in extra production of hormone. The most frequent of these is prolactinoma, which results in extra production of prolactin, which affects bone strength and fertility. Less commonly, the thymus and adrenal glands may also be affected, and in rare cases a tumor called a carcinoid may develop. Unlike MEN2, the thyroid gland is rarely involved in MEN1 symptoms.

Patients with MEN2A experience two main symptoms: medullary thyroid carcinoma (MTC) and a tumor of the adrenal gland known as pheochromocytoma. Medullary thyroid carcinoma is a slowly growing cancer that is preceded by a condition called C-cell hyperplasia. C-cells are cells within the thyroid gland that produce a hormone called calcitonin. About 40% to 50% of individuals with MEN2A develop C-cell hyperplasia followed by MTC by the time they are 50 years old, and 70% will have done so by the time they are 70 years old. In some cases, individuals develop C-cell hyperplasia and MTC in childhood. Medullary thyroid carcinoma tumors are often multifocal and bilateral.

Pheochromocytoma is usually a benign tumor that causes excessive secretion of adrenal hormones, which in turn can cause life-threatening hypertension (high blood pressure) and cardiac arrhythmia (abnormal heart rate and rhythm). About 40% of people with MEN2A develop a pheochromocytoma. Individuals with MEN2A also have a tendency for the parathyroid gland to increase in size (hypertrophy), and they may develop tumors in the parathyroid gland. About 25% to 35% of individuals with MEN2A will develop parathyroid involvement.

Individuals with MEN2B also develop MTC and pheochromocytoma. However, the medullary thyroid carcinomas often develop at much younger ages—often before the age of one year—and they tend to be more aggressive tumors. About half of the individuals with MEN2B develop a pheochromocytoma, with some cases diagnosed in childhood. All individuals with MEN2B develop additional conditions, which make it distinct from MEN2A. These extra features include a characteristic facial appearance with swollen lips; tumors of the mucous membranes of the eye, mouth, tongue, and nasal cavity; enlarged colon; and skeletal abnormalities, such as long bones and problems with spinal curving. Hyperparathyroidism is not seen in MEN2B as it is in MEN2A. Unlike the other three MEN syndromes, individuals with MEN2B might not have a family history of MEN2B. In at least half of the cases, the condition is new in the individual affected.

Medullary thyroid carcinoma may also occur in families, but family members do not develop the other endocrine conditions seen in MEN2A and MEN2B. This is referred to as familial medullary thyroid carcinoma (FMTC) and is a subtype of MEN2. Familial medullary thyroid cancer is suggested when other family members have also developed MTC, if the tumor is bilateral, and/or if it is multifocal. In comparison to MEN2A and MEN2B, individuals with FMTC tend to develop MTC at older ages, and the disease appears to be more indolent or slow to progress. About 25% of MTC occurs in individuals who have MEN2A, MEN2B, and FMTC.

MEN4 was identified through the observation that 5% to 10% of patients with MEN1 syndrome do not have a corresponding mutation in the *MEN1* gene. Research using a rat model system of MEN-like symptoms called MENX resulted in the identification of the link between MENX and mutations in the *rCDNK1B* gene. Further investigation of the MEN1 patients without the *MEN1* gene mutation determined that 3% of these individuals carried a mutation in the *CDNK1B* gene. Individuals affected with MEN4 exhibit the hyperparathyroidism and *MEN1*-associated tumors, such as parathyroid adenomas, pituitary adenomas, and pancreatic neuroendocrine tumors (NETs) in association with gonadal, adrenal, renal, and thyroid tumors.

Genetic profile

All three MEN syndromes follow autosomal dominant inheritance, meaning that every individual diagnosed with a MEN syndrome has a 50% (one in two) chance of passing the condition on to each of his or her children.

MEN1 results from alterations or mutations in the *MEN1* gene located on chromosome 11q13. Nearly every individual inheriting the *MEN1* gene alteration will develop hyperparathyroidism, although the age at which it is diagnosed may differ among family members. Individuals inheriting the familial mutation may also develop one of the other characteristic features of MEN1; however, this often differs among family members as well.

The three subtypes of MEN2 are caused by mutations in another gene known as *RET* located on chromosome 10q11.2. Every individual who inherits a *RET* mutation will develop MTC during his or her lifetime, although the age at the time of diagnosis is often different in each family member. Multiple different mutations have been identified in individuals and families who have MEN2A. Likewise, several different mutations have been identified in individuals and families with FMTC. One interesting finding has been that a few families who clearly have MEN2A and a few families who clearly have FMTC have the same mutation. The reason the families developed different clinical features is not yet known. In contrast to MEN2A and FMTC, individuals with MEN2B have been found, in more than 90% of cases, to have the same *RET* mutation. This mutation is located in a part of the gene that has never been affected in individuals and families with MEN2A and FMTC.

The difference between MEN1 and MEN4 is the germline gene mutation. MEN4 shares an overlapping phenotype with MEN and results from alterations or mutations in the *CDKN1B* gene located on chromosome 12p13.1-p12. MEN4 has been associated with hyperparathyroidism and the development of parathyroid and pituitary adenoma, reproduction organ tumors (e.g., testicular cancer, neuroendocrine cervical carcinoma), and adrenal and renal tumors.

Demographics

MEN syndromes are rare. It has been estimated that MEN1 occurs in three to 20 out of every 100,000 people. MEN syndromes affect both men and women, and they occur worldwide. The incidence of MEN2 has not been published, but it has been reported that MEN2B is far less common than MEN2A. Because very few cases of MEN4 have been reported, and many remain undiagnosed, the precise incidence and prevalence of MEN4 are uncertain. Similarly, as of 2021, the age of onset of disease in MEN4 remains unclear.

Signs and symptoms

General symptoms of the characteristic features of the MEN syndromes and their causes include the following:

- Hyperparathyroidism, which may or may not cause symptoms. Symptoms that occur are related to the high levels of calcium in the bloodstream such as kidney stones, fatigue, muscle or bone pain, indigestion, and constipation.
- Medullary thyroid carcinoma may cause diarrhea, flushing, and depression.
- Pheochromocytoma may cause a suddenly high blood pressure and headache, palpitations or pounding of the heart, a fast heartbeat, excessive sweating without exertion, and/or development of these symptoms after rising suddenly from bending over.

Diagnosis

In the past, diagnosis of the MEN syndromes depended on clinical features and laboratory test results. Since the genes responsible for these conditions were identified, genetic testing provides another means of diagnosing individuals and families with these conditions. However, all of these tumors have a higher incidence of sporadic cases. It is important to ask patients about family members when one of these types of tumor is diagnosed.

MEN1 and MEN4 are typically diagnosed from clinical features and from testing for parathyroid hormone (PTH). Elevated PTH indicates that hyperparathyroidism is present. When an individual develops a MEN1-related symptom or tumor, a complete family history should be obtained. If no family history of MEN1 or related problems such as kidney stones and peptic ulcers exists, and close family members (i.e., parents, siblings, and children) have normal serum calcium levels, then it is unlikely that the person has MEN1. However, if the individual is found to have a second symptom or tumor characteristic of MEN1, the family history is suggestive of MEN1, and/or close family members have increased serum calcium levels, then MEN1 may be the correct diagnosis.

Genetic testing for the *MEN1* gene has helped to evaluate individuals and families for MEN1. If an individual apparently affected by MEN1 is found to have a mutation in the *MEN1* gene, then this positive test result confirms the diagnosis, while identification of a mutation in the *CDKN1B* gene is a diagnostic of MEN4. However, genetic testing of the *MEN1* and *CDKN1B* genes does not identify all mutations causing MEN1; consequently, a negative test result does not rule out the diagnosis. In up to 30% of MEN1 patients diagnosed based on clinical criteria, MEN1 mutations are not identified. Identification of susceptibility genes for endocrine tumor syndromes that have at least one common feature with MEN1 has helped to extend the genetic diagnosis of MEN1 mutation-negative cases to include those additional genes in the

KEY TERMS

Bilateral—Relating to or affecting both sides of the body or both of a pair of organs.

Endocrine glands—A system of ductless glands that regulate and secrete hormones directly into the bloodstream.

Hormone—A chemical messenger produced by the body that regulates specific bodily functions such as growth, development, and reproduction.

Hyperplasia—An overgrowth of normal cells within an organ or tissue.

Magnetic resonance imaging (MRI)—A diagnostic procedure that uses a combination of high-powered magnets, radio frequencies, and computers to generate detailed images of structures within the body.

Medullary thyroid cancer (MTC)—A slowly growing tumor associated with MEN.

Multifocal—A pathological term meaning that instead of finding one tumor in the tissue, multiple tumors are found.

Neoplasm—An abnormal growth of tissue; for example, a tumor.

Parathyroid glands—A pair of glands adjacent to the thyroid gland that primarily regulates blood calcium levels.

Pheochromocytoma—A small vascular tumor of the inner region of the adrenal gland. The tumor causes uncontrolled and irregular secretion of certain hormones.

Pituitary gland—A small gland at the base of the brain that is responsible for releasing many hormones, including luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Thyroid gland—A gland located in the front of the neck that is responsible for normal body growth and metabolism. The thyroid traps a nutrient called iodine and uses it to make thyroid hormones, which allow for the breakdown of nutrients needed for growth, development, and body maintenance.

Ultrasound examination—A procedure that examines the tissue and bone structures of an individual or a developing baby.

genetic testing. Accurate identification is important, since research reported in 2021 indicates that individuals with MEN1 who are genotype positive have a different clinical course from those who are genotype negative.

MEN2A is typically diagnosed from clinical features and laboratory testing of calcitonin levels. Elevated calcitonin levels indicate that C-cell hyperplasia and/or MTC is present. When an individual develops a MEN2A-related symptom or tumor, a complete family history should be obtained. If no family history of related problems exists, and close family members (i.e., parents, siblings, and children) have normal calcitonin levels, then it is unlikely that the person has MEN2A. However, if the individual is found to have a second symptom or tumor characteristic of MEN2A, the family history is suggestive of MEN2A, and/or close family members have increased calcitonin levels, then MEN2A may be the correct diagnosis.

Genetic testing for the *RET* gene has helped with evaluating an individual and/or family for MEN2A. If an individual apparently affected by MEN2A is found to have a mutation in the *RET* gene, then this positive test result confirms the diagnosis. Genetic testing of the *RET* gene does not identify all mutations causing MEN2A and FMTC; consequently, a negative test result does not rule out the diagnosis.

Diagnosis of MEN2B can be made by physical examination and a complete medical history.

Diagnosis of FMTC can be made when the family history includes four other family members who have developed MTC with no family member who has developed a pheochromocytoma or pituitary tumor. Genetic testing of the *RET* gene may also assist with diagnosis.

Genetic testing of the *MEN1* gene and of the *RET* gene allows individuals to be diagnosed prior to the onset of symptoms; this is often called predictive genetic testing. It is important to note that individuals should not undergo predictive genetic testing prior to the identification of the familial genetic mutation. Genetic testing of a family member who is clinically affected by the condition needs to be performed first in order to identify the familial mutation. If that is not done, a negative result in an asymptomatic individual might not be a true negative test result.

Prenatal diagnosis of unborn babies is now technically possible via amniocentesis or chorionic villus sampling (CVS). However, prior to undergoing these procedures, the familial mutation needs to have been identified. One additional issue in prenatal diagnosis is how the test result will be used with regard to continuation of the pregnancy. Individuals considering prenatal diagnosis of MEN1 or MEN2 should confirm its availability prior to conception.

Genetic testing is best done in consultation with a geneticist (a doctor specializing in genetics) and/or a genetic counselor.

QUESTIONS TO ASK YOUR DOCTOR

- What are the most serious medical consequences associated with MEN?
- Are there medicines that can be taken to relieve the symptoms of MEN to reduce their severity?
- What screening recommendations are usually made for individuals with MEN syndrome?
- What is the prognosis for a child born with this disorder, and on what factors is this prognosis based?

Treatment and management

No cure or comprehensive treatment is available for the MEN syndromes. However, some of the consequences of the MEN syndromes can be symptomatically treated, and complications may be lessened or avoided by early identification.

For individuals affected by MEN1 and MEN4, hyperparathyroidism is often treated by surgery. The parathyroids may be partially or entirely removed. If they are entirely removed, the individual will need to take calcium and vitamin D supplements. Pancreatic tumors that develop may also be removed surgically, or pharmacological treatment (medication) may be given to provide relief from symptoms. The pituitary tumors that develop may not require treatment, but if they do, medication is often effective. Surgery and radiation are used in rare cases.

Children of an individual affected by MEN1 and MEN4 should begin regular medical screening in childhood. It has been suggested that beginning at five to ten years of age, children have annual measurements of serum calcium; serum prolactin; and the pancreatic, pituitary, and parathyroid hormones. Children should also undergo radiographic imaging (ultrasound, MRI examination) of the pancreas and pituitary. When the family history indicates the development of symptoms at younger-than-usual ages, the children may need to begin medical screening earlier.

For the three types of MEN2, the greatest concern is the development of medullary thyroid carcinoma. Medullary thyroid carcinoma can be detected by measuring levels of the thyroid hormone, calcitonin. Treatment of MTC is surgical removal of the thyroid and the neighboring lymph nodes, although doctors may disagree about which stage to remove the thyroid. After thyroidectomy,

the patient will receive normal levels of thyroid hormone orally or by injection. Even when surgery is performed early, metastatic spread of the cancer may have already occurred. Since this cancer is slowly growing, metastasis may not be obvious. Metastasis is very serious in MTC, because chemotherapy and radiation therapy are not effective in controlling its spread.

In the past, children who had a parent affected by one of the MEN2 syndromes were screened for MTC by annual measurement of calcitonin levels. More recently, it has been determined that MTC can be prevented by prophylactic thyroidectomy, meaning that the thyroid gland is removed before it is obviously affected by cancer. It is not uncommon for a child as young as one year of age (when the family history is of MEN2B) or six years of age (when the family history is of MEN2A or FMTC) to undergo prophylactic thyroidectomy in order to prevent the occurrence of MTC.

Pheochromocytomas that occur in MEN2A and MEN2B can be cured by surgical removal of this slowly growing tumor. Pheochromocytomas may be screened for using annual abdominal ultrasound or CT examination and laboratory testing. For individuals diagnosed with MEN2, it is also recommended that the pituitary be screened by laboratory tests.

In general, each tumor may be approached surgically. Problems occur when the tumors are multiple, when the whole gland is involved (hyperplasia as opposed to tumor), when replacement therapy is difficult (pituitary or adrenal), or when the gland makes multiple hormones. (If the gland is removed, hormone replacement therapy becomes necessary.)

Prognosis

Diagnosed early, the prognosis for the MEN conditions is reasonably good, even for MEN2B, the most dangerous of the forms. Individuals with MEN1 may have a shorter life expectancy, because the numbers and aggressiveness of their tumors may impair the effectiveness of treatment. The prognosis is better when tumors are detected before they become symptomatic. Since 1997, when the MEN1 gene was identified, genetic screening has enabled clinicians to anticipate the diagnosis of MEN1 in asymptomatic carriers more than 10 years before the appearance of signs of the disease. Some epigenetic factors, including microRNAs (miRNAs), single-stranded non-coding small RNAs that negatively regulate gene expression, have been associated with MEN1 tumor development. Research is underway to determine whether the involvement of miRNAs in MEN1 tumor development makes them useful prognostic biomarkers and targets for molecular therapies.

Medullary thyroid cancer can be cured when identified early. Ideally, the availability of genetic testing to identify family members at risk for developing the conditions will lead to earlier treatment and improved outcomes.

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Multiple epiphyseal dysplasia

Definition

Multiple epiphyseal dysplasia (MED) is a hereditary disorder characterized by abnormal epiphyses (bone extremities) that lead to early-onset joint pain and recurrent inflammation of cartilage and bone. There are five subtypes of MED, each with varying clinical manifestations and inheritance patterns.

Description

Multiple epiphyseal dysplasia (MED) is a hereditary condition characterized by abnormal development of cartilage and bone. The epiphysis is the portion at the end of a long bone where growth occurs. Dysplasia is an abnormality in development leading to alteration in size, shape, and organization of cells. Thus, in MED, the epiphyses of the long bones are dysplastic and joint pain and inflammation result. On x-ray, the epiphyses appear flattened and irregular. Cartilage in the joints becomes irregular and this leads to early-onset osteoarthritis. Patients often have short hands and stubby fingers.

MED can be divided into five subtypes, four of which are inherited in an autosomal dominant fashion (EDM1, EDM2, EDM3, and EDM5) and one of which is inherited in an autosomal recessive fashion (EDM4). All of the subtypes are characterized by early-onset joint pain, most often in the hips and knees. Most individuals with MED have adult heights that are in the low range of normal, although some may have slightly short stature.

Dominant MED

Dominant MED was initially divided into two forms: a mild form, called Ribbing disease, and a more severe form, called Fairbank disease. Dominant MED has been further classified into four subtypes to accommodate the extreme clinical variability that exists. In addition to hip and knee pain and occasional short stature, individuals with dominant MED may have a waddling gait and their limbs may be relatively short when compared to the trunk. Joint pain and deformity become worse with age in these patients and early-onset osteoarthritis is often a problem, especially in the large, weight-bearing joints.

Recessive MED

Recessive MED is also known as EDM4 and rMED. In addition to early-onset joint pain and possible short stature, this disorder is associated with scoliosis (curvature of the spine), as well as malformations of the hands, feet, and knees. Some affected individuals may also present with a clubfoot or an abnormality of the kneecap, called a double-layered patella. This finding is very suggestive of recessive MED.

Genetic profile

Dominant MED

Mutations in five different genes have been associated with dominant MED:

- EDM1 is caused by mutations in the *COMP* gene, which codes for the cartilage oligomeric matrix protein. This gene is also responsible for the more severe disorder, called pseudoachondroplasia.
- EDM2 and EDM3 result from mutations in two of the three genes that code for the protein chains of type IX collagen. *COL9A2* mutations lead to EDM2 and *COL9A3* mutations lead to EDM3. Mutations in these genes can also lead to lumbar/intervertebral disk disease (IDD), which is a very common musculoskeletal disorder.
- Defects in the matrilin 3 protein, caused by mutations in the *MATN3* gene, lead to a diagnosis of EDM5. Matrilin 3 plays a key role in the cartilage extracellular matrix.

Extreme variability in clinical manifestations can be seen both between and within families with mutations in the various genes responsible for dominant MED.

EDM1, EDM2, EDM3, and EDM5 are all dominant forms of MED and are inherited in an autosomal dominant pattern. Thus, the majority of affected individuals have a parent that is affected as well. However, this is not always the case as there may be a new (*de novo*) mutation in the affected individual that was not present in either parent. Additionally, there may appear to be a lack of family history due to the affected parent dying at a young age or the failure to recognize symptoms of the disorder in a parent. Asymptomatic parents of affected individuals should be given a careful clinical and radiographic examination to completely rule out any signs of the disorder.

Most often, one parent of the affected individual will have signs of dominant MED and/or a disease-causing mutation. In this case, siblings of the affected individual have a 50% chance of inheriting the same mutation and being affected as well. However, if a mutation is identified in the affected individual and both parents test

negative for this mutation, it is likely that the gene mutation is *de novo* and, therefore, recurrence risk to siblings is very low. The prevalence of *de novo* mutations in dominant MED is unknown.

Another possibility is germline mosaicism. In this case, the gene mutation may be present only in the egg cells of the mother or the sperm cells of the father. Thus, the parent will not show signs of the disorder, since the gene mutation is confined to the sex cells. However, the mutations present in the egg or sperm would leave a significant recurrence risk for future pregnancies.

No matter how the affected individual inherits the gene mutation, each of his or her children has a 50% chance to inherit the disease-causing mutation and, therefore, be affected with dominant MED.

Recessive MED

Recessive MED is caused by mutations in the *SLC26A2* gene, also known as *DTDST*. Mutations in this gene cause a spectrum of skeletal disorders of which recessive MED is the mildest. *SLC26A2* codes for a protein that plays a key role in the normal development of cartilage and its conversion to bone. When the *SLC26A2* gene is mutated, cartilage cannot develop properly and, as a result, bones do not form correctly and skeletal problems result.

As implied by its name, recessive MED is inherited in an autosomal recessive manner. This means that an affected individual will have two abnormal copies of the *SLC26A2* gene in each cell. Most often, the parents of an affected individual each carry a mutation on one of their two copies of the *SLC26A2* gene. Mutation carriers do not show signs or symptoms of recessive MED. Siblings of affected individuals have a 25% chance of being affected with the disorder and a 50% chance of being carriers of the disorder. Offspring of an affected individual will be obligate carriers of an *SLC26A2* gene mutation, but will not show signs or symptoms of the disorder.

Demographics

Dominant MED

Dominant MED is thought to present in at least 1 in 10,000 births. Due to the clinical variability and range of severity associated with the disorder, it is likely that many individuals have yet to be diagnosed. There are no reports of the condition being more common in specific ethnic groups or geographical regions.

Recessive MED

The prevalence of recessive MED was unknown as of 2015. There are no reports of the condition being more

common in specific ethnic groups or geographical regions. Due to the mild signs and symptoms of the disorder, it is likely that the disease is underdiagnosed and is more common than once thought.

Signs and symptoms

Dominant MED

Dominant MED often presents in early childhood with pain in the hips and/or knees. Affected patients often complain of this pain, accompanied by fatigue, after physical activity. Over time, this pain progressively worsens, joints become deformed, and early osteoarthritis results, most often in the large, weight-bearing joints. In some cases, joint replacement may be necessary.

Individuals with dominant MED may walk with a waddling gait. Restriction in the range of motion in the elbows is apparent in many cases, as is hypermobility in the knee and finger joints. Characteristic radiographic findings of dominant MED include abnormalities of the epiphyses of the long tubular bones, especially in the hips and/or knees. These abnormalities are due to delayed ossification and manifest as small and irregular ossification centers. This finding may be present very early, even before other clinical signs and symptoms are evident. Later, in adulthood, signs of osteoarthritis can be seen on x-rays and the tubular bones may be slightly shortened. The spine is generally not involved in dominant MED. Adult height may be slightly shorter than normal and the limbs are often short relative to the trunk. Intelligence is normal.

There are various clinical manifestations that distinguish the subtypes of dominant MED:

- EDM1 is characterized by mild to moderate short stature and the limbs are usually short when compared to the trunk. Individuals with EDM1 may have minor spine irregularities that can be seen on x-ray, but nothing as severe as the scoliosis associated with EDM4. The fingers and metacarpals (bones from the wrists to the fingers) are usually shortened. The main complication of this subtype is early arthritis of the hip.
- EDM2 and EDM3 are associated with mild short stature. There is more severe knee involvement in these subtypes and hip problems are often less severe. The courses of EDM2 and EDM3 are milder than EDM1 and EDM4. In EDM2, the hands are somewhat short but in EDM3, they tend to be normal with shortened metacarpals.
- EDM5 is the mildest form of MED. Affected patients usually have normal stature and less severe involvement of joints. Mild abnormalities in the pelvis seem to be more common in this subtype compared to the others.

Recessive MED

Approximately 50% of individuals affected with recessive MED show signs or symptoms of the disorder at birth. Examples include clubfoot, cleft palate, ear swelling, or clinodactyly (a condition where the little finger is curved towards the ring finger). Joint pain in the hips and knees is very common in affected individuals and most often onsets in late childhood. However, this pain may begin at various times in different individuals and is not always present. Individuals affected with recessive MED are of normal stature, although some may be slightly shorter than expected in adulthood. As in dominant MED, intelligence is normal.

Affected individuals tend to have characteristic facial features, such as anteverted nares (nasal passages) and a round, flat face. They may also be myopic (nearsighted). Malformations of the hands, feet, and knees are very common. These may include brachydactyly (abnormal shortness) of toes and fingers, small hands/feet, and absent/small fingernails. A double-layered patella (kneecap) is found in 60% of patients and is very suggestive of recessive MED. This finding seems to be age-dependent and may disappear when the affected individual reaches adulthood. Scoliosis is fairly common in affected individuals as well and this finding distinguishes recessive MED from dominant forms of MED. Occasionally, recessive MED may be associated with sensorineural deafness, hip anomalies, wrist anomalies, or delayed bone age.

Diagnosis

Dominant MED

Clinical and radiographic findings of the patient and family members can assist in the diagnosis of dominant MED. Even before the onset of clinical signs and symptoms, x-rays often show delayed ossification of the epiphyses of the long tubular bones. This delayed ossification is usually most noticeable in the hips and/or knees. Additionally, the x-rays may show slightly shortened long tubular bones. Radiographic diagnosis of MED is often difficult, if not impossible, in adults. Thus, x-rays should be completed in childhood, if possible. Due to the autosomal dominant pattern of inheritance, there are usually multiple family members affected with the disorder.

Molecular genetic testing can be used to confirm a diagnosis of dominant MED in a patient with characteristic clinical and radiographic features. Sequence analysis is available to analyze all five genes implicated in dominant MED. Mutations are found in the *COMP* gene in approximately 35% of cases, in the *MATN3* gene in

KEY TERMS

Amniocentesis—A prenatal test in which a hollow needle is inserted through the abdominal wall and into the uterus of a pregnant female in order to obtain amniotic fluid, which contains cells from the fetus. These cells can be examined to determine the sex of the fetus or to look for genetic diseases.

Chorionic villus sampling (CVS)—Biopsy of the placenta through the abdominal wall or by way of the vagina and uterine cervix to obtain fetal cells for the prenatal diagnosis of a genetic disorder.

Osteoarthritis—A disease of the cartilage in joints that causes progressive breakdown of cartilage until the bones, which were once separated by cartilage, rub against each other. This results in damage to the tissue and underlying bone, causing joint pain.

Radiographic—Involving an x-ray.

approximately 10% of cases, and in the *COL9A2* and *COL9A3* genes in less than 5% of cases. However, in about 50% of individuals with clinical and radiographic features consistent with dominant MED, no mutation can be found by molecular genetic testing. Thus, it is believed that other unidentified genes are likely responsible for this disorder. However, there are other conditions that can result from mutations in some of these genes (namely, *COMP*, *COL9A2*, and *COL9A3*). The type of disorder that results depends on the type of mutation in the gene. Thus, genetic test results must be interpreted based on clinical and radiographic findings.

Prenatal diagnosis for at-risk pregnancies is possible via molecular genetic testing, but is not commonly requested. Once a disease-causing mutation has been found in a family, fetal cells obtained by chorionic villus sampling (CVS) or amniocentesis can be analyzed for this mutation to determine the mutation status of the fetus.

Recessive MED

A diagnosis of recessive MED is based on clinical and x-ray findings during childhood or early in adult life. The disorder is suspected when an autosomal recessive pattern of inheritance is seen and when characteristic signs and symptoms are noted, such as hip and knee pain; malformations of hands, feet, and knees; and scoliosis. X-rays may show flat epiphyses with early arthritis, mild brachydactyly, and the characteristic double-layered patella.

The diagnosis of recessive MED can be confirmed via molecular genetic testing of the *SLC26A2* gene. A mutation is found in approximately 70% of patients who are suspected to have the disorder based on clinical and radiographic features. Interestingly, mutations were found in 100% of patients with double-layered patella, which is a very specific sign for recessive MED. There are three common mutations in the *SLC26A2* gene that account for approximately 90% of genetically characterized cases of recessive MED. Thus, molecular genetic testing often begins with analysis for these three mutations. It can be followed by full gene sequence analysis if necessary. There are three other autosomal recessive skeletal dysplasias that can result from mutations in the *SLC26A2* gene. The type of disorder that results depends on the severity of the genetic mutations in the gene. Thus, genetic test results must be interpreted based on clinical and radiographic findings.

Carrier testing for at-risk family members who do not show any clinical signs of the disorder is available once the *SLC26A2* gene mutations have been identified in an affected individual. Carrier detection in reproductive partners of *SLC26A2* gene carriers is available as well. If a mutation is found in a reproductive partner, details about the severity of that mutation should be provided due to the fact that various *SLC26A2* mutations can lead to various genetic conditions.

Prenatal diagnosis for at-risk pregnancies is possible in the same manner as dominant MED.

Treatment and management

Dominant MED

The goal for patients with dominant MED is to decrease pain, restrict joint destruction, and prevent the development of osteoarthritis. Pain is often difficult to control in affected individuals. However, analgesics (that is, nonsteroidal anti-inflammatory drugs) and physiotherapy have been shown to be effective in some cases. An orthopedic surgeon can advise patients on whether surgical procedures (that is, realignment osteotomy or acetabular osteotomy) might slow the progression of symptoms. In some patients, joint replacement may be necessary. Affected patients should avoid obesity and activities that strain affected joints.

Recessive MED

Individuals with recessive MED should be seen by an orthopedist who can assess the possibility of treatment. This may include physiotherapy for the purpose of strengthening muscles, use of analgesics (i.e., nonsteroidal anti-inflammatory drugs), and the timing of surgery, if

necessary. As in dominant MED, affected patients should avoid obesity and activities that strain affected joints.

Prognosis

Patients with dominant and recessive MED have a normal life expectancy and generally lead productive and healthy adult lives.

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- International Skeletal Dysplasia Registry—UCLA-OHRC, 615 Charles E. Young Dr. South, Room 410, Los Angeles, CA 90095, (310) 825-8998, AZargaryan@mednet.ucla.edu, <http://ortho.ucla.edu/body.cfm?id=279>
- Little People of America, National Headquarters, 250 EL Camino Real, Suite 211, Tustin, CA 92780, (888) LPA-2001, info@lpaonline.org, <http://www.lpaonline.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, info@lpaonline.org, <http://www.rarediseases.org>

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Multiple lentigines syndrome

Definition

Multiple lentigines syndrome is a rare genetic condition that causes the affected individual to have many dark

brown or black freckle-like spots on the skin, as well as other symptoms.

Description

Multiple lentigines syndrome is a genetic disorder that results in characteristic marking of the skin, abnormalities in the structure and function of the heart, hearing loss, wide-set eyes, and other symptoms. Other terms for multiple lentigines syndrome include cardiomyopathic lentiginosis and LEOPARD syndrome. LEOPARD syndrome is an acronym for the seven most commonly observed symptoms of the disorder:

- (L)entigines, or small dark brown and black spots on the skin
- (E)lectrocardiographic conduction defects, or abnormalities of the muscle activity in the heart
- (O)cular hypertelorism, or eyes that are spaced farther apart than normal
- (P)ulmonary stenosis, or narrowing of the lower right ventricle of the heart
- (A)bnormalities of the genitals, such as undescended testicles or missing ovaries
- (R)etarded growth leading to shortness of stature
- (D)eafness or hearing loss

The lentigines observed in multiple lentigines syndrome are similar in size and appearance to freckles, but unlike freckles they are not affected by sun exposure. The disorder was first described in 1936 with a limited number of syndromes including lentigines, ocular hypertelorism, and abnormal development of the breast and jaw bones. In the 1960s the disorder was further characterized to include the additional symptoms that are known today.

Genetic profile

Multiple lentigines syndrome is inherited as an autosomal dominant trait. Autosomal means that the syndrome is not carried on a sex chromosome, while dominant means that only one parent has to pass on the gene mutation in order for the child to be affected with the syndrome.

LEOPARD syndrome is part of a family of syndromes caused by mutations in the Ras/MAPK pathway; multiple lentigines syndrome is caused by mutations in the genes for on-receptor type 11 (*PTPN11*), which encodes for a protein tyrosine phosphatase that removes phosphates from tyrosine molecules; Raf-1 proto-oncogene, serine/threonine kinase (*RAF1*); and B-Raf proto-oncogene, serine/threonine kinase (*BRAF*). All of these genes encode kinase proteins that are important for signal pathways required for the formation and

KEY TERMS

Lentigo (plural, lentigines)—A dark colored spot on the skin.

Scoliosis—Abnormal curvature of the spine, usually defined as greater than ten degrees to the right or left as the doctor faces the patient.

Stenosis—The constricting or narrowing of an opening or passageway.

development of several types of tissues. These pathways include regulation of cell division, cell migration, and cell differentiation. In cases of multiple lentigines syndrome, approximately 90% are due to mutations in *PRPN11*, and the other 10% are caused by mutations in the *RAF1* and *BRAF* genes.

Demographics

Multiple lentigines syndrome is extremely rare, and due to the small number of reported cases, demographic trends for the disease have not been established. There does not seem to be any clear ethnic pattern to the disease. Both males and females appear to be affected with the same probability.

Signs and symptoms

The most characteristic symptom of the disease is the presence of many dark brown or black spots, ranging in size from barely visible to 2.5 in. (5 cm) in diameter all over the face, neck, and chest. They may also be present on the arms and legs, genitalia, palms of the hands, and soles of the feet. The spots appear in infancy or early childhood and become more numerous until the age of puberty. There may also be lighter brown birthmarks on the skin.

Heart defects, such as the pulmonary stenosis and electrocardiographic conduction abnormalities, are another hallmark of multiple lentigines syndrome. Other narrowing (stenosis) in different areas of the heart may be present, as well as abnormalities in the atrial septum, or the wall between the upper left and right chambers of the heart. There is an increased risk of heart disease and tumors of the heart in people with multiple lentigines syndrome.

Other features can include widely spaced eyes, low-set or prominent ears, drooping eyelids, a short neck, or a projecting jaw. In some cases of multiple lentigines syndrome, additional skeletal malformations have been reported, including a sunken breastbone, rib anomalies,

QUESTIONS TO ASK YOUR DOCTOR

- Why is multiple lentigines syndrome also called LEOPARD syndrome?
- At what stage in fetal or child development can multiple lentigines syndrome be diagnosed?
- What tests or other procedures are used to diagnose this condition?
- Can multiple lentigines syndrome be cured and, if not, what kinds of treatment are available?

curvature of the spine (scoliosis), and webbing of the fingers.

Deafness or hearing loss is observed in about 25% of the cases of multiple lentigines syndrome. Some people affected with the syndrome also exhibit mild developmental delays. Other reported neurological findings include seizures, eye tics, and abnormal electrical activity in the brain.

People with multiple lentigines syndrome often exhibit genital abnormalities such as undescended testicles or a small penis in men, or missing or underdeveloped ovaries in women. The onset of puberty may be delayed or even absent. Affected individuals are usually under the 25th percentile in height, although their body weight is in the normal range.

Diagnosis

Diagnosis is usually made based on the observation of multiple lentigines and the presence of two or more of the other symptoms that form the LEOPARD acronym. Because there are so few documented cases of the multiple lentigines, it is often hard to determine if other diseases are actually part of the syndrome. A family history can be helpful in the diagnosis since the syndrome has dominant inheritance. As some genetic contributors of the syndrome are known, in some cases DNA testing can be used to confirm multiple lentigines in some patients. However, there is no readily available medical test that can definitively confirm the diagnosis of multiple lentigines syndrome.

Treatment and management

Treatment is directed toward the specific conditions of the individual. For example, heart conditions can be managed with the use of a pacemaker and appropriate medications, as well as regular medical monitoring. Hearing loss may be improved with the use of hearing aids.

Genetic counseling is recommended when there is a family history of freckle-like spotting of the skin and heart defects, as these suggest the possibility of inherited multiple lentigines syndrome.

Prognosis

The prognosis for people with multiple lentigines syndrome is good provided that the appropriate care for any associated medical conditions is available. Due to the multiple symptoms, it is suggested that a cardiologist, endocrinologist, dermatologist, and other appropriate specialists routinely see patients as symptoms present. Treatment generally focuses on palliative care of symptoms associated with the syndrome.

As the syndrome is passed on to offspring in a dominant inheritance pattern, those with the multiple lentigines who are reproductively healthy should seek genetic counseling to better understand the chances of passing it along to their children. In most cases of autosomal dominant diseases there is a 50% chance that children of affected individuals will inherit the disease.

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National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Multiple sclerosis

Definition

Multiple sclerosis (MS) is a chronic, degenerative disorder affecting the central nervous system (CNS), which is made up of the brain, spinal cord, and optic nerves. A fatty tissue called myelin coats and protects the nerve fibers in the CNS. Myelin may be damaged or destroyed in the CNS, either by inflammation, stroke, immune disorders, metabolic disorders or nutritional deficiencies. When this occurs, scar tissue or sclerosis may form in multiple areas of the nerve fibers. As a result, the ability of the nerves to conduct electrical impulses from the brain to the rest of the body is impaired, and a wide variety of symptoms may appear.

Description

The exact cause of multiple sclerosis is not known, but researchers believe that it is caused by an inflammatory response directed at the cells of the nervous system. The reasons for this abnormal autoimmune response are uncertain, but most scientists agree that several triggers are involved, including genetics, gender, and the environment (e.g., viruses, trauma, and heavy metals).

Evidence suggests that genes associated with MS are not abnormal, but include some variations that may or may not occur in the general population. In certain combinations, however, these normal genes appear to predispose some people to develop MS after exposure to unidentified environmental factors. People with close relatives who have MS are more susceptible to

developing the disease, but there is no evidence to suggest that MS is inherited directly.

The course of the disease is unpredictable. Although MS affects each person differently, the disease generally occurs in one of four patterns, which are sometimes referred to as chronic progressive MS. The four forms of MS are relapsing-remitting, primary-progressive, secondary-progressive, and progressive-relapsing. Each of these forms may also be mild, moderate, or severe.

At initial diagnosis, the most common form of MS is relapsing-remitting, occurring in approximately 85% of those with the disease. Individuals with this form of MS experience clearly defined flare-ups (also called relapses, attacks, or exacerbations). There are episodes of acute worsening neurologic function, followed by partial or complete periods of recovery (remission) that are free of disease progression.

The primary-progressive form of MS is relatively rare, occurring in approximately 10% of patients. People with this type of MS experience a slow but nearly continuous worsening of their disease from the time of disease onset, and have no clear relapses or remissions. There are, however, variations in rates of progression over time, occasional plateaus, and temporary minor improvements.

About 50% of people with relapsing-remitting MS develop secondary-progressive MS within ten years of their initial diagnosis and before the introduction of disease-modifying drugs. Long-term data are not yet available to demonstrate if this form of MS is significantly delayed by treatment. People with secondary-progressive MS experience an initial period of relapsing-remitting disease followed by a steady progression of

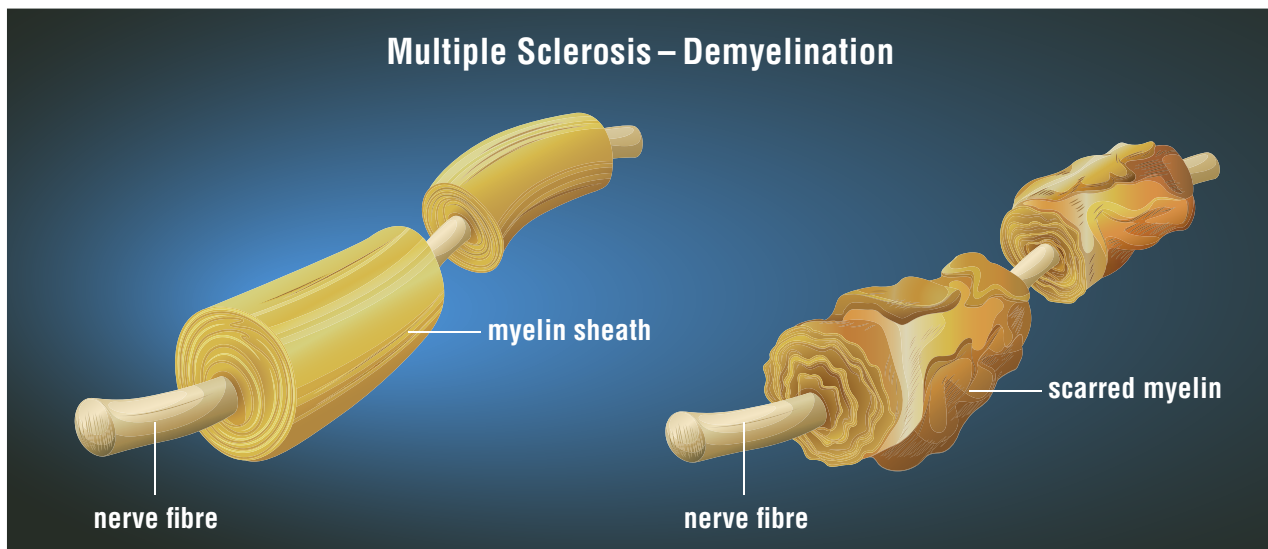


Illustration showing a normal nerve fiber (left) and one affected by multiple sclerosis. (BlueRingMedia/Shutterstock)

disease course that may or may not be accompanied by occasional flare-ups, minor remissions, or plateaus.

The progressive-relapsing form of MS is relatively rare, occurring in approximately 5% of patients. People with this form of MS experience a consistent progression of disease from the onset but also have clear acute relapses, with or without recovery. As opposed to relapsing-remitting MS, the disease continues to progress between periods of relapse.

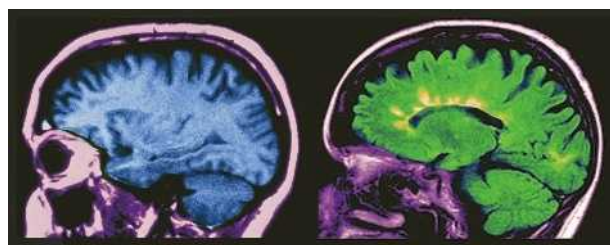
Genetic profile

Results from studies indicate that genes not only influence who is at risk for MS but also affect the clinical features of the disease, such as age of symptom onset, severity, progression, and response to drugs. In addition, there is some evidence to suggest that the different forms of MS have different underlying genetic causes. In addition to genes, other components such as exposure to viruses or environmental factors play a part in causing MS. For this reason, researchers believe that MS is not inherited directly even though genetic factors determine who is susceptible to the unknown outside trigger.

Epidemiologic studies have determined that the risk of developing MS increases several-fold if a close family member, including a first-, second-, or third-degree relative, has the disease. Studies in twins have demonstrated that a monozygotic, or identical twin, with a sibling with MS has a higher risk (estimated at 25%–30%) of developing the disease than a dizygotic, or fraternal twin (estimated at 2%–5%). Thus, a significant genetic component is involved in transmitting the susceptibility to the disease in families even if the disease is not directly inherited.

Genetically, MS is a complex disease that is not strictly dominant, recessive, or sex-linked. Discovering the genes involved in MS requires careful scanning of the entire genome (the entire genetic composition of an organism) of patients and their relatives to identify small chromosomal regions linked to the disease. Once they are discovered these genomic segments are examined in detail to determine the specific locus (location in the genome) and characteristics of the MS-associated genes.

Studies have identified approximately 60 genomic regions that may be involved in MS with 13 common regions harboring disease susceptibility, supporting the view that multiple genes are involved in this disorder. Seven of those have been confirmed with results from teams in Canada, Finland, and England that generated the first MS genetic map. These studies have sparked a global effort to search for the cause of MS susceptibility and a second-generation genome screen is near completion. Further work is needed to identify the complete list



MRI of a normal brain (left) and one with multiple sclerosis (right). The affected brain shows hyperintense lesions (yellow areas) in the periventricular white matter. (Jessica Wilson/Science Source)

of MS loci (locations) and to map the complete set of MS-associated genes.

Thus far, the HLA-DR2 haplotype (a set of closely linked alleles, or alternative forms of genes) within the major histocompatibility complex (MHC) on the short arm of chromosome 6 has the strongest genetic effect identified in MS. This haplotype has consistently demonstrated both linkage and association in family and case-control studies.

Chromosome 19q13 has been under evaluation since 1993, when the first description of positive linkage was established. Genomic screens have shown some evidence for linkage to this region, which has been identified as the second most significant region after MHC. The effect of this locus is rather modest and is estimated to account for only 4%–6% of the overall genetic component in MS. Because MS is a complex disease the data are not entirely consistent and not all studies have shown evidence of linkage.

Demographics

Multiple sclerosis is one of the most common diseases affecting the CNS. It is estimated that about 300,000 people in North America and more than 2.5 million people worldwide are affected. Peak onset occurs between the ages of 20 and 30. Almost 70% of individuals experience symptoms between the ages of 21 and 40. Although MS rarely occurs in those younger than 10 or older than 60, some cases have been reported. In addition, the disease is two to three times more common in women than men.

Although the reasons for the differences in susceptibility are not known, Caucasians are more than twice as likely as other races to develop MS. The disease is five times more common in temperate climates, such as the northern United States, Canada, and Europe, than in tropical climates. Native Americans in North America, however, rarely develop the disease. Multiple sclerosis is uncommon in Japan, China, and South America, and is

KEY TERMS

Antibodies—Proteins that are manufactured by the immune system and attack foreign substances known as antigens.

Cerebrospinal fluid (CSF)—Colorless liquid circulating through the brain and spinal cord.

Evoked response tests—Tests that measure the speed of brain connections.

Magnetic resonance imaging (MRI)—A procedure that produces images of various portions of the body using high frequency radio waves within a strong magnetic field.

Myelin—A substance rich in protein and fatty substances that forms layers around nerve fibers and acts as insulation to help transmit electrochemical messages between the brain and the rest of the body.

Poser criteria—Criteria proposed in 1983 as an update to the Schumacher criteria for diagnosing MS; developed to aid neurologists in determining the existence of lesions and other para-clinical evidence of MS.

nearly unknown among the indigenous people of equatorial Africa and the native Inuit of Alaska.

Signs and symptoms

Multiple sclerosis symptoms often progress gradually and vary in intensity and predictability because different areas of myelin are attacked in each person. Each attack produces different symptoms and new areas of the nervous system are affected. There is usually an increasing progression of symptoms, with episodes lasting days, weeks, or months, alternating with disease-free periods of remission. The disease may progress, however, without any periods of remission.

Early symptoms of MS may include the following:

- numbness and/or paresthesias (tingling) in the arms or legs
- mono- or paraparesis (partial paralysis affecting one or both of the lower limbs)
- double or blurred vision
- optic neuritis (nerve inflammation)
- ataxia (lack of muscle coordination)
- bowel- or bladder-control problems

Later symptoms of MS may include the following:

- more prominent upper motor neuron signs, such as increased spasticity (stiff or awkward movements), and increasing para- or quadriparesis
- vertigo (sensation of self or objects moving or spinning)
- lack of coordination (loss of balance) and other cerebellar problems
- depression
- emotional instability
- difficulty walking or gait abnormalities
- dysarthria (impaired speech)
- fatigue
- pain

Diagnosis

Because there is no definitive test that can identify or rule out MS, and the symptoms of MS mimic a number of other diseases, a combination of tests or procedures is required to diagnose the disease. Moreover, for some people (about 10%–15%) a definitive diagnosis is not possible even after thorough testing. In most cases with time and follow-up clinical examinations in which the condition is monitored closely, diagnosis is possible.

Diagnostic evaluation begins with a complete medical history, which assesses overall health status including an evaluation of symptoms and time of onset. Physical examination includes an evaluation of nervous system functioning by testing of reflexes, balance, coordination, and vision, as well as checking for areas of numbness or weakness.

Diagnostic testing may include:

- Magnetic resonance imaging (MRI): This provides a detailed view of the brain.
- Evoked potential tests: These measure how quickly and accurately the nervous system responds to certain stimulation; the most common of these tests include the visual evoked response test, the brainstem auditory evoked response test, and the sensory evoked response test.
- Lumbar puncture: A sample of cerebrospinal fluid (CSF) is taken from the lumbar area of the spine.
- Electrophoresis: The CSF is analyzed in a laboratory procedure used to evaluate protein levels in the CSF.

The following standard criteria, called the Poser criteria, are often used in diagnosing MS:

- Clinically definite MS is diagnosed with two attacks and clinical evidence of two separate lesions; two attacks, clinical evidence of one lesion, and para-clinical (beyond clinical) evidence of another lesion.

- Laboratory-supported definite MS is diagnosed with two attacks, either clinical or para-clinical evidence of one lesion, and CSF immunologic abnormalities; one attack, clinical evidence of two separate lesions, and CSF abnormalities; one attack, clinical evidence of one lesion and para-clinical evidence of another separate lesion, and CSF abnormalities.
- Clinically probable MS is diagnosed with two attacks and clinical evidence of one lesion; one attack and clinical evidence of two separate lesions; one attack, clinical evidence of one lesion, and para-clinical evidence of another separate lesion.
- Laboratory-supported probable MS is diagnosed with two attacks and CSF abnormalities.

Treatment and management

There is no cure for MS. Nevertheless, there are numerous drug and nondrug therapies available to manage and treat the symptoms of the disease. It is standard practice to wait until a person has experienced two or more MS attacks before initiating drug treatment. Studies indicate that initiating treatment in the early stages of the disease may lessen damage to the CNS and potentially slow disease progression. The type of treatment a patient receives is based on a wide variety of factors, including the course and severity of disease.

The U.S. Food and Drug Administration (FDA) have approved six disease-modifying drugs for use in people with MS. The drugs approved for relapsing-remitting MS include interferon beta-1a (Avonex, Rebif), interferon beta-1b (Betaseron), and glatiramer acetate (Copaxone).

These drugs, which are injected either under the skin or into the muscle, reduce the number and severity of attacks and some may slow the onset of disability. Interferons are naturally occurring proteins that fight invading viruses and although the mechanism of action of these drugs is not fully understood in MS, the drugs appear to protect the CNS from the body's attack of its own immune system. Glatiramer acetate is a synthetic compound made from substances found in myelin, and is thought to help alter the body's immune system.

The most commonly used MS drugs that have potentially serious adverse side effects include:

- Natalizumab (Tysabri, formerly known as Antegren), which was voluntarily suspended from marketing by the FDA as of February 28, 2005. This drug was approved for the treatment of relapsing forms of MS and was administered by infusion every four weeks. It is a monoclonal antibody that prevents certain white blood cells from moving into the CNS, thus decreasing inflammation and potentially allowing the body to repair

QUESTIONS TO ASK YOUR DOCTOR

- Please describe the bodily changes that take place as a result of MS.
- Why is MS considered to be a genetic disorder?
- If I have relatives with MS, is there a risk of my developing the disease?
- How is MS likely to affect my quality of life?

the damaged myelin. Although generally well tolerated, the drug was implicated in three cases of progressive multifocal leukoencephalopathy, a usually fatal brain wasting disease, among patients in long-term clinical trials. In March 2006 the FDA reevaluated Tysabri, and on June 5, 2006 the FDA approved the marketing of Tysabri under a special restricted distribution program; patients must talk to their doctor, understand the risks and benefits of Tysabri, and agree to all of the instructions in the TOUCH Prescribing Program.

- Mitoxantrone (Novantrone) is approved in the treatment of secondary-progressive, progressive-relapsing, and worsening relapsing-remitting MS. The drug has been shown to decrease relapses and slow the progression of disability. Mitoxantrone is administered intravenously and is thought to work by suppressing the immune system. Mitoxantrone has many potentially serious side effects, some of which are heart-related.
- Steroids were the gold standard of treatment for patients with MS until the discovery of the disease-modifying drugs. Although steroids are still prescribed and administered intravenously, primarily to reduce inflammation and manage acute attacks, they produce serious adverse side effects and most often are used for short periods of time. The most commonly prescribed steroids include dexamethasone (Decadron), methylprednisone (Solu-Medrol), and prednisone (Deltasone).
- Copolymer 1 is being investigated in clinical trials and may decrease disease activity. Other drugs are also used to treat the symptoms of the disease, such as fatigue, bladder control problems, and pain.

A nondrug treatment option is plasmapheresis (plasma separation or plasma exchange). This is a procedure in which the patient's blood is drawn and the plasma (liquid portion) is replaced with other fluids; an anticoagulating agent (anticoagulant) is given intravenously during the procedure. Plasma contains antibodies, and thus, this type of therapy removes antibodies that may attack myelin. The plasma-free blood is then returned to the patient.

by transfusion. This procedure, which is used to treat other autoimmune diseases, such as myasthenia gravis, Lambert-Eaton syndrome, and Guillain-Barré syndrome, has had mixed results in patients with primary- and secondary-progressive forms of MS.

Complementary and alternative therapies include vitamin D and antioxidant vitamin supplementation, as well as diets low in saturated fat and high in omega-3 fatty acids. The efficacy of these treatments has not been determined.

New treatment options include immunotherapy, in which drugs and other procedures are used to suppress the immune system; and manipulating the immune system by destroying or damaging cells that attack myelin.

Prognosis

Although the average lifespan of those diagnosed with MS is difficult to estimate because the disease pattern and severity vary among individuals, the estimate often given is 25–35 years after diagnosis.

For all MS patients, the chance of walking without assistance in 15 years following disease onset is 50%. About half of all patients require assistance in walking or will be wheelchair bound, while the other 50% of patients will be able to walk without assistance.

Some of the most common causes of death among patients with MS are related to secondary complications associated with immobility, urinary tract infections, swallowing, or breathing. Although the rate of suicide among those with MS is approximately 7.5 times higher than in the general population, the suicide rate does not correlate with disability.

Factors that tend to influence a favorable prognosis include the following:

- being female
- low relapse rate
- complete recovery from first attack
- symptoms primarily sensory in nature
- younger age of onset
- low disability at two to five years from disease onset
- later cerebellar involvement
- involvement of only one CNS component at the time of onset

Resources

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ORGANIZATIONS

Multiple Sclerosis Association of America, 706 Haddonfield Road, Cherry Hill, NJ 08002, (800) 532-7667, <http://www.msaa.org>

Multiple Sclerosis Foundation, 6350 North Andrews Ave., Ft. Lauderdale, FL 33309-2130, (954) 776-6805 or (888) 673-6287, <http://www.msfocus.org>

Multiple Sclerosis International Federation, Skyline House, 200 Union Street, London SE1 0LX, UK +44 (0) 20 7620 1911, <http://www.msif.org>

National Multiple Sclerosis Society, 733 Third Avenue 6th Floor, New York, NY 10017-3288, (800) 344-4867, <http://www.nationalmssociety.org>

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Muscular dystrophy

Definition

Muscular dystrophy is the name for a group of inherited disorders in which strength and muscle bulk gradually decline. Nine types of muscular dystrophies are generally recognized.

Description

The muscular dystrophies include the following:

- Duchenne muscular dystrophy (DMD): DMD affects young boys, causing progressive muscle weakness,

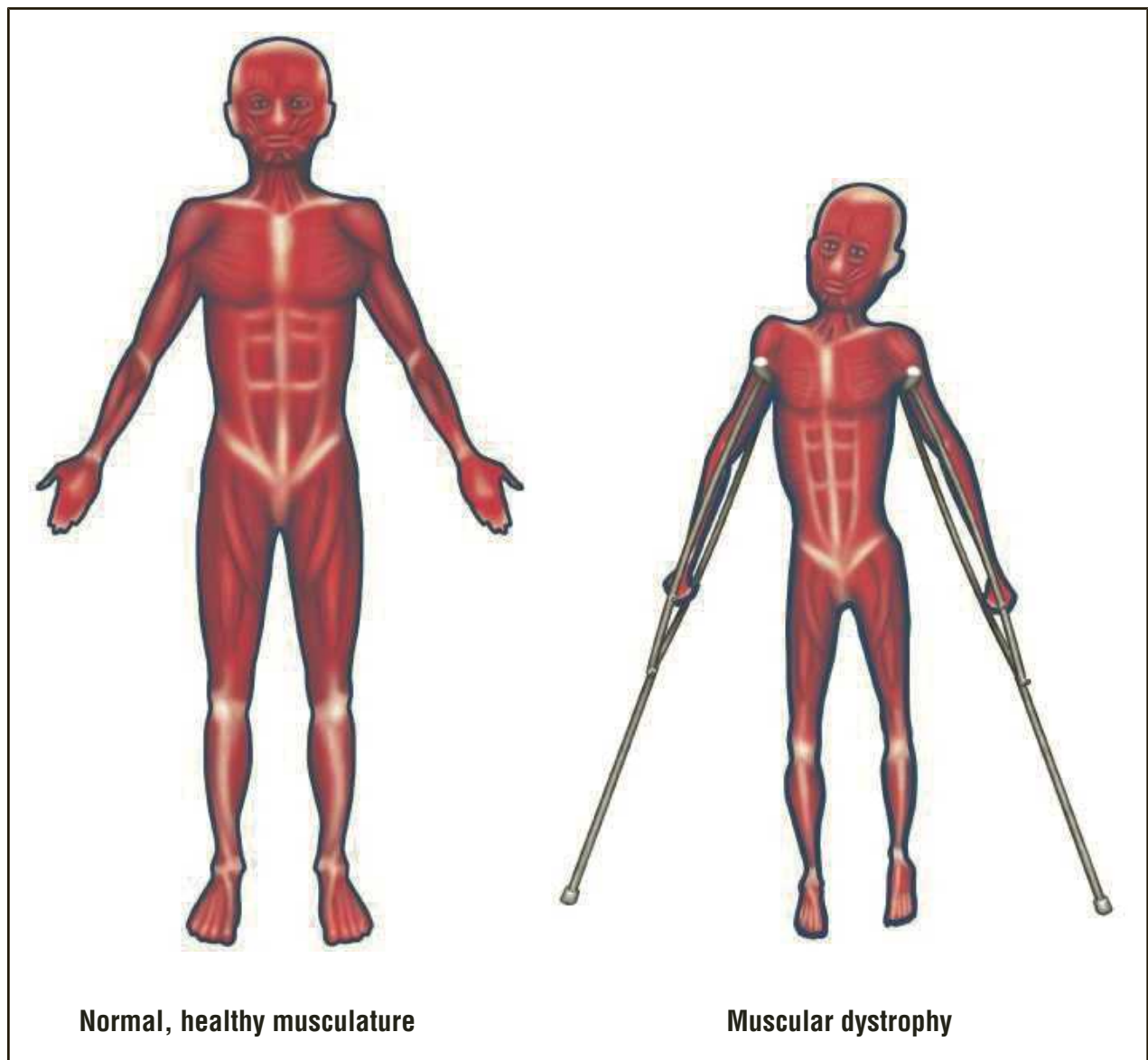


Illustration showing the musculature of two humans. The one on the left is normal, while the other has muscular dystrophy. (Gale)

usually beginning in the legs. It is a severe form of muscular dystrophy. DMD occurs in about 1 in 3,500 male births, and affects approximately 8,000 boys and young men in the United States. A milder form occurs in a very small number of female carriers.

- Becker muscular dystrophy (BMD): BMD affects older boys and young men, following a milder course than DMD. It occurs in about 1 in 30,000 male births.
- Emery-Dreifuss muscular dystrophy (EDMD): EDMD affects both males and females because it can be inherited as an autosomal dominant or recessive disorder. Symptoms include contractures and weakness in the calves, weakness in the shoulders and upper arms,

and problems in the way electrical impulses travel through the heart to make it beat (heart conduction defects). Fewer than 300 cases of EDMD have been reported in the medical literature.

- Limb-girdle muscular dystrophy (LGMD): LGMD begins in late childhood to early adulthood and affects both men and women, causing weakness in the muscles around the hips and shoulders, and weakness in the limbs. It is the most variable of the muscular dystrophies, and there are several different forms of the condition now recognized. Many people with suspected LGMD have probably been misdiagnosed in the past, and therefore, the prevalence of the condition is difficult to

estimate. The highest prevalence of LGMD is in a small mountainous Basque province in northern Spain, where the condition affects 69 persons per million.

- **Facioscapulohumeral muscular dystrophy (FSH):** FSH, also known as Landouzy-Dejerine condition, begins in late childhood to early adulthood and affects both men and women, causing weakness in the muscles of the face, shoulders, and upper arms. The hips and legs may also be affected. FSH occurs in about 1 out of every 20,000 people, and affects approximately 13,000 people in the United States.
- **Myotonic dystrophy:** Also known as Steinert's disease, it affects both men and women, causing generalized weakness first seen in the face, feet, and hands. It is accompanied by the inability to relax the affected muscles (myotonia). Symptoms may begin from birth through adulthood. It is the most common form of muscular dystrophy, affecting more than 30,000 people in the United States.
- **Oculopharyngeal muscular dystrophy (OPMD):** OPMD affects adults of both sexes, causing weakness in the eye muscles and throat. It is most common among French-Canadian families in Quebec, and in Spanish-American families in the Southwestern United States.
- **Distal muscular dystrophy (DD):** DD is a group of rare muscle diseases that have weakness and wasting of the distal (farthest from the center) muscles of the forearms, hands, lower legs, and feet in common. In general, the DDs are less severe, progress more slowly, and involve fewer muscles than the other dystrophies. DD usually begins in middle age or later, causing weakness in the muscles of the feet and hands. It is most common in Sweden, and rare in other parts of the world.
- **Congenital muscular dystrophy (CMD):** CMD is a rare group of muscular dystrophies that have in common the presence of muscle weakness at birth (congenital) and abnormal muscle biopsies. CMD results in generalized weakness, and usually progresses slowly. A subtype, called Fukuyama CMD, also involves intellectual disability and is more common in Japan.

Genetic profile

The muscular dystrophies are caused by alterations in genes in an autosomal recessive pattern of inheritance. Some forms of LGMD and DD exhibit this pattern of inheritance, as does CMD. A person with only one altered copy, called a carrier, will not have the condition, but may pass the altered gene on to his children. When two carriers have children, the chances of having a child with the condition are one in four for each pregnancy.

Other conditions occur when only one altered gene copy is present. Such conditions are called autosomal

dominant conditions. DM, FSH, and OPMD exhibit this pattern of inheritance, as do some forms of DD and LGMD. When a person affected by the condition has a child with someone not affected, the chances of having an affected child are one in two.

Because of chromosomal differences between the sexes, some genes are not present in two copies. The chromosomes that determine whether a person is male or female are called the X and Y chromosomes. A person with two X chromosomes is female, while a person with one X and one Y is male. While the X chromosome carries many genes, the Y chromosome carries almost none. Therefore, a male has only one copy of each gene on the X chromosome, and if it is altered, he will have the condition that alteration causes. Such conditions are said to be X-linked. X-linked conditions include DMD, BMD, and EDMD. Women are not usually affected by X-linked conditions, since they will likely have one unaltered copy between the two chromosomes. Some female carriers of DMD have a mild form of the condition, probably because their one unaltered gene copy is shut down in some of their cells.

Female carriers of X-linked conditions have a one in two chance of passing the altered gene on to each child born. Daughters who inherit the altered gene will be carriers. A son born without the altered gene will be free of the condition and cannot pass it on to his children. A son born with the altered gene will have the condition. He will pass the altered gene on to each of his daughters, who will then be carriers, but to none of his sons (because they inherit his Y chromosome).

Not all genetic alterations are inherited. As many as one third of the cases of DMD are due to *de novo* mutations during egg formation. New mutations are less common in other forms of muscular dystrophy.

Several of the muscular dystrophies, including DMD, BMD, CMD, and most forms of LGMD, are due to alterations in the genes for a complex of muscle proteins. This complex spans the muscle cell membrane (a thin sheath that surrounds each muscle cell) to unite a fibrous network on the interior of the cell with a fibrous network on the outside. Theory holds that by linking these two networks, the complex acts as a shock absorber, redistributing and evening out the forces generated by contraction of the muscle, thereby preventing rupture of the muscle membrane. Alterations in the proteins of the complex lead to deterioration of the muscle during normal contraction and relaxation cycles. Symptoms of these conditions set in as the muscle gradually exhausts its ability to repair itself.

Both DMD and BMD are caused by alterations in the gene for the protein called dystrophin. The alteration

leading to DMD prevents the formation of any dystrophin, while that of BMD allows some protein to be made, accounting for the differences in severity and age of onset between the two conditions. Differences among the other muscular dystrophies in terms of the muscles involved and the ages of onset are less easily explained.

A number of genes have been found to cause LGMD. A majority of the more severe autosomal recessive types of LGMD with childhood-onset are caused by alterations in the genes responsible for making proteins called sarcoglycans. The sarcoglycans are a complex of proteins that are normally located in the muscle cell membrane along with dystrophin. Loss of these proteins causes the muscle cell membrane to lose some of its shock-absorber qualities. The genes responsible include *LGMD2D* on chromosome 17, which codes for the alpha-sarcoglycan protein; *LGMD2E* on chromosome 4, which codes for the beta-sarcoglycan protein; *LGMD2C* on chromosome 13, which codes for the gamma-sarcoglycan protein; and *LGMD2F* on chromosome 5, which codes for the delta-sarcoglycan protein. Some cases of autosomal recessive LGMD are caused by an alteration in a gene, *LGMD2A*, on chromosome 15, which codes for a muscle enzyme, calpain 3. The relationship between this alteration and the symptoms of the condition is unclear. Alterations in a gene called *LGMD2B* on chromosome 2 that codes for the dysferlin protein are also responsible for a minority of autosomal recessive LGMD cases. The exact role of dysferlin is not known. Finally, alterations in the *LGMD2G* gene on chromosome 17 that codes for a protein, telethonin, are responsible for autosomal recessive LGMD in two reported families. The exact role of telethonin is not known. Some families with autosomal recessive LGMD are not accounted for by alterations in any of the mentioned genes, indicating that there are as yet undiscovered genes that can cause LGMD. The autosomal dominant LGMD genes have mostly been described in single families. These types of LGMD are considered quite rare.

The genes causing these types of LGMD, their chromosomal location, and the proteins they code for (when known) are listed:

- *LGMD1A* (chromosome 5): myotilin
- *LGMD1B* (chromosome 1): laminin
- *LGMD1C* (chromosome 3): caveolin
- *LGMD1D* (chromosome 6)
- *LGMD1E* (chromosome 7)
- *COL6A1* (chromosome 21): collagen VI alpha 1
- *COL6A2* (chromosome 21): collagen VI alpha 2
- *COL6A3* (chromosome 2): collagen VI alpha 3

The causes of the other muscular dystrophies are not as well understood:

- EDMD is due to an alteration in the gene for a protein called emerin, which is found in the membrane of the nucleus, but whose exact function is unknown.
- Myotonic dystrophy is caused by alterations in a gene on chromosome 19 for an enzyme called myotonin protein kinase that may control the flow of charged particles within muscle cells. This gene alteration is called a triple repeat, meaning it contains extra triplets of DNA code. It is possible that this alteration affects nearby genes as well, and that the widespread symptoms of myotonic dystrophy are due to a range of genetic disruptions.
- The gene for OPMD appears to also be altered with a triple repeat. The function of the affected protein may involve translation of genetic messages in the nucleus.
- The gene(s) for FSH is located on the long arm of chromosome 4 at gene location 4q35. Nearly all cases of FSH are associated with a deletion (missing piece) of genetic material in this region. Researchers are investigating the molecular connection of this deletion and FSH. It is not yet certain whether the deleted material contains an active gene or changes the regulation or activity of a nearby FSH gene. A small number of FSH cases are not linked to chromosome 4. Their linkage to any other chromosome or genetic feature is under investigation.
- The gene(s) responsible for DD have not yet been found.
- About 50% of individuals with CMD have their condition as a result of deficiency in a protein called merosin, which is made by a gene called laminin. The merosin protein usually lies outside muscle cells and links them to the surrounding tissue. When merosin is not produced, the muscle fibers degenerate soon after birth. A second gene called integrin is responsible for CMD in a few individuals but alterations in this gene are a rare cause of CMD. The gene responsible for Fukuyama CMD is *FCMD* and it is responsible for making a protein called fukutin whose function is not clear.

Demographics

Muscular dystrophy in all its varying forms occurs worldwide, affecting all races and ages. The disease incidence varies, as some forms are more common than others. The most common form in children, Duchenne muscular dystrophy, affects approximately 1 in every 3,500 to 6,000 male births each year in the United States. Some types of MD are more prevalent in certain countries and regions of the world. Several versions of the disorder are familial; however, Duchenne cases often have no prior family history. This is likely due to the large size

of the dystrophin gene that is implicated in the disorder, making it a more significant target for mutations.

Signs and symptoms

All of the muscular dystrophies are marked by muscle weakness as the major symptom. The distribution of symptoms, age of onset, and progression differ significantly. Pain is sometimes a symptom of each, usually due to the effects of weakness on joint position.

DUCHENNE MUSCULAR DYSTROPHY (DMD). A boy with Duchenne muscular dystrophy usually begins to show symptoms as a pre-schooler. The legs are affected first, making walking difficult and causing balance problems. Most patients walk three to six months later than expected and have difficulty running. Later on, a boy with DMD will push his hands against his knees to rise to a standing position, to compensate for leg weakness. About the same time, his calves will begin to enlarge, though with fibrous tissue rather than with muscle, and feel firm and rubbery; this condition gives DMD one of its alternate names, pseudohypertrophic muscular dystrophy. He will widen his stance to maintain balance, and walk with a waddling gait to advance his weakened legs. Contractures (permanent muscle tightening) usually begin by age five or six, most severely in the calf muscles. This pulls the foot down and back, forcing the boy to walk on tip-toes, and further decreases balance. Climbing stairs and rising unaided may become impossible by age nine or ten, and most boys use a wheelchair for mobility by the age of 12. Weakening of the trunk muscles around this age often leads to scoliosis (a side-to-side spine curvature) and kyphosis (a front-to-back curvature).

The most serious weakness of DMD is weakness of the diaphragm, the sheet of muscles at the top of the abdomen that perform the main work of breathing and coughing. Diaphragm weakness leads to reduced energy and stamina, and increased lung infection because of the inability to cough effectively. Young men with DMD often live into their 20s and beyond, provided they have mechanical ventilation assistance and good respiratory hygiene.

Among males with DMD, the incidence of cardiomyopathy (weakness of the heart muscle) increases steadily in teenage years. Almost all patients have cardiomyopathy after 18 years of age. It has also been shown that carrier females are at increased risk for cardiomyopathy and should also be screened.

About one third of males with DMD experience specific learning disabilities, including difficulty learning by ear rather than by sight and difficulty paying attention to long lists of instructions. Individualized educational programs usually compensate well for these disabilities.

BECKER MUSCULAR DYSTROPHY (BMD). The symptoms of BMD usually appear in late childhood to early adulthood. Though the progression of symptoms may parallel that of DMD, the symptoms are usually milder and the course more variable. The same pattern of leg weakness, unsteadiness, and contractures occurs later for the young man with BMD, often allowing independent walking into the 20s or early 30s. Scoliosis may occur, but is usually milder and progresses more slowly. Cardiomyopathy occurs more commonly in BMD. Problems may include irregular heartbeats (arrhythmias) and congestive heart failure. Symptoms may include fatigue, shortness of breath, chest pain, and dizziness. Respiratory weakness also occurs, and may lead to the need for mechanical ventilation.

EMERY-DREIFUSS MUSCULAR DYSTROPHY (EDMD). This type of muscular dystrophy usually begins in early childhood, often with contractures preceding muscle weakness. Weakness affects the shoulder and upper arm initially, along with the calf muscles, leading to foot-drop. Most men with EDMD survive into middle age, although an abnormality in the heart's rhythm (heart block) may be fatal if not treated with a pacemaker.

LING-GIRDLE MUSCULAR DYSTROPHY (LGMD). While there are several genes that cause the various types of LGMD, two major clinical forms of LGMD are usually recognized. A severe childhood form is similar in appearance to DMD, but is inherited as an autosomal recessive trait. Symptoms of adult-onset LGMD usually appear in a person's teens or 20s, and are marked by progressive weakness and wasting of the muscles closest to the trunk. Contractures may occur, and the ability to walk is usually lost about 20 years after onset. Some people with LGMD develop respiratory weakness that requires use of a ventilator. Lifespan may be somewhat shortened. Autosomal dominant forms usually occur later in life and progress relatively slowly.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSH). FSH varies in its severity and age of onset, even among members of the same family. Symptoms most commonly begin in the teens or early 20s, though infant or childhood onset is possible. Symptoms tend to be more severe in those with earlier onset. The condition is named for the regions of the body most severely affected by the condition: muscles of the face (facio-), shoulders (scapulo-), and upper arms (humeral). Hips and legs may be affected as well. Children with FSH may develop partial or complete deafness.

The first symptom noticed is often difficulty lifting objects above the shoulders. The weakness may be greater on one side than the other. Shoulder weakness also causes the shoulder blades to jut backward, called scapular winging. Muscles in the upper arm often lose

bulk sooner than those of the forearm, giving a “Popeye” appearance to the arms. Facial weakness may lead to loss of facial expression, difficulty closing the eyes completely, and inability to drink through a straw, blow up a balloon, or whistle. A person with FSH may not be able to wrinkle their forehead. Contracture of the calf muscles may cause foot-drop, leading to frequent tripping over curbs or rough spots. People with earlier onset often require a wheelchair for mobility, while those with later onset rarely do.

MYOTONIC DYSTROPHY. Symptoms of myotonic dystrophy include facial weakness and a slack jaw, drooping eyelids (ptosis), and muscle wasting in the forearms and calves. A person with myotonic dystrophy has difficulty relaxing his grasp, especially if the object is cold. Myotonic dystrophy affects heart muscle, causing arrhythmias and heart block, and the muscles of the digestive system, leading to motility disorders and constipation. Other body systems are affected as well; myotonic dystrophy may cause cataracts, retinal degeneration, mental deficiency, frontal balding, skin disorders, testicular atrophy, sleep apnea, and insulin resistance. An increased need or desire for sleep is common, as is diminished motivation. The condition is extremely variable; some individuals show profound weakness as a newborn (congenital myotonic dystrophy), others show intellectual disability in childhood, and many show characteristic facial features and muscle wasting in adulthood, while the most mildly affected individuals show only cataracts in middle age with no other symptoms. Individuals with a severe form of myotonic dystrophy typically have severe disabilities within 20 years of onset, although most do not require a wheelchair even late in life.

OCULOPHARYNGEAL MUSCULAR DYSTROPHY (OPMD). OPMD usually begins in a person’s 30s or 40s, with weakness in the muscles controlling the eyes and throat. Symptoms include drooping eyelids and difficulty swallowing (dysphagia). Weakness progresses to other muscles of the face, neck, and occasionally the upper limbs. Swallowing difficulty may cause aspiration, or the introduction of food or saliva into the airways. Pneumonia may follow.

DISTAL MUSCULAR DYSTROPHY (DD). DD usually begins in the 20s or 30s, with weakness in the hands, forearms, and lower legs. Difficulty with fine movements such as typing or fastening buttons may be the first symptom. Symptoms progress slowly, and the condition usually does not affect lifespan.

CONGENITAL MUSCULAR DYSTROPHY (CMD). CMD is marked by severe muscle weakness from birth, with infants displaying floppiness, very poor muscle tone, and trouble moving their limbs or head against gravity.

Mental function is normal but some are never able to walk. They may live into young adulthood or beyond. In contrast, children with Fukuyama CMD are rarely able to walk, and have severe intellectual disability. Most children with this type of CMD die in childhood.

Diagnosis

The diagnosis of muscular dystrophy involves a careful medical history and a thorough physical exam to determine the distribution of symptoms and to rule out other causes. Family history may give important clues, since all the muscular dystrophies are genetic conditions (though no family history will be evident in the event of new mutations; in autosomal recessive inheritance, the family history may also be negative).

Lab tests may include:

- **Blood level of the muscle enzyme creatine kinase (CK):** CK level increases due to muscle damage, and may be seen in some conditions even before symptoms appear.
- **Muscle biopsy:** A small piece of muscle tissue is removed for microscopic examination. Changes in the structure of muscle cells and presence of fibrous tissue or other aberrant structures are characteristic of different forms of muscular dystrophy. The muscle tissue can also be stained to detect the presence or absence of particular proteins, including dystrophin.
- **Electromyogram (EMG):** This electrical test is used to examine the response of the muscles to stimulation. Decreased response is seen in muscular dystrophy. Other characteristic changes are seen in DM.
- **Genetic tests:** Several of the muscular dystrophies can be positively identified by testing for the presence of the altered gene involved. Accurate genetic tests are available for DMD, BMD, DM, several forms of LGMD, and EDMD. Genetic testing for some of these conditions in future pregnancies of an affected individual or parents of an affected individual can be done before birth through amniocentesis or chorionic villus sampling.
- **Other specific tests as necessary:** For EDMD, DMD, and BMD, for example, an electrocardiogram may be needed to test heart function, and hearing tests are performed for children with FSH.

For most forms of muscular dystrophy, accurate diagnosis is not difficult when done by someone familiar with the range of conditions. There are some exceptions, even with a muscle biopsy; it may be difficult to distinguish between FSH and another muscle condition, polymyositis. Childhood-onset LGMD is often mistaken for the much more common DMD, especially when it occurs in boys. BMD with an early onset appears very similar to

DMD, and a genetic test may be needed to accurately distinguish them. The muscular dystrophies may be confused with conditions involving the motor neurons, such as spinal muscular atrophy; conditions of the neuromuscular junction, such as myasthenia gravis; and other muscle conditions, as all involve generalized weakness of varying distribution.

Prenatal diagnosis (testing of the baby while in the womb) can be done for those types of muscular dystrophy where the specific disease-causing gene alteration has been identified in a previously affected family member. Prenatal diagnosis can be done utilizing DNA extracted from tissue obtained by chorionic villus sampling or amniocentesis.

Treatment and management

Drugs

There are no cures for any of the muscular dystrophies. Prednisone, a corticosteroid, has been shown to delay the progression of DMD somewhat, for reasons that are still unclear. Some have reported improvement in strength and function in patients treated with a single dose. Improvement begins within ten days and plateaus after three months. Long-term benefit has not been demonstrated. Prednisone is also prescribed for BMD, though no controlled studies have tested its benefit. A study is under way in the use of gentamicin, an antibiotic that may slow down the symptoms of DMD in a small number of cases. Treatment of muscular dystrophy is mainly directed at preventing the complications of weakness, including decreased mobility and dexterity, contractures, scoliosis, heart alterations, and respiratory insufficiency.

Physical therapy

Physical therapy, regular stretching in particular, is used to maintain the range of motion of affected muscles and to prevent or delay contractures. Braces are used as well, especially on the ankles and feet to prevent tip-toeing. Full-leg braces may be used in children with DMD to prolong the period of independent walking. Strengthening other muscle groups to compensate for weakness may be possible if the affected muscles are few and isolated, as in the earlier stages of the milder muscular dystrophies. Regular, non-strenuous exercise helps maintain general good health. Strenuous exercise is usually not recommended, since it may damage muscles further.

Surgery

When contractures become more pronounced, tenotomy surgery may be performed. In this operation, the tendon of the contracted muscle is cut, and the limb is braced in its normal resting position while the tendon

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman’s abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother’s vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Dystrophin—A protein that helps muscle tissue repair itself. Both Duchenne muscular dystrophy and Becker muscular dystrophy are caused by flaws in the gene that instructs the body how to make this protein.

Myotonic dystrophy—A form of muscular dystrophy, also known as Steinert’s condition, characterized by delay in the ability to relax muscles after forceful contraction, and wasting of muscles, as well as other abnormalities.

regrows. In FSH, surgical fixation of the scapula can help compensate for shoulder weakness. For a person with OPMD, surgical lifting of the eyelids may help compensate for weakened muscular control. For a person with DM, sleep apnea may be treated surgically to maintain an open airway. Scoliosis surgery is often needed in boys with DMD, but much less often in other muscular dystrophies. Surgery is recommended at a much lower degree of curvature for DMD than for scoliosis due to other conditions, since the decline in respiratory function in DMD makes surgery at a later time dangerous. In this surgery, the vertebrae are fused together to maintain the spine in the upright position. Steel rods are inserted at the

time of operation to keep the spine rigid while the bones grow together. When any type of surgery is performed in patients with muscular dystrophy, anesthesia must be carefully selected. People with MD are susceptible to a severe reaction, known as malignant hyperthermia, when given halothane anesthetic.

Occupational therapy

The occupational therapist suggests techniques and tools to compensate for the loss of strength and dexterity. Strategies may include modifications in the home, adaptive utensils and dressing aids, compensatory movements and positioning, wheelchair accessories, or communication aids.

Nutrition

Good nutrition helps to promote general health in all the muscular dystrophies. No special diet or supplement has been shown to be of use in any of the conditions. The weakness in the throat muscles seen especially in OPMD and later DMD may necessitate the use of a gastrostomy tube, inserted in the stomach to provide nutrition directly.

Cardiac care

The arrhythmias of EDMD and BMD may be treatable with antiarrhythmia drugs. A pacemaker may be implanted if these do not provide adequate control. Heart transplants are increasingly common for men with BMD. A complete cardiac evaluation is recommended at least once in all carrier females of DMD and EDMD.

Respiratory care

People who develop weakness of the diaphragm or other ventilatory muscles may require a mechanical ventilator to continue breathing deeply enough. Air may be administered through a nasal mask or mouthpiece, or through a tracheostomy tube, which is inserted through a surgical incision through the neck and into the windpipe. Most people with muscular dystrophy do not need a tracheostomy, although some may prefer it to continual use of a mask or mouthpiece. Supplemental oxygen is not needed. Good hygiene of the lungs is critical for health and long-term survival of a person with weakened ventilatory muscles. Assisted cough techniques provide the strength needed to clear the airways of secretions; an assisted cough machine is also available and provides excellent results.

Experimental treatments

Two experimental procedures aiming to cure DMD have attracted a great deal of attention. In myoblast transfer, millions of immature muscle cells are injected into an affected muscle. The goal of the treatment is to

QUESTIONS TO ASK YOUR DOCTOR

- Why does my doctor use the term “muscular dystrophies” rather than just “muscular dystrophy”?
- Are there ways I can help my child maintain muscle function as her condition develops?
- What is the long-term prognosis for the type of muscular dystrophy my child has?
- What is the status of current research on cures for muscular dystrophy?

promote the growth of the injected cells, replacing the abnormal host cells with healthy new ones. Myoblast transfer is under investigation but remains experimental.

Gene therapy introduces unaltered copies of the altered gene into muscle cells. The goal is to allow the existing muscle cells to use the new gene to produce the protein it cannot make with its abnormal gene. Problems with gene therapy research have included immune rejection of the virus used to introduce the gene, loss of gene function after several weeks, and an inability to get the gene to enough cells to make a functional difference in the affected muscle. Researchers are preparing for the first gene therapy trial for LGMD in the United States. The goal will be to replace the missing sarcoglycan gene(s). Additionally, clinical trials have tested the use of oligonucleotide (2'OMe [PRO051] and PMO [AVI-4658]) therapy for MDM and have seen very promising improvements in the levels of dystrophin observed both with local or systemic injections. However, there are two observed obstacles to these therapies. First, effective cell penetration of the tested formulations is lacking, and second, the effect of the current formulations on the cardiac muscle is very limited. To address these issues alternate formulations have been created utilizing cell penetrating peptides (CPP)-conjugated PMO (PPMO) and seem to be promising, though these new formulas are still being investigated.

Genetic counseling

Individuals with muscular dystrophy and their families may benefit from genetic counseling for information on the condition and recurrence risks for future pregnancies.

Prognosis

The expected lifespan for a male with DMD has increased significantly. Most young men will live into their early or mid 20s. Respiratory infections become an

increasing problem as their breathing becomes weaker, and these infections are usually the cause of death.

The course of the other muscular dystrophies is more variable; expected lifespans and degrees of disability are hard to predict, but may be related to age of onset and initial symptoms. Prediction is made more difficult because, as new genes are discovered, it is becoming clear that several of the dystrophies are not uniform disorders, but rather symptom groups caused by different genes.

People with dystrophies with significant heart involvement (BMD, EDMD, myotonic dystrophy) may nonetheless have almost normal lifespans, provided that cardiac complications are monitored and treated aggressively. The respiratory involvement of BMD and LGMD similarly require careful and prompt treatment. There is no way to prevent any of the muscular dystrophies in a person who has the genes responsible for these disorders. Accurate genetic tests, including prenatal tests, are available for some of the muscular dystrophies. Results of these tests may be useful for purposes of family planning.

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ORGANIZATIONS

- Muscular Dystrophy Association, 222 S. Riverside Plaza, Suite 1500, Chicago, IL 60606, (520) 529-2000 or (800) 572-1717, <http://www.mda.org>

Myotonic Dystrophy Foundation, 1004A O'Reilly Ave., San Francisco, CA 94129, (866) 968-6642, info@myotonic.org, <http://www.myotonic.org>

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Mutations (on-target and off-target)

Definition

On-target mutations are intentional changes, and off-target mutations are unintentional changes in the genetic material (genome) of an organism caused by genome editing.

Description

Genome editing is a technique used by researchers to change the genetic sequence of an organism. In humans, it is done to fix errors in the sequence and treat or prevent genetic disease. In agriculture and food production, genome editing is used to improve certain traits of the plant or animal, such as disease tolerance and yield.

Often genome editing involves changes to the DNA sequence, which contains the instructions for creating proteins. A three-base sequence in the DNA contains the instructions for making a particular amino acid. Proteins are made up of one amino acid or several amino acids strung together.

An intentional change made through genome editing is called on-target mutation. Such changes are often designed to fix an error. On-target mutations in genome editing include adding a piece of DNA (insertion), removing a piece of DNA (deletion), or causing a point mutation. On-target point mutations in genome editing involve substituting one DNA base for another, or inserting or deleting one base.

Unfortunately genome editing techniques can result in unintended mutations, called off-target mutations. Off-target mutations can include point mutations, deletions, insertions, sequences switched around (inversions), and pieces moved from one area to another (translocations).

Sometimes off-target mutations are silent, meaning they do not affect the organism. Other times they disrupt a gene and result in the production of absent or abnormal proteins.

KEY TERMS

Cell—Building block that provides structure to the body and performs all the functions of the body. Cells contain genetic information and can copy themselves. The four main types of cells are: skin, nerve, muscle, and connective tissue.

Chromosome—The package of DNA found in each cell of the human body apart from the red blood cells. Humans have 22 pairs of autosomes (1 to 22) and one pair of sex chromosomes (XY). Females have two X chromosomes, and males have an X and Y. Normally, individuals inherit one chromosome of each pair from their mother and one from their father.

Deletion—Mutation where a single base pair or sequence of base pairs is missing.

DNA (deoxyribonucleic acid)—The genetic material that contains the instructions for creating proteins.

DNA base—One unit in a DNA sequence. The four DNA bases are adenine (A), cytosine (C), guanine (G), and thymine (T). The sequence of these bases is the genetic code that contains the instructions for creating proteins.

DNA sequence—The sequence of DNA bases that contains the instructions for creating proteins. A three base sequence in the DNA contains the instructions for making a particular amino acid. For example, CGC codes for the amino acid alanine. Proteins are made up of one amino acid or several amino acids strung together. The instructions for a particular protein are made up of a number of three base sequences.

Gene—A sequence of bases in a DNA sequence that contains the instructions for one protein.

Genome—The complete set of genetic instructions of an organism.

Genome editing—A technique used by researchers to change the sequence of genetic material, for example, the DNA, of an organism. It can be used to fix a pathogenic mutation that can cause disease.

Insertion—Mutation where there is an extra single base pair or sequence of base pairs.

Oncogene—A pathogenic variant (mutation) in a proto-oncogene that turns it into an oncogene which does not regulate the cell well, making it more likely to become cancerous.

On-target point mutation—The substitution of one DNA base for another or insertion or deletion of one base.

Pathogenic variant—Any change in the sequence of a genome that causes disease.

Point mutation (DNA)—Error in the DNA sequence where one DNA base is substituted for another or inserted or deleted.

Sickle cell disease—A genetic disease that causes abnormal red blood cells that cannot properly carry oxygen throughout the body.

Tissue—Matter made up of cells that have a common function. The four types of tissue are: connective, epithelial (skin), muscle, and nervous.

Tumor suppressor genes—Genes that normally help prevent cancer from developing in a cell. Variants (mutations) in tumor suppressor genes make the cell more likely to become cancerous.

Variant—Change in the sequence of DNA.

Whole genome sequencing—A way to look at the sequence of an organism's genome by looking for variants (mutations) in the whole genome.

Mutations in somatic and germline genome editing

Genome editing can be accomplished in either somatic or germline cells. Somatic genome editing involves changing the genetic sequence in a tissue or cell other than an egg or sperm cell. Somatic genome editing is often used to correct an error in the genetic sequence that results in a missing or abnormal protein. Somatic genome editing fixes that error so that a functioning protein is produced in the cells that are targeted. This procedure can be performed on cells outside the body (in vitro), which are then transferred to the patient or directly on cells in the body (in vivo).

Germline genome editing changes the genetic material in either an egg or sperm or early embryo. Germline genome editing will cause permanent changes in the individual and that individual's offspring, and can be used to prevent a genetic disease.

The risk of off-target mutation is increased with in vivo somatic genome editing in which the genome editing is done directly in the body. In this case, in vivo somatic genome editing may cause off-target mutations in a variety of cells and tissues in the body. In vitro genome editing, by contrast, will only result in off-target mutations in the specific cells that are being targeted outside the body.

In vivo genome editing is used in treatment of Hunter syndrome, in which mutations in the IDS gene cause the IDS protein not to function properly. Sugars build up in the body, which can damage organs and result in brain, heart, and lung damage, and early death. To treat this condition, a normal IDS gene is injected into patients with Hunter syndrome. The gene contains the instructions for the production of a normal IDS protein. The hope is that by inserting a normal gene into the cells enough normal protein will be produced to prevent the accumulation of sugars. Gene editing for conditions such as Hunter syndrome may be worth the risk provided that researchers thoroughly examine the target sequence and other areas of the genome that could be unintentionally targeted.

One advantage of somatic genome editing is that off-target mutations will not result in permanent changes that can affect future generations. Also the off-target mutations will not affect all the cells of the body.

Off-target mutations in germline editing, by contrast, results in permanent changes to the whole embryo, which can be passed on to future generations. One study of genome editing on embryos found that, in addition to the typical small insertions and deletions, about 16% of the embryos had large off-target mutations that would not have been detected through traditional methods for detecting DNA changes. Other studies have found an increased risk of mosaic embryos resulting from genome editing. A mosaic embryo has some cells without the genetic change and some with the genetic change. This condition can result in abnormalities in the embryo.

Methods of decreasing off-target mutations

Modern genome editing techniques involve the use of guide RNAs, which guide a genome editor to a target location on the DNA or RNA. The genome editor includes a nuclease that makes a cut in the DNA. Then either the genome editor creates the on-target mutation, or it tricks the DNA repair mechanism of the organism to make the change. If there is a sequence of DNA in another location that is similar to the target location, then the RNA guide may also guide the editor to make a change in this site, which results in an off-target mutation.

When possible, it is important to choose a target location that has a different sequence than other non-targeted locations in the DNA. For example, one study found that the number of off-target mutations decreased significantly when the target sequence had three mismatches or more to any other similar sequences in the DNA.

Newer genome editing techniques, such as base editing and prime editing, are more precise and require a cut in only one strand of the DNA. They generally result in

fewer off-target mutations than genome editing systems that rely on a double stranded break in the DNA, such as nuclease-zinc-finger nuclease (ZFN), TALEN, or CRISPR-Cas.

Before physicians perform genome editing for a particular disease, they must determine what off-target mutations are likely and how serious they might be. For example, if physicians are planning to treat a disease such as sickle cell disease by doing somatic genome editing in blood cells, then off-target mutations that make changes in a gene only found in the muscle cells will be less concerning. If they are trying to treat muscular dystrophy by somatic genome editing of muscle cells, then off-target mutations in beta-globin genes, which are not active in muscle cells, are likely acceptable.

Possible off-target mutations in genes that can cause cancer, such as tumor suppressor genes or oncogenes, should be avoided. Even if these off-target mutations only happen in a few cells, there is a high risk of cancer. That is because mutations in an oncogene or tumor suppressor gene would give these cells a growth advantage that could help them overtake the normal cells.

This problem occurred in genome editing clinical trials involving patients who had severe abnormalities in their immune system. The vector transporting the genome editing material integrated into the DNA near an oncogene and activated it in some cells. Activation of this oncogene caused the affected cells to grow out of control and resulted in leukemia. There were so few cells that had the activated oncogene that it was impossible to detect with DNA sequencing techniques that look for mutations in the whole genome (whole genome sequencing). Thus, when physicians consider potential targets for genome editing, they must select sequencing that looks at specific oncogene and tumor suppressor genes rather than relying only on whole genome sequencing.

On-target and off-target mutations in agriculture

Genome editing is used on crops and livestock to improve favorable traits such as disease resistance. It is easier to deal with off-target mutations when using genome editing on plant crops and livestock. Genome editing can be done on cells from semen and seeds. Plants or animals from the first generation after genome editing can be examined to see if there are any adverse effects on the health of the organism or the quality of the food produced. Genome editing can also be done to look for off-target mutations. Many serious off-target mutations can prevent the plant or animal from reproducing. Off-target mutations that do not cause any obvious adverse effect are usually tolerated. Many existing strains of crop

plants have mutations that resulted from early genome editing techniques using radiation or chemicals.

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Myasthenia gravis

Definition

Myasthenia gravis (MG) is an autoimmune neuromuscular disease that causes muscle weakness in certain voluntary muscle groups.

Description

The name myasthenia gravis literally means "grave muscle weakness." MG affects the neuromuscular junction, interrupting the communication between nerve and muscle, and thereby causing weakness. A person with MG may have difficulty moving their eyes, walking, speaking clearly, swallowing, and even breathing, depending on the severity and distribution of weakness. Increased weakness with exertion, and improvement with rest, is a characteristic feature of MG.

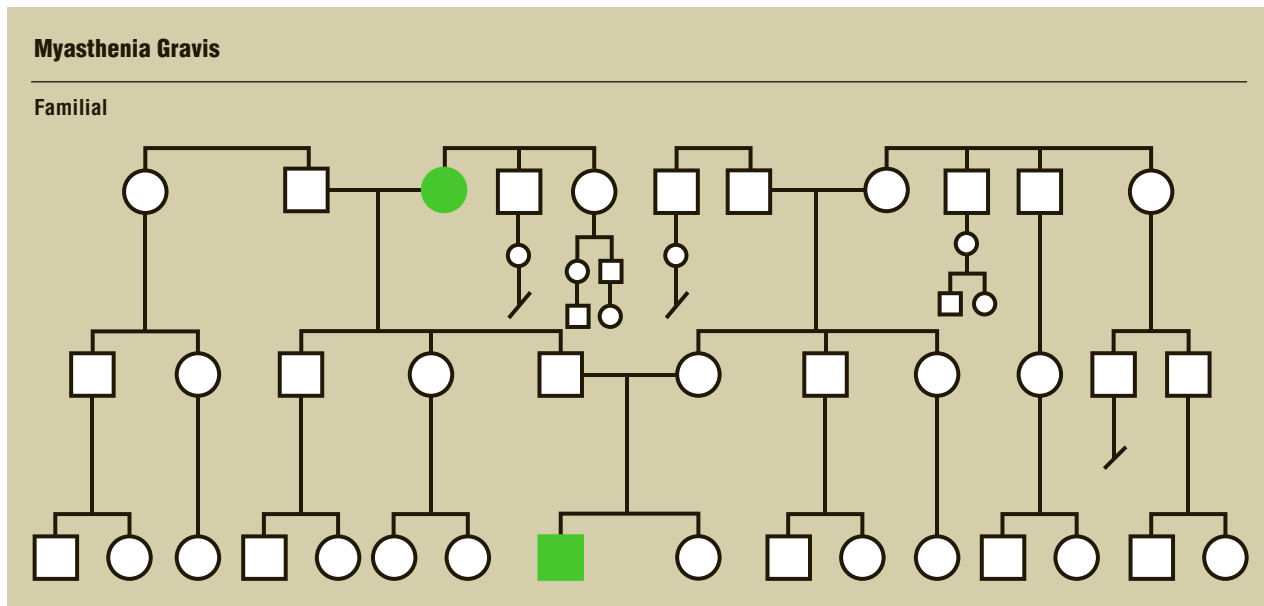
In MG, the immune system attacks a receptor on the surface of muscle cells. This prevents the muscle from receiving the nerve impulses that normally make it respond. MG affects voluntary muscles, which are those muscles under conscious control responsible for movement. It does not affect heart muscle or the smooth muscle found in the digestive system and other internal organs.

A muscle is stimulated to contract when the nerve cell controlling it releases acetylcholine molecules onto its surface. The acetylcholine binds to a muscle protein called the acetylcholine receptor. This leads to rapid chemical changes in the muscle, causing contraction. Acetylcholine is then broken down by acetylcholinesterase enzyme, preventing further stimulation.

In MG, immune cells create antibodies against the acetylcholine receptor. Antibodies are proteins normally involved in fighting infection. When these antibodies attach to the receptor, they prevent it from receiving acetylcholine, decreasing the ability of the muscle to respond to stimulation.

Why the immune system creates these self-reactive autoantibodies is unknown, although there are several hypotheses:

- During fetal development, the immune system generates many B cells that can make autoantibodies, but B cells that could harm the body's own tissues are screened out and destroyed before birth. It is possible that the stage is set for MG when some of these cells escape detection.
- Genes controlling other parts of the immune system, called Major Histone Compatibility (MHC) genes, appear to influence how susceptible a person is to developing autoimmune disease.
- Infection may trigger some cases of MG. When activated, the immune system may mistake portions of the acetylcholine receptor for portions of an invading virus, though no candidate virus has yet been identified conclusively.
- About 10% of those with MG also have thymomas, or benign tumors of the thymus gland. The thymus is a principal organ of the immune system, and researchers speculate that thymic irregularities are involved in the progression of MG.



Familial inheritance of Myasthenia gravis (Gale)

Some or all of these factors (developmental, genetic, infectious, and thymic) may interact to create the autoimmune reaction.

Genetic profile

Myasthenia gravis is similar to many autoimmune diseases. It is a multifactorial, non-inherited disease with documented genetic contributing factors. Genome-wide association studies conducted in 2015 have identified three gene variants that are susceptible loci: *CTLA4* (rs231770), *HLA-DQA1* (rs9271871), and *TNFRSF11A* (rs4263037). MG is a very heterogeneous disease varying in severity of symptoms, autoantigens produced, and ages of onset. Three autoantigens have been identified to cause 90%–95% of clinical cases. The muscle acetylcholine receptor (AChR) accounts for up to 85% of diagnosed cases, and the remaining cases have been identified as autoantibodies against the muscle-specific tyrosine kinase (MuSK) and the low-density-lipoprotein-receptor-related protein 4 (LRP4). It is important to note that there are many possible epitope variations of these three targets, and that individuals may have autoantibodies to more than one epitope.

Demographics

About 36,000 people in the United States are affected by MG, roughly 14 people per 100,000. The age of onset delineates patients into two subgroups: early-onset MG (EOMG), where patients develop the disease before the age of 40, and late-onset MG (LOMG),

where patients develop the disease after 40 years of age. The two subgroups are further characterized by gender predominance, with EOMG being predominantly female (3:1) and LOMG predominantly male. Pathology of the thymus within each subgroup has been documented. EOMG is characterized by hyperplastic thymus pathology, and LOMG typically has either normal or atrophic pathology. Occasionally the disease is present in more than one person in a family.

Signs and symptoms

The earliest symptoms of MG often result from weakness of the extra-ocular muscles, which control eye movements. Symptoms involving the eye (ocular symptoms) include double vision (diplopia), especially when not gazing straight ahead, and difficulty raising the eyelids (ptosis). A person with ptosis may need to tilt his or her head back to see. Eye-related symptoms remain the only symptoms for about 15% of MG patients. Another common early symptom is difficulty chewing and swallowing, due to weakness in the bulbar muscles, which are in the mouth and throat. Choking becomes more likely, especially with food that requires extensive chewing.

Weakness usually becomes more widespread within several months of the first symptoms, reaching their maximum within a year in two-thirds of patients. Weakness may involve muscles of the arms, legs, neck, trunk, and face, and affect the ability to lift objects, walk, hold the head up, and speak.

Symptoms of MG become worse upon exertion and better with rest. Heat, including heat from the sun, hot showers, and hot drinks may increase weakness. Infection and stress may worsen symptoms. Symptoms may vary from day to day and month to month, with intervals of no weakness interspersed with a progressive decline in strength.

Myasthenic crisis is an emergency condition requiring immediate treatment. It may occur when the breathing muscles become too weak to provide adequate respiration. Symptoms include weak and shallow breathing, shortness of breath, pale or bluish skin color, and a racing heart. In patients treated with anticholinesterase agents, myasthenic crisis must be differentiated from cholinergic crisis related to overmedication.

Pregnancy worsens MG in about one third of women, has no effect in one third, and improves symptoms in another third. About 12% of infants born to women with MG have neonatal myasthenia, a temporary but potentially life-threatening condition caused by the transfer of maternal antibodies into the fetal circulation just before birth. Symptoms include weakness, poor muscle tone, feeble cry, and difficulty feeding. The infant may have difficulty breathing, requiring the use of a ventilator. Neonatal myasthenia usually clears up within a month.

Diagnosis

Myasthenia gravis is often diagnosed accurately by a careful medical history and a neuromuscular exam, but several tests are used to confirm the diagnosis. Other conditions causing worsening of bulbar and skeletal muscles must be considered, including drug-induced myasthenia,

KEY TERMS

Antibody—A protein produced by the mature B cells of the immune system that attach to invading pathogens/antigens and target them for destruction by other immune system cells.

Autoantibody—An antibody that reacts against part of the self.

Autoimmune disease—Describes a group of diseases characterized by an inflammatory immune reaction erroneously directed toward ‘self’ tissues.

Bulbar muscles—Muscles that control chewing, swallowing, and speaking.

Epitope—The specific piece of an antigen that an antibody binds to.

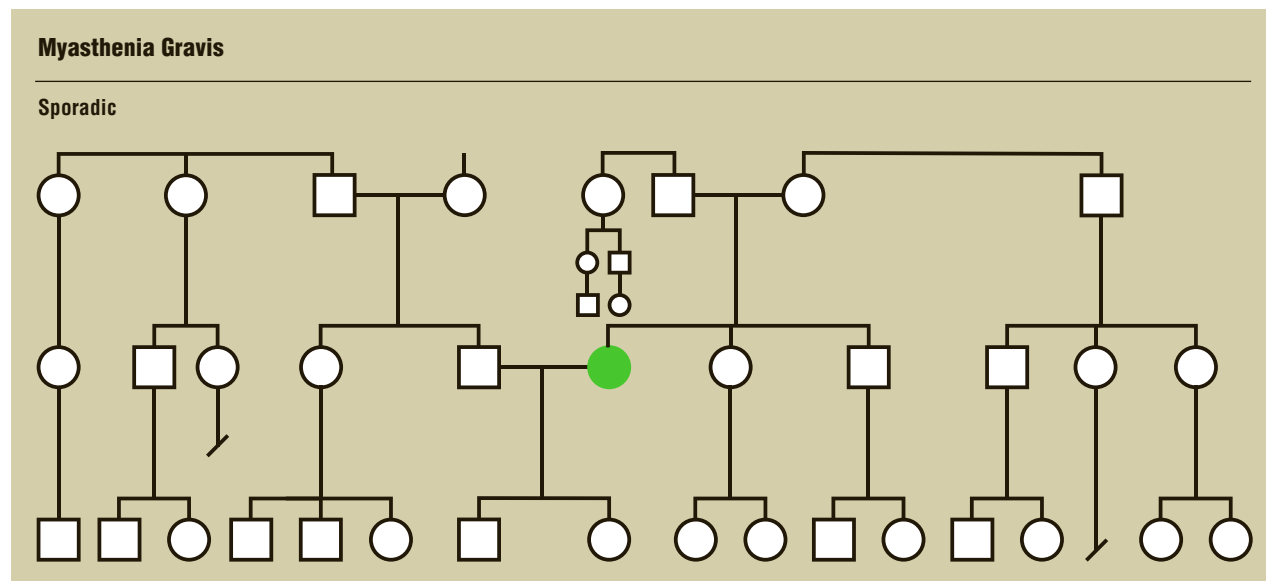
Neuromuscular junction—The site at which nerve impulses are transmitted to muscles.

Pyridostigmine bromide (Mestinon)—An anticholinesterase drug used in treating myasthenia gravis.

Thymus gland—An endocrine gland located in the front of the neck that houses and transports T cells, which help to fight infection.

thyroid disease, Lambert-Eaton myasthenic syndrome, botulism, and inherited muscular dystrophies.

MG causes characteristic changes in the electrical responses of muscles that may be observed with an electromyogram, which measures muscular response to



Sporadic occurrence of Myasthenia gravis in a family (Gale)

electrical stimulation. Repetitive nerve stimulation leads to reduction in the height of the measured muscle response, reflecting the muscle's tendency to become fatigued.

Blood tests may confirm the presence of the antibody to the acetylcholine receptor, though up to a quarter of MG patients will not have detectable levels. A chest x-ray or chest computed tomography scan (CT scan) may be performed to look for thymomas.

Treatment and management

While there is no cure for myasthenia gravis, there are a number of treatments that effectively control symptoms in most people. Pyridostigmine (Mestinon) is usually the first drug prescribed. Pyridostigmine blocks acetylcholinesterase, is longer-acting, taken by mouth, and well-tolerated. Loss of responsiveness and disease progression combine to eventually make pyridostigmine ineffective in tolerable doses in many patients.

Thymectomy, or removal of the thymus gland, has increasingly become standard treatment for MG. Up to 85% of people with MG improve after thymectomy, with complete remission eventually seen in about 30%. The improvement may take months or even several years to fully develop. Thymectomy is not usually recommended for children with MG, since the thymus continues to play an important immune role throughout childhood.

Immune-suppressing drugs are used to treat MG if response to pyridostigmine and thymectomy are not adequate. Drugs include corticosteroids such as prednisone, and the non-steroids azathioprine (Imuran) and cyclosporine (Sandimmune).

Plasma exchange may be performed to treat myasthenic crisis or to improve very weak patients before thymectomy. In this procedure, blood plasma is removed and replaced with purified plasma free of autoantibodies. It can produce a temporary improvement in symptoms, but is too expensive for long-term treatment. Another blood treatment, intravenous immunoglobulin therapy, is also used for myasthenic crisis. In this procedure, large quantities of purified immune proteins (immunoglobulins) are injected. For unknown reasons, this leads to symptomatic improvement in up to 85% of patients. It is also too expensive for long-term treatment.

People with weakness of the bulbar muscles may need to eat softer foods that are easier to chew and swallow. In more severe cases, it may be necessary to obtain nutrition through a feeding tube placed into the stomach (gastrostomy tube).

QUESTIONS TO ASK YOUR DOCTOR

- How do you plan to treat my myasthenia gravis syndrome?
- Are there treatment options?
- Is surgery required?
- What is the expected outcome?
- How do autoimmune diseases develop?

Some drugs should be avoided by people with MG because they interfere with normal neuromuscular function. Drugs to be avoided or used with caution include:

- Several antibiotics, including erythromycin, streptomycin, and ampicillin
- Cardiovascular drugs, including verapamil, betaxolol, and propranolol
- Drugs used in psychiatric conditions, including chlorpromazine, clozapine, and lithium

Many other drugs may exacerbate symptoms, so patients should check with the doctor who treats their MG before taking any new medications.

A Medic-Alert card or bracelet provides an important source of information to emergency providers about the special situation of a person with MG. They are available from health care providers.

Prognosis

Most people with MG can be treated successfully enough to prevent their condition from becoming debilitating. In some cases, however, symptoms may worsen even with vigorous treatment, leading to generalized weakness and disability. MG rarely causes early death except from myasthenic crisis. There is no known way to prevent myasthenia gravis. Thymectomy improves symptoms significantly in many patients, and relieves them entirely in some. Avoiding heat can help minimize symptoms.

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ORGANIZATIONS

Muscular Dystrophy Association, 222 S. Riverside Plaza, Suite 1500, Chicago, IL 60606, (800) 572-1717, <http://www.mda.org>
 Myasthenia Gravis Foundation of America, 355 Lexington Ave., 15th Floor, New York, NY 10017, (800) 541-5454, (212) 370-9047, <http://www.myasthenia.org>

Catherine L. Tesla, MS, CGC
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MYH9-related disorders

Definition

MYH9-related disorders are extremely rare genetic diseases that result in impaired blood clotting function and abnormal platelet formation. Another name for *MYH9*-related disorders is autosomal dominant macrothrombocytopenia with leukocyte inclusions.

Description

MYH9-related disorders are classified as one of the inherited giant platelet disorders (IGPDs). Platelet cells are components of the blood that play a key role in blood clotting. All IGPDs are associated with bleeding disorders due to few platelets, improper platelet function, and increased platelet cell size. A subclass of IGPDs include the non-muscle myosin-heavy chain 9 (*MYH9*)-related disorders (*MYH9*-RD). Mutations in the *MYH9* gene result in several disease pathologies, including Sebastian syndrome, May-Hegglin anomaly, Epstein syndrome, and Fechtner syndrome, which are characterized by the distinct disease symptoms. People affected by *MYH9*-related disorders have mild, non-life-threatening dysfunction of the blood related to decreased blood clotting function. They may bruise easily or be prone to nosebleeds.

Genetic profile

MYH9-related disorders are inherited as an autosomal dominant trait. Autosomal means that the syndrome is not carried on a sex chromosome, while dominant

KEY TERMS

Epstein syndrome—A subgroup of the *MYH9*-related disorders characterized by the platelet disorder, kidney disease, and hearing loss.

Fechtner syndrome—A subgroup of the *MYH9*-related disorders characterized by the platelet disorder and inclusion bodies in the white blood cells, kidney disease, hearing loss, and cloudiness of the eye.

Inherited giant platelet disorder (IGPD)—A group of hereditary conditions that cause abnormal blood clotting and other conditions.

May-Hegglin anomaly—A subgroup of the *MYH9*-related disorders characterized by the platelet disorder and inclusion bodies in the white blood cells.

Myosin heavy chain 9 (*MYH9*)-related disorders (*MYH9*-RD)—A group of inherited macrothrombocytopenias caused by mutations in the *MYH9* gene that cause abnormal blood clotting and other symptoms.

Platelets—Small disc-shaped structures that circulate in the blood stream and participate in blood clotting.

Sebastian syndrome—A subgroup of the *MYH9*-related disorders characterized by the platelet disorder and inclusion bodies in the white blood cells.

means that only one parent has to pass on the gene mutation in order for the child to be affected with the syndrome.

Genetic studies in the year 2000 proved that *MYH9*-related disorders are due to a mutation in the gene that encodes a specific enzyme known as non-muscle myosin heavy chain 9 (the *MYH9* gene). The gene locus is 22q13.1, or the 13th band of the q arm of chromosome 22. Research determined that mutations in the same gene are responsible for four subgroups: Sebastian syndrome, May-Hegglin anomaly, Epstein syndrome, and Fechtner syndrome.

Demographics

MYH9-related disorders are extremely rare. The incidence of all four subgroups is limited; only 257 affected families had been reported in the medical literature as of 2015. Due to the very small number of cases, demographic trends for the disease have not been established.

Affected individuals have been identified in Caucasian, Japanese, African-American, Spanish, and Saudi Arabian families, so there does not seem to be any clear ethnic pattern to the disease. Both males and females appear to be affected with the same probability.

Signs and symptoms

The symptoms of *MYH9*-related disorders include bleeding problems, hearing problems, kidney (renal) disease, and cloudiness of the eye (cataract), which further distinguishes the subgroups. All four *MYH9*-related disorder subgroups are characterized by megathrombocytopenia (low numbers of large platelets), with Sebastian syndrome and May-Hegglin anomaly presenting small alterations (inclusion bodies) in the white blood cells. Epstein syndrome does not present with the white blood cell inclusion bodies, rather is distinguished by the additional symptoms of kidney disease and hearing loss. Fechtner syndrome includes all of the symptoms observed in Epstein syndrome, and includes the presentation of cataracts.

The physical symptoms of *MYH9*-related disorders are a propensity for nosebleeds, bleeding from the gums, mildly increased bleeding time after being cut, and a tendency to bruise easily. Women may experience heavier than normal menstrual bleeding. People with *MYH9*-related disorders may experience severe hemorrhage after undergoing surgery for any reason. Some individuals with *MYH9*-related disorders, particularly Sebastian syndrome, may not have any observable physical signs of the disorder at all.

Diagnosis

Diagnostic blood tests to confirm the decreased blood clotting function seen in *MYH9*-related disorders may include a complete blood count (CBC) to determine the number of platelets in a blood sample, blood coagulation studies, or platelet aggregation tests. Further quantitative analysis of the affected cellular receptors may be performed using flow cytometry or fluorescent and electron microscopy. DNA sequence-based procedures such as whole exome sequencing may provide further insight into the disease.

There are several other disorders, including non-genetic diseases, which may cause symptoms similar to those seen in *MYH9*-related disorders. A family history of easy bleeding or bruising is an important clue in diagnosing *MYH9*-related disorders. Once the hereditary nature of the disease is confirmed, establishing a dominant inheritance pattern can separate *MYH9*-related disorders from other inherited giant platelet disorders.

QUESTIONS TO ASK YOUR DOCTOR

- What is an inherited giant platelet disorder, and how do *MYH9*-related disorders differ from other forms of this condition?
- What are the most serious medical problems that arise because of *MYH9*-related disorders?
- What kinds of treatments or medications are available for the control of *MYH9*-related disorders?
- Is it necessary to have periodic medical check-ups to monitor the progress of my *MYH9*-related disorder?

Microscopic studies of the blood can reveal the enlarged platelets and the specific shape and structure characteristics associated with *MYH9*-related disorders. These characteristics include a shape that is less disc-like than normal platelets. There are also bluish inclusions, or small foreign bodies, observed in the white blood cells.

Genetic sequencing to confirm the presence of a mutation on the *MYH9* gene is another method to positively diagnose Sebastian syndrome, although this would rarely be performed in lieu of other methods.

Treatment and management

No treatment is required for the majority of people affected with *MYH9*-related disorders. After surgery, platelet transfusion may be required in order to avoid the possibility of hemorrhage. People diagnosed with *MYH9*-related disorders should be made aware of the risks associated with excessive bleeding. There have been two completed clinical trials undertaken to evaluate and develop therapies for *MYH9*-related disorders and two that were recruiting subjects as of 2015. Treatment of *MYH9*-related disorders with an agonist (eltrombopag) to stimulate platelet production was evaluated in a small-group phase-2 clinical trial in Italy in 2010 with favorable results. A larger observational clinical trial in France collected data from 360 patients from 2009 to 2015, examining the phenotype and genotype correlations of patients with *MYH9* mutations.

Prognosis

People with *MYH9*-related disorders can be expected to have a normal lifespan. The main risk for some patients is the chance of severe bleeding after surgery or injury.

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ORGANIZATIONS

National Kidney Foundation, 30 E. 33rd St., New York, NY 10016, (855) 653-2273, (212) 689-9261, nkfcare@kidney.org, <https://www.kidney.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, nkfcare@kidney.org, <http://www.rarediseases.org>

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Myopia

Definition

Myopia is the medical term for nearsightedness. Myopia is caused when refracted parallel rays of light are brought into focus in front of the retina of a resting eye rather than directly onto the retina. People with myopia see objects more clearly when they are close to the eye, while distant objects appear blurred or fuzzy.

Description

To understand myopia, it is necessary to have a basic knowledge of the main parts of the eye's focusing system: the cornea, the lens, and the retina. The cornea is a tough, transparent, dome-shaped tissue that covers the front of the eye (not to be confused with the white, opaque sclera). It lies in front of the iris (the colored part of the eye). The lens is a transparent, double-convex structure located behind the iris. The retina is a thin membrane that lines the rear of the eyeball. Light-sensitive retinal cells convert incoming light rays into electrical signals

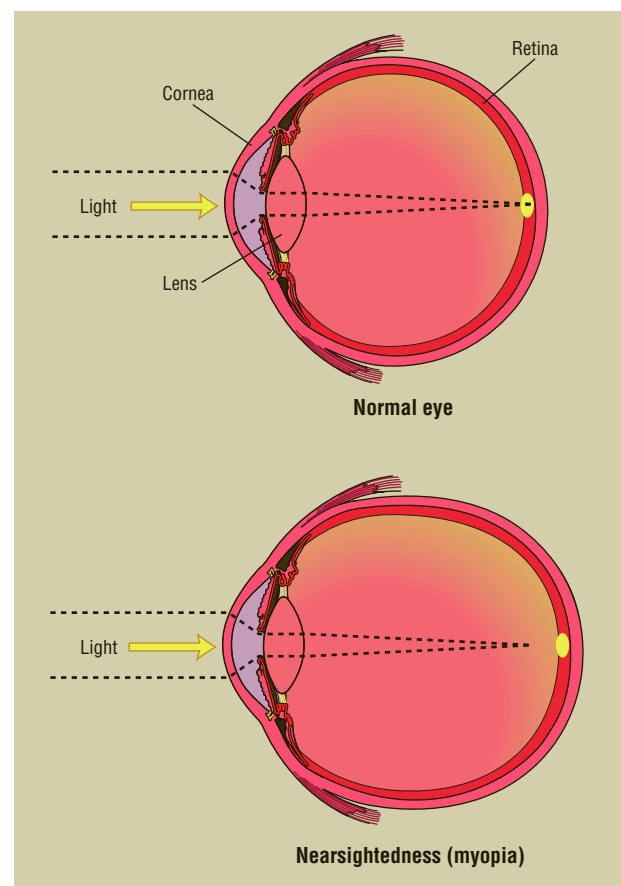
that are sent along the optic nerve to the brain, which then interprets the images.

In people with normal vision, parallel light rays enter the eye and are bent by the cornea and lens (in a process called refraction) to focus precisely on the retina, providing a crisp, clear image. In the myopic eye, the focusing power of the cornea (the major refracting structure of the eye) and the lens is too great with respect to the length of the eyeball. Light rays are bent too much, and they converge in front of the retina. This inaccuracy is called a refractive error. In other words, an overfocused fuzzy image is sent to the brain.

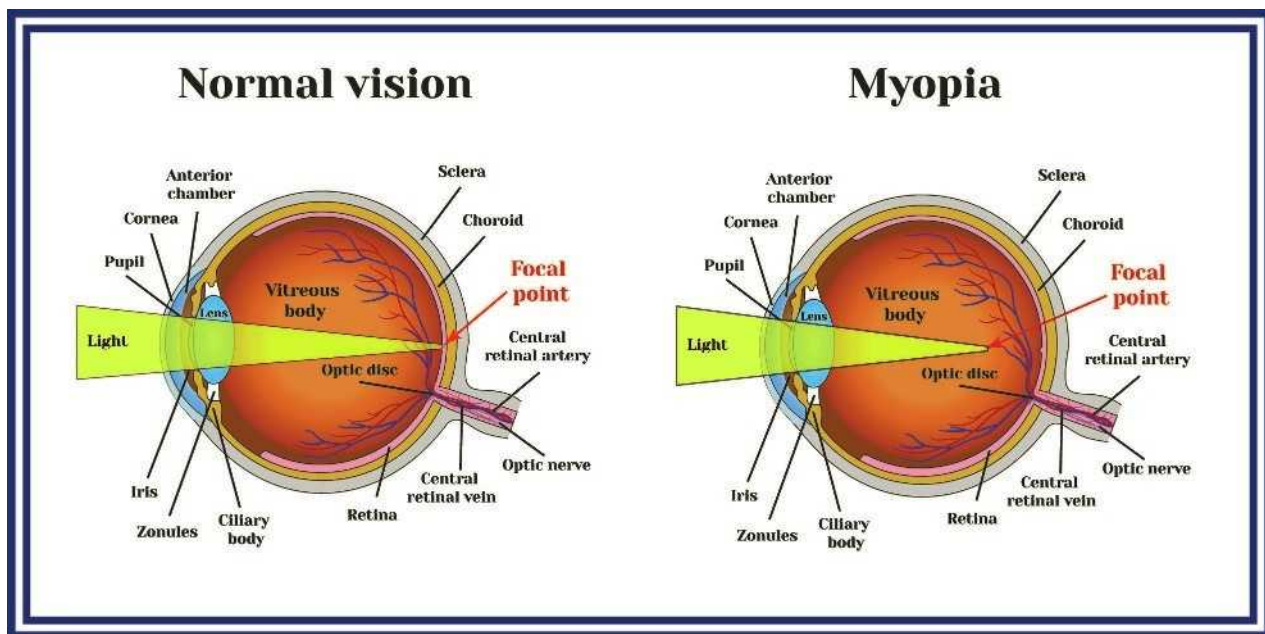
There are many types of myopia. Some common types include:

- physiologic
- pathologic
- acquired

By far the most common form, physiologic myopia develops in children sometime between the ages of five and ten and gradually progresses until the eye is fully



This illustration compares the difference between a normal eye shape and light refraction versus a myopic eye. (Gale)



Myopia. (Shutterstock/Mrs_Bazilio)

grown. Physiologic myopia may include refractive myopia (the cornea and lens-bending properties are too strong) and axial myopia (the eyeball is too long). Pathologic myopia is a far less common abnormality. This condition begins as physiologic myopia, but rather than stabilizing, the eye continues to enlarge at an abnormal rate (progressive myopia). This more advanced type of myopia may lead to degenerative changes in the eye (degenerative myopia). Acquired myopia occurs after infancy. This condition may be seen in association with uncontrolled diabetes and certain types of cataracts. Anti-hypertensive drugs and other medications can also affect the refractive power of the lens.

Genetic profile

Eye care professionals have debated the role of genetics in the development of myopia for many years. Some believe that a tendency toward myopia may be inherited, but that the actual disorder results from a combination of environmental and genetic factors. Environmental factors include close work; work with computer monitors or other instruments that emit some light (e.g., electron microscopes, photographic equipment, or lasers); emotional stress; and eye strain. Recent epidemiological data has shown outdoor activity as a key environmental determinant of myopia. Studies in both Singaporean and Australian children correlate more time spent outdoors with less myopic refraction regardless of the indoor or outdoor activity. Twin studies have provided the strongest evidence of the role of heredity in

myopia. The degree of refractive error is seen in monozygotic twins when compared to dizygotic twins.

A variety of genetic patterns for inheriting myopia have been suggested, ranging from a recessive pattern with complete penetrance in people who are homozygotic for myopia to an autosomal dominant pattern; an autosomal recessive pattern; and various mixtures of these patterns. One explanation for this lack of agreement is that the genetic profile of high myopia (defined as a refractive error greater than -6 diopters) may differ from that of low myopia. Some researchers believe that high myopia is determined by genetic factors to a greater extent than low myopia.

The lack of clear consensus concerning the precise role of heredity in myopia may be due to the sensitivity of the human eye to very small changes in its anatomical structure. Since even small deviations from normal structure cause significant refractive errors, it may be difficult to single out any specific genetic or environmental factor as their cause.

Genetic markers and gene mapping

Since 1992, genetic markers that may be associated with genes for myopia have been located on human chromosomes 1, 2, 12, and 18. There is some genetic information on the short arm of chromosome 2 in highly myopic people. Genetic information for low myopia appears to be located on the short arm of chromosome 1, but it is not known whether this information governs the structure of the eye itself or vulnerability to environmental factors.

In 1998, a team of American researchers presented evidence that a gene for familial high myopia with an autosomal dominant transmission pattern could be mapped to human chromosome 18 in eight North American families. The same group also found a second locus for this form of myopia on human chromosome 12 in a large German/Italian family. In 1999, a group of French researchers found no linkage between chromosome 18 and 32 French families with familial high myopia. These findings have been taken to indicate that more than one gene is involved in the transmission of the disorder.

The heritability of high-grade myopia has been confirmed. Multiple high-grade myopia genetic loci have been identified, and confirmatory studies identifying high-grade and moderate myopia loci have also occurred. By 2021, more than 125 myopia susceptibility genes were documented in “Online Mendelian Inheritance in Man” (OMIM).

A study published in 2020 identified some previously unknown genetic mechanisms involved with myopia. Researchers identified about 1,000 genetic variations in nearly 450 genes that likely contribute to, or account for, many cases of moderate or severe myopia. Interestingly, genes involved in governing circadian rhythm (sleep and wake cycles) and genes responsible for pigmentation of the eyes, skin, and hair are also involved in myopia. Identification of these genetic markers and use of a polygenic risk score may help to predict which children will develop myopia and may provide clues about how to prevent and treat myopia.

Family studies

It has been known for some years that a family history of myopia is one of the most important risk factors for developing the condition. Only 6% to 15% of children with myopia come from families in which neither parent is myopic. In families with one myopic parent, 23% to 40% of the children develop myopia. If both parents are myopic, the rate rises to 33% to 60% for their children. One American study found that children with two myopic parents are six times as likely to develop myopia themselves as children with only one or no myopic parents. The precise interplay of genetic and environmental factors in these family patterns, however, is not yet known.

One multigenerational study of Chinese patients indicated that third-generation family members had a higher risk of developing myopia even if their parents were not myopic. The researchers concluded that, at least in China, the genetic factors in myopia have remained constant over the past three generations, while the environmental factors have intensified. The increase in the

percentage of people with myopia over the last 50 years in the United States has led American researchers to the same conclusion.

Demographics

Myopia is the most common eye disorder in humans around the world, reaching epidemic levels. In various reports, incidence frequently varies with age, sex, race, ethnicity, occupation, environment, and other factors. Myopia is more common in Central and Eastern Europe than in Northern Europe, Britain, and the United States. It is also very common in certain populations, such as Chinese, Japanese, Arab, and Jewish groups. Myopia is uncommon in black, Nubian, and Sudanese persons.

Myopia is a leading cause of blindness worldwide and the leading cause of preventable visual impairment in children. In 2020, the prevalence of refractive error in the United States is reported in multiple studies at 30% and is expected to rise to 50% by 2050. It has been reported that the incidence in females is higher, and onset is earlier, than in males and that white people have a significantly higher prevalence of the condition than African Americans. The Chinese and Japanese populations have one of the highest rates of myopia at greater than 50% to 70%.

Other factors that affect the demographic distribution of myopia are income level, education, and residential location. Myopia also appears to be more prevalent among people who perform a great deal of near-distance work for prolonged periods. Other factors, including nutrition, smoking during pregnancy, and exposure to digital screens may increase risk for myopia, but as of 2021, the relationships among these environmental and behavioral factors and myopia remained unclear.

Signs and symptoms

Myopia is caused by an elongation of the eyeball. The oblong (as compared to normal spherical) shape of the myopic eye causes the cornea and lens to focus at a point in front of the retina. A more precise explanation is that there is an inadequate correlation between the focusing power of the cornea and lens and the length of the eye.

People are generally born with a small amount of hyperopia (farsightedness), but that decreases as the eye grows, and myopia does not become evident until later. This change is one reason why some researchers think that myopia is an acquired, rather than inherited, trait.

The symptoms of myopia are blurred distance vision, eye discomfort, squinting, and eye strain.

KEY TERMS

Accommodation—The ability of the lens to change its focus from distant to near objects. It is achieved through the action of the ciliary muscles that change the shape of the lens.

Cornea—The transparent structure of the eye over the lens that is continuous with the sclera in forming the outermost, protective, layer of the eye.

Diopter (D)—A unit of measure for describing refractive power.

Epi-LASIK—A surgical procedure that uses a blunt, plastic oscillating blade called an epithelial separator to cut a flap in the cornea.

Laser-assisted in-situ keratomileusis (LASIK)—A surgical procedure that uses a cutting tool and a laser to modify the cornea and correct moderate to high levels of myopia.

Laser-assisted sub-epithelial keratomileusis (LASEK)—A surgical procedure in which the epithelium is loosened on the corneal surface. The loosened epithelium is then reflected away from the cornea, and laser ablation performed.

Lens—The transparent, elastic, curved structure behind the iris (colored part of the eye) that helps to focus light on the retina.

Optic nerve—A bundle of nerve fibers that carries visual messages from the retina in the form of electrical signals to the brain.

Orthokeratology—A method of reshaping the cornea using a contact lens. It is not considered a permanent method to reduce myopia.

Peripheral vision—The ability to see objects that are not located directly in front of the eye. Peripheral vision allows people to see objects located on the side or edge of their field of vision.

Photorefractive keratectomy (PRK)—A procedure that uses an excimer laser to make modifications to the cornea and permanently correct myopia.

Radial keratotomy (RK)—A surgical procedure involving the use of a diamond-tipped blade to make several spoke-like slits in the peripheral (non-viewing) portion of the cornea to improve the focus of the eye and correct myopia by flattening the cornea.

Refraction—The bending of light rays as they pass from one medium through another. Used to describe the action of the cornea and lens on light rays as they enter the eye. Also used to describe the determination and measurement of the eye's focusing system by an optometrist or ophthalmologist.

Refractive eye surgery—A general term for surgical procedures that can improve or correct refractive errors by permanently changing the shape of the cornea.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Visual acuity—The ability to distinguish details and shapes of objects.

Diagnosis

The diagnosis of myopia is typically made during the first several years of elementary school, when a teacher notices a child having difficulty seeing the chalkboard, reading, or concentrating. The teacher or school nurse often recommends an eye examination by an ophthalmologist or optometrist. An ophthalmologist—MD or DO (Doctor of Osteopathy)—is a medical doctor trained in the diagnosis and treatment of eye problems. Ophthalmologists also perform eye surgery. An optometrist (OD) diagnoses, manages, and/or treats eye and visual disorders. In many states, optometrists are licensed to use diagnostic and therapeutic drugs.

A patient's distance vision is tested by reading letters or numbers on a chart posted a set distance away (usually 20 ft. [7 m]). The doctor asks the patient to view images through a

variety of lenses to obtain the best correction. The doctor also examines the inside of the eye and the retina. An instrument called a slit lamp is used to examine the cornea and lens. The eyeglass prescription is written in terms of diopters (D), which measure the degree of refractive error. Mild to moderate myopia usually falls between -1.00D and -6.00D. Normal vision is commonly referred to as 20/20 to describe the eye's focusing ability at a distance of 20 ft. (7 m) from an object. For example, 20/50 means that a myopic person must stand 20 ft. away from an eye chart to see what a normal person can see at 50 ft. (7 m). The larger the bottom number is, the greater the degree of myopia.

Treatment and management

People with myopia have three main options for treatment: optical devices, such as specialized eyeglasses

and contact lenses; refractive eye surgery; and intraocular surgical procedures. Recent clinical trials have tested new therapeutic options to slow the progression of myopia in children. Treatments tested include atropine eye drops and pirenzepine 2% gel. Atropine is a non-selective muscarinic antagonist that clinical trials showed significantly reduced the progression of myopia by 77%. Pirenzepine gel is a selective M-1 antagonist for the M1 muscarinic receptor that negates the unwanted side effects of atropine (mydriasis and cycloplegia) and when applied twice daily, it can reduce the progression of myopia by 50%. However, regulatory and financial challenges have plagued the development of atropine drops, and studies of pirenzepine have ended.

Optical devices

EYEGLASSES. Eyeglasses are the most common method used to correct myopia. Concave glass or plastic lenses are placed in frames worn in front of the eyes. The lenses are ground to the thickness and curvature specified in the eyeglass prescription. The lenses cause the light rays to diverge so that they focus further back, directly on the retina, producing clear distance vision.

CONTACT LENSES. Contact lenses are a second option for treatment. They are extremely thin round discs of plastic that are worn on the eye in front of the cornea. Although there may be some initial discomfort, most people quickly grow accustomed to contact lenses. Hard contact lenses, made from a material called PMMA, are virtually obsolete. Rigid gas permeable lenses (RGP) are made of plastic that holds its shape but allows the passage of some oxygen into the eye. Some believe that RGP lenses may halt or slow the progression of myopia because they maintain a constant, gentle pressure that flattens the cornea. In 2004, results of a NEI-sponsored study called the Contact Lens and Myopia Progression (CLAMP) Study, were published. Researchers found that RGP contact lenses slowed the progression of myopia in young children. They also found that RGP contact lenses did not slow the growth of the eye, responsible for the majority of myopia in children. Instead of slowing the growth of the eye, RGP lenses kept the cornea from changing shape more than soft contact lenses did.

Soft contact lenses are made of flexible plastic and can be up to 80% water. Soft lenses offer increase comfort and the advantage of extended wear; some can be worn continuously for up to one week. While oxygen passes freely through soft lenses, bacterial contamination and other problems can occur, requiring replacement of lenses on a regular basis. It is very important to follow the cleaning and disinfecting regimens prescribed, because protein and lipid buildup can occur on the lenses, causing discomfort and/or increasing the risk of infection.

Contact lenses offer several benefits over glasses, including better vision, less distortion, clear peripheral vision, and cosmetic appeal. In addition, contacts will not fog up from perspiration or changes in temperature.

Refractive eye surgery

For people who find glasses and contact lenses inconvenient or uncomfortable, and who meet selection criteria in terms of age, degree of myopia, or general health, refractive eye surgery is a third treatment alternative. Radial keratotomy was the first such procedure developed, but it has been replaced since the mid-1990s by photorefractive keratectomy (PRK), laser-assisted in-situ keratomileusis (LASIK), Epi-LASIK, and laser-assisted sub-epithelial keratomileusis (LASEK). Refractive eye surgery improves myopic vision by permanently changing the shape of the cornea so that light rays focus properly on the retina. These procedures are performed on an outpatient basis and generally take 10 to 30 minutes.

PHOTOREFRACTIVE KERATECTOMY (PRK). PRK involves the use of a computer to measure the shape of the cornea. Using these measurements, the surgeon uses a computer-controlled excimer laser to make modifications to the cornea. The PRK procedure flattens the cornea by vaporizing small amounts of tissue from the cornea's surface, thereby improving the cornea's refractive properties in focusing light on the retina. The ultra-thin, outer layer of the eye (epithelium) is removed completely by laser energy during the PRK procedure, and it eventually grows back. PRK was approved by the Food and Drug Administration (FDA) for myopia in 1995, and the first excimer lasers used to perform PRK have been improved significantly in terms of size, efficiency, and accuracy. PRK can treat mild to moderate forms of myopia.

LASER-ASSISTED IN-SITU KERATOMILEUSIS (LASIK). LASIK has been approved by the FDA for several different laser platforms. About five million procedures have been performed in the United States since the approval of the excimer laser for refractive surgery in late 1995. It is recommended for moderate to severe cases of myopia. LASIK is perhaps best thought of as PRK performed under a flap instead of on the corneal surface. The flap is flipped back to expose the inner layers of the cornea. The cornea is treated with a laser to change the shape and focusing properties, and then the flap is replaced. For myopic LASIK ablations, most of the laser energy is directed at the center of the treatment zone, and the central cornea is thus flattened.

LASER-ASSISTED SUB-EPITHELIAL KERATOMILEUSIS (LASEK). In a LASEK procedure, the epithelium is chemically loosened using dilute alcohol on the corneal surface. The loosened epithelium is then reflected away from the

cornea, and laser ablation is performed. The procedure preserves the extremely thin epithelial layer by lifting it from the eye's surface before using a laser for reshaping. After the LASEK procedure, the epithelium is replaced on the eye's surface.

EPI-LASIK. In Epi-LASIK, the surgeon uses a blunt, plastic oscillating blade called an epithelial separator to cut a flap in the cornea. Instead of the alcohol used in LASEK to loosen the epithelial sheet, the epithelial separator is used to separate the sheet from the eye. This avoids the possibility of an adverse reaction from the alcohol. Because it is more difficult to create the epithelial flap in people with steeper corneas (who have higher amounts of myopia), the procedure is considered more appropriate for people with less-steep corneas (who have low myopia).

Intraocular surgical procedures

These procedures involve extraction of the clear lens with or without lens implantation and the use of intraocular lens (IOL) implants. IOLs have been used since 1999 to correct large refractive errors in myopia. An IOL is a microscopic lens that can be placed inside the eye to correct certain vision problems. For patients who are extremely nearsighted and may have contraindications to LASIK, an IOL may be implanted in front of the iris to correct their distance vision and provide normal focusing ability and near vision. Although IOLs are intended to be permanent, the procedure is reversible.

Risks

All of these surgical procedures carry risks. The most serious are corneal scarring, corneal rupture, infection, flap problems, dry eye, cataracts, and loss of vision. The National Eye Institute (NEI) warns that before agreeing to refractive surgery, patients should get a clear picture of what they can expect. Surgeons should explain the risks and possible complications as well as potential side effects.

Since refractive eye surgery does not guarantee 20/20 vision, it is important to have realistic expectations before choosing this treatment. For example, the American Academy of Ophthalmology (AAO) reports that nine out of ten patients achieve 20/20 vision, but 20/20 does not always mean perfect vision. Detailed, precise vision may be slightly diminished. Even if the patient gains near-perfect vision, irritating side effects are also possible, such as post-operative pain, poor night vision, variation in visual acuity, light sensitivity and glare, and optical distortion. Finally, refractive eye surgeries are considered elective procedures and are rarely covered by insurance plans.

QUESTIONS TO ASK YOUR DOCTOR

- What are the treatment options for myopia?
- How do I choose between contact lenses and glasses?
- If I have other eye conditions, how can I best manage them together?
- Am I a candidate for eye surgery?

Alternative treatments

Some eye care professionals recommend treatments to help improve circulation, reduce eye strain, and relax the eye muscles. It is possible that by combining exercises with changes in behavior, the progression of myopia may be slowed or prevented. Alternative treatments include visual therapy (also referred to as vision training or eye exercises); discontinuing close work; reducing eye strain (taking a rest break during periods of prolonged near-vision tasks); and wearing bifocals to decrease the need to accommodate when doing close-up work.

Clinical trials

As of 2021, there were more than 140 clinical trials on myopia planned, or underway, sponsored by the National Institutes of Health (NIH) and other agencies. Clinical trial information is constantly updated by NIH, and the most recent information on myopia trials can be found at <http://clinicaltrials.gov>.

Prognosis

Glasses and contact lenses can (but not always or completely) correct the patient's vision to 20/20. Refractive surgery can make permanent improvements for the right candidates.

While the genetic factors that influence the transmission and severity of myopia cannot be changed, some environmental factors can be modified. They include spending time outdoors, reducing close work, reading and working in good light, taking frequent breaks when working at a computer or microscope for long periods of time, maintaining good nutrition, and practicing visual therapy (when recommended).

Eye strain can be prevented by using sufficient light for reading and close work, and by wearing corrective lenses as prescribed. Everyone should have regular eye examinations to see whether their prescription has changed or whether any other problems have developed. This

is particularly important for people with high (degenerative) myopia who are at a greater risk of developing retinal detachment, retinal degeneration, glaucoma, or other problems.

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- American Academy of Ophthalmology, P.O. Box 7424, San Francisco, CA 94120-7424, (415) 561-8500, (415) 561-8533, <http://www.aao.org>
- American Optometric Association (AOA), 243 N. Lindbergh Boulevard, St. Louis, MO 63141-7881, (800) 365-2219, <http://www.aoa.org>
- National Eye Institute (NEI), Information Office, 31 Center Drive MSC 2510, Bethesda, MD 20892-3655, (301) 496-5248, 2020@nei.nih.gov, <http://www.nei.nih.gov>

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Myotonia atrophica see **Myotonic dystrophy**

Myotonia congenita

Definition

Myotonia congenita (MC) is a genetic disorder of the muscle fiber membranes in skeletal muscle. It is classified as a channelopathy, because it is caused by the dysfunction of chloride ion channels. The disorder is characterized by muscle hyperexcitability, leading to difficulty relaxing muscles after contracting them (myotonia); muscular stiffness and rigidity; enlargement (hypertrophy) of some muscles or muscle groups; and temporary cramping sensations or weakness in the muscles.

MC has two forms: Thomsen disease (THD), caused by autosomal dominant mutations in the *CLCN1* gene on chromosome 7, and Becker disease, caused by autosomal recessive mutations in the same gene. Thomsen disease is named for a Danish physician, Asmus Julius Thomsen, who had the disease himself, recognized that it is a hereditary disorder when three of his sons developed symptoms of it, and published a description of it in 1876. Becker disease is named for Peter Emil Becker, a German geneticist who identified the autosomal recessive form of myotonia congenita in 1966. Becker disease is the more common and more severe form of MC.

Description

Both forms of MC are marked by difficulty relaxing skeletal muscles after voluntary contraction, by muscle hypertrophy, and by general stiffness of the muscles.

Thomsen disease

In Thomsen disease, the symptoms first appear during infancy through two to three years of age and are most likely to affect the muscles of the hands, legs, tongue, and eyelids. In some cases, patients with Thomsen disease develop spasms of the muscles in the face and trunk. Spasms in the muscles that control the movement of the eyeballs may cause temporary double vision or crossed eyes (strabismus), while myotonia in the muscles of the throat or tongue may cause occasional difficulty in chewing, swallowing, or speaking after a period of silence.

Males with Thomsen disease are generally more severely affected than females, although the severity of symptoms can vary considerably among members of the same family. Women with THD often find that their symptoms are more severe during menstrual periods and pregnancy and are relieved after menopause. Some patients also report that cold weather aggravates the symptoms of Thomsen disease, while warm weather or alcoholic beverages relieve the symptoms. Thomsen

KEY TERMS

Channelopathy—A type of disease caused by disturbances in the function of ion channels or the proteins that regulate them. Channelopathies may be either genetic or acquired later in life.

Congenital—Present at birth.

Hyperexcitability—The abnormally intense response of muscle fiber membranes to stimulation.

Ion channels—Proteins or protein complexes that open or close the flow of ions (atoms or molecules with a positive or negative electrical charge) across cell membranes.

Loss-of-function mutation—Any mutation that causes a gene to lose its ability to encode a protein, either partially or completely.

Malingering—Exaggerating or faking the symptoms of a physical or psychiatric illness in order to avoid work, school, or military service; obtain fraudulent financial compensation; or attract sympathy or attention.

Myotonia—Sustained contraction or delayed relaxation of a muscle following voluntary contraction of that muscle.

Percussion—A technique used in physical diagnosis in which the examiner taps on the surface of the body to determine the condition of the structure beneath the skin. Percussion is used when examining a patient for myotonia congenita to see whether the tapping will cause the muscle beneath the skin to contract.

Warm-up phenomenon—The progressive easing of the myotonic contraction of a muscle (in a patient with myotonia congenita) with repeated voluntary contractions of the muscle.

disease, however, is not progressive, which means that the symptoms do not get worse as the patient grows older, nor do they move from one part of the body to another.

Becker disease

The term “congenital” is something of a misnomer when applied to the Becker form of MC, because the symptoms of this subtype do not appear until later childhood (about age four) or even as late as age 18. The symptoms of Becker disease are more severe than those of Thomsen disease, with myotonia and muscle stiffness becoming progressively worse with age. The muscular symptoms also progress from the legs upward to other

parts of the body in Becker disease, most often to the arms, face, throat, and trunk.

Muscle hypertrophy is usually more marked in Becker disease than in Thomsen disease; paradoxically, muscle weakness and pain (myalgia) are also more common in the Becker form of MC than in Thomsen disease. Patients with Becker disease, however, are not usually affected by exposure to cold.

Genetic profile

Both subtypes of myotonia congenita are caused by loss-of-function mutations in the *CLCN1* gene on the long arm of chromosome 7 at 7q35. A loss-of-function mutation is one in which the gene loses part or all of its ability to encode its protein product. The *CLCN1* gene normally encodes a protein called CIC-1, which is a chloride channel (a specialized protein) that controls the flow of chloride ions into skeletal muscle cells. Under normal circumstances, the contraction and relaxation of muscle cells is coordinated so that the body or its various parts can move smoothly and efficiently. Chloride ions stabilize the electrical charge of muscle cells, preventing them from contracting abnormally. Mutations in the *CLCN1* gene, however, result in alterations in the CIC-1 channel that disrupt the flow of chloride ions into the muscle cells, resulting in the sustained muscle contractions that form the primary symptom of MC.

Thomsen disease differs from Becker disease in its pattern of inheritance, however. It is inherited in an autosomal dominant pattern, which means that only one defective copy of the *CLCN1* is needed for the offspring to develop the symptoms of the disorder, although the severity of the symptoms may vary from one family member to another.

Becker disease is inherited in an autosomal recessive pattern, which means that a child must inherit two copies of a defective *CLCN1* gene, one from each parent, in order to manifest the disease. Becker disease has been reported in a number of consanguineous families, in which marriage between blood relatives increases the risk of inheriting autosomal recessive genetic disorders.

Demographics

Overall, MC is a rare disease, with an estimated worldwide prevalence of one case per million population. It is, however, much more common in northern Scandinavia than in other countries, with an estimated prevalence of one case in every 10,000 people. The Becker subtype of MC is one of 40 disorders designated as a Finnish heritage disease, which means that it is particularly common among ethnic Finns and persons of Finnish ancestry living in Sweden and northwestern Russia.

QUESTIONS TO ASK YOUR DOCTOR

- Have you ever treated a patient with either form of myotonia congenita?
- If so, what treatment(s) did you recommend?
- How effective are medications in treating myotonia congenita?
- What are the chances of our family's having a second child with MC?
- Should other family members be tested for the disorder?

Both forms of MC affect males and females with equal frequency.

Mechanisms

Recessive MC, or Becker disease, is a heritable skeletal muscle disease caused by mutated chloride channels in the muscles that do not work properly. Muscle rapidly cycles between hyper- and hypoexcitability as individual fibers switch from experiencing myotonia (causing stiffness) to the generation of plateau potentials (causing weakness), respectively. The state of the muscle depends on the strength of the signal experienced by the muscle fibers. Mild depolarization triggers myotonia, and more severe depolarization triggers the generation of a plateau potential. Both calcium and sodium ion channels are involved in creating a plateau potential. Sodium channels trigger this state, while calcium channels are responsible for maintaining it.

Signs and symptoms

The most noticeable symptom of MC is myotonia, or inability to relax the muscles after contracting them. Myotonia is most apparent after a period of rest, as when the patient is trying to get out of bed in the morning, arising from a chair, starting to run or walk after sitting or standing still for a period of time, or opening the eyelids after sneezing or blinking. Another common form of myotonia is the inability to relax a hand grip; for example, releasing a handshake or removing the hands from the steering wheel of a car after driving for a period of time.

Myotonia in people with MC may be affected by medications or psychological conditions. Certain diuretics worsen myotonia by lowering the levels of magnesium and calcium in the body, and emotional stress

worsens myotonia by stimulating the release of adrenaline/epinephrine, a hormone involved in the “fight-or-flight” reaction. Persons with MC may find themselves completely unable to move when feeling pressured or upset.

Muscle hypertrophy, found in both forms of MC, refers to the abnormal enlargement of skeletal muscles. It is not unusual for patients with MC to develop a “body builder” appearance, particularly in the muscles of the legs. As noted above, this sign of the disorder is particularly marked in Becker disease.

One distinctive sign of both types of MC is the so-called warm-up phenomenon, first noticed by Julius Thomsen and described in his 1876 report. The warm-up phenomenon refers to the gradual relaxation of a myotonic muscle when the patient intentionally contracts the muscle several times. After a few contractions, the myotonia disappears for a period of several minutes. Several different explanations have been offered for the warm-up phenomenon, but none has been universally accepted.

Diagnosis

Diagnosis of MC is based on a combination of clinical observations, diagnostic testing, and molecular genetic testing.

Thomsen disease is usually diagnosed in infants or young children when the parents or the pediatrician notice such symptoms as gagging or choking on food, stiff movements that appear to be improved when the child repeats them, frequent falls, and difficulty opening the eyes after a crying spell. The pediatrician may take a family history to see whether other family members have reported similar symptoms, and may percuss (thump or tap) the child's arm, finger, or leg muscles to elicit a myotonic response. Another common test that can be done in the doctor's office is to ask the child to grasp an object or the examiner's hand to see how quickly the child can release his or her grip.

Laboratory testing for MC may include electromyography (EMG), a technique for measuring and recording the electrical activity in skeletal muscles by means of electrodes placed on the surface of the skin or inserted into the muscle being tested. One typical EMG finding in patients with MC is repetitive spontaneous electrical activity in the muscles, known as myotonic runs. Another laboratory test that can be used to evaluate patients for MC measures the level of creatine kinase (CK) in the patient's blood serum. Creatine kinase is an enzyme found in elevated levels in the blood when muscle tissue is damaged or inflamed.

The definitive diagnosis of MC is made by molecular genetic testing for mutations in the *CLCN1* gene. About 95% of cases of MC, whether autosomal dominant or autosomal recessive, can be identified by genetic testing.

Treatment and management

There is no cure for MC, but the disorder can usually be managed by a combination of medications, physical therapy, and vocational or psychological counseling. Some patients with very mild symptoms may not require any treatment.

The medication that is most often used to treat the muscle stiffness associated with MC is mexiletine (Mexilitil), a sodium channel blocker that was originally developed to treat heart arrhythmias. Other drugs that are used to treat muscle stiffness in MC include quinine, phenytoin (an anticonvulsant drug), and procainamide. Another antiarrhythmic, tocainide, is used in Europe to treat MC but was taken off the market in the United States. Some patients with MC have been helped by dantrolene, a muscle relaxant, or carbamazepine, another anticonvulsant.

Physical therapy is often beneficial to patients with MC, because the therapist can devise individualized exercises to alleviate myotonia in specific muscle groups or areas of the patient's body.

Patients with MC sometimes need psychological counseling, because the symptoms of the disorder often appear to others as either malingered or acting out. For example, one of Julius Thomsen's three affected sons was accused of draft-dodging when he tried to explain his disability to the military physicians who examined him. It was only after two months of further examinations that the doctors recognized that his symptoms were genuine, and released him from military service.

Prognosis

Neither form of MC is a life-threatening disease or accompanied by intellectual disability; most patients can complete their education, enjoy productive lives, and have normal lifespans. However, patients with MC are at increased risk of falls, particularly when under emotional stress, and may suffer serious injuries or accidental drowning.

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ORGANIZATIONS

Muscular Dystrophy Association (MDA), 161 N. Clark, Suite 3550, Chicago, IL 60606, (800) 572-1717, ResourceCenter@mdausa.org, <http://www.mda.org>

National Institute of Neurological Disorders and Stroke (NINDS), P.O. Box 5801, Bethesda, MD 20824, (301) 496-5751 or (800) 352-9424, <https://www.ninds.nih.gov/>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 263-9938, <http://rarediseases.org>

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Myotonic dystrophy

Definition

Myotonic dystrophy is a progressive disease in which the muscles are weak and are slow to relax after contraction.

Description

There are two types of myotonic dystrophy, type 1 (DM1) and type 2 (DM2). Myotonic dystrophy, type 1 is also called Steinert's disease. Both types are inherited in an autosomal dominant manner meaning the disease can affect both males and females. Symptoms may appear at any time from infancy to adulthood. DM causes general weakness, usually beginning in the muscles of the hands, feet, neck, or face. It slowly progresses to involve other muscle groups, including the heart. DM affects a wide variety of other organ systems as well.

A severe form of DM, congenital myotonic dystrophy, may appear in newborns of mothers who have DM. Congenital means that the condition is present from birth.

Type 2 myotonic dystrophy is also known as Proximal Myotonic Myopathy (PROMM). The symptoms of DM2 include myotonia, muscle weakness, muscle pain, and stiffness. Other symptoms of this form of myotonic dystrophy include testicular failure, insulin-insensitive type 2 diabetes, cataracts, and some types of cardiac abnormalities.

Genetic profile

DM1 is caused by a mutation in a gene called myotonic dystrophy protein kinase (*DMPK*). The *DMPK* gene is located on chromosome 19. When there is a mutation in this gene, a person develops DM1. The specific mutation that causes DM1 is called a trinucleotide repeat expansion.

DM2 is caused by a mutation in the *CNBP* gene located on chromosome 3. The specific mutation that

causes DM2 is a complex expansion of CCTG nucleotides in the *CNBP* gene. The mean number of CCTG repeats that causes DM2 is 5,000, with a range between 75 to over 11,000.

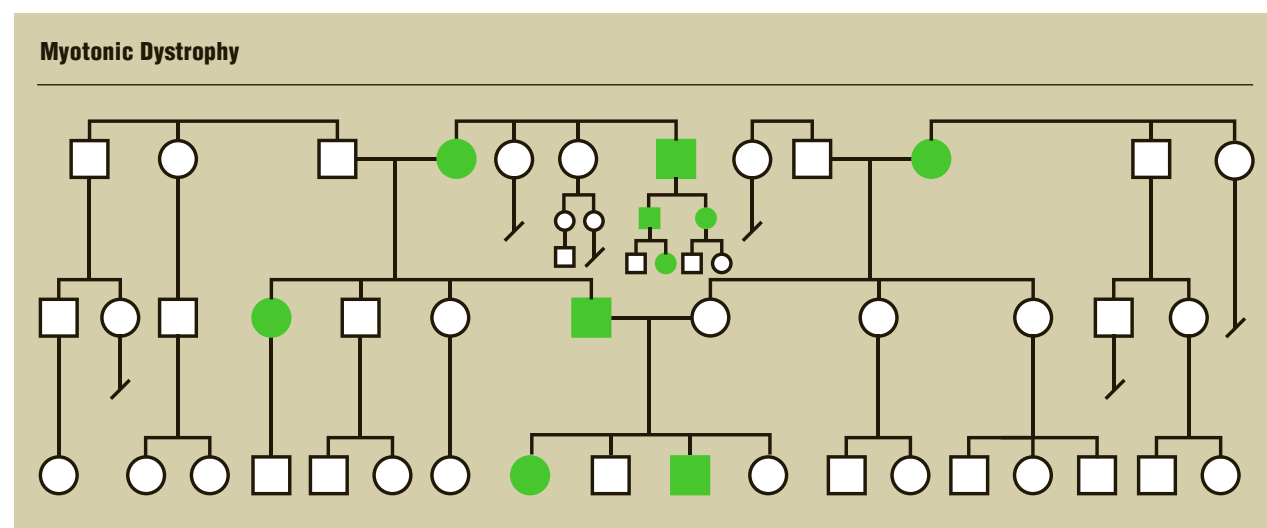
Trinucleotide repeats

In the *DMPK* gene, there is a section of the genetic code where the three letters CTG are repeated a certain number of times. In people who have DM1, these letters are repeated too many times—more than 34 times—and thus this section of the gene is too big. This enlarged section of the gene is called a trinucleotide repeat expansion.

People who have repeat numbers in the normal range will not develop DM1 and cannot pass it to their children. Having more than 50 repeats causes DM1. People who have 35–49 CTG repeats have a premutation and will not develop DM1 but can pass DM1 onto their children. Having repeat numbers greater than 1,000 causes congenital myotonic dystrophy (the most severe form of DM1).

In general, the more repeats in the affected range that someone has, the earlier the age of onset of symptoms and the more severe the symptoms. However, this is a general rule. It is not possible to look at a person's repeat number and predict at what age he or she will begin to have symptoms or how the condition will progress.

Exactly how the trinucleotide repeat expansion causes myotonia, the inability to relax muscles, is not yet understood. The disease somehow blocks the flow of electrical impulses across the muscle cell membrane. Without proper flow of charged particles, the



Myotonic Dystrophy: pedigree analysis chart (Gale)

Relationship between phenotype and CTG repeat length in myotonic dystrophy

Phenotype	Clinical signs	CTG repeat size	Age of onset (Years)	Average age of death (Years)
Premutation	None	38 to ~49	Normal	Normal
Mild	Cataracts	50 to ~150	20–70	60—normal
Classical	Mild myotonia	~100 to ~1000–1500	10–30	48–55
	Weakness			
	Myotonia			
	Cataracts			
	Balding			
	Cardiac arrhythmia	~1000 to 2000	Birth to 10	45
	Others			
	Infantile hypotonia			
	Respiratory deficits			
	Mental retardation			

(Gale)

muscle cannot return to its relaxed state after it has contracted.

Anticipation

Sometimes when a person who has repeat numbers in the affected or premutation range has children, the expansion grows larger. This is called anticipation. A larger expansion can result in an earlier age of onset in children than in their affected parent. Anticipation happens more often when a mother passes DM1 onto her children than when it is passed from the father. Occasionally repeat sizes stay the same or even get smaller when they are passed to a person's children.

As of July 2015, it was still debated whether anticipation occurs with DM2. In addition, at this time, it is believed that there is no congenital form of DM2.

Inheritance

DM is inherited through autosomal dominant inheritance. This means that equal numbers of males and females are affected. It also means that an individual only needs one gene mutation in order to be affected. Since a person only passes one copy of each gene on to his or her children, there is a 50% or one in two chance that a person who has DM will pass it on to each of his or her children. This percentage is not changed by results of other pregnancies. A person with a premutation also has a 50%, or one in two, chance of passing the altered gene on to each of his or her children. However, whether or not his or her children will develop DM1 depends on whether the trinucleotide repeat becomes further expanded. A person who has repeat numbers in the normal range cannot pass DM1 onto his or her children.

Demographics

DM occurs in about 1 in 8,000 to 1 in 20,000 people and has been described in people from all over the world. It is unknown which percentage of myotonic dystrophy cases are type 1 versus type 2.

Signs and symptoms

There are three forms of DM1: mild DM1, classic DM1, and congenital DM1. The severity of symptoms in each form of DM1 varies between affected individuals with the same form, and not everyone will have all of the symptoms listed for each form.

Mild DM1

This form of DM1 causes weakness and delayed muscle relaxation called myotonia as well as cataracts and muscle weakness.

Classic DM1

Symptoms of classic DM1 include facial weakness and a slack jaw, drooping eyelids called ptosis, and muscle wasting in the forearms and calves. A person with DM has difficulty relaxing his or her grasp, especially in the cold. DM affects the heart muscle, causing irregularities in the heartbeat. It also affects the muscles of the digestive system, causing constipation and other digestive problems. DM may cause cataracts, retinal degeneration, low IQ, frontal balding, skin disorders, atrophy of the testicles, and diabetes. It can also cause sleep apnea—a condition in which normal breathing is interrupted during sleep. DM increases the need for sleep and decreases motivation. Severe disabilities do not set in until about 20 years after symptoms begin. Most people with myotonic dystrophy maintain the ability to walk, even late in life.

KEY TERMS

Electrocardiogram (ECG, EKG)—A test that uses electrodes attached to the chest with an adhesive gel to transmit the electrical impulses of the heart muscle to a recording device.

Electromyography (EMG)—A test that uses electrodes to record the electrical activity of muscle. The information gathered is used to diagnose neuromuscular disorders.

Muscular dystrophy—A group of inherited diseases characterized by progressive wasting of the muscles.

Sleep apnea—Temporary cessation of breathing while sleeping.

Trinucleotide repeat expansion—A sequence of three nucleotides that is repeated too many times in a section of a gene.

Congenital DM1

A severe form of DM, congenital myotonic dystrophy, may appear in newborns of mothers who have DM1. Congenital myotonic dystrophy is marked by severe weakness, poor sucking and swallowing responses, respiratory difficulty, delayed motor development, and intellectual disability. Death in infancy is common in this type.

Some people who have a trinucleotide repeat expansion in their *DMPK* gene do not have symptoms or have very mild symptoms that go unnoticed. It is not unusual for a woman to be diagnosed with DM after she has an infant with congenital myotonic dystrophy.

Myotonic dystrophy type 2 (DM2) has very similar symptoms as DM1 with most affected individuals presenting with complaints of muscle weakness. Affected individuals often have difficulties climbing stairs and standing up from a seated position. Other symptoms of DM2 include difficulties releasing a tightened fist, known as myotonia or sustained muscle contraction. Similar to DM1, individuals with DM2 may develop diabetes because of this condition and be at risk for serious heart complications, either cardiac conduction problems or cardiomyopathy. Cataracts are another symptom of DM2. Males who have this form of myotonic dystrophy may also be diagnosed with low testosterone or low sperm count, both of which can cause infertility.

Predictive testing

It is possible to test people at risk for developing DM1 and DM2 before they are showing symptoms to see

whether they inherited an expanded nucleotide repeat. This is called predictive testing. Predictive testing cannot determine the age of onset that someone will begin to have symptoms, or the course of the disease.

Diagnosis

Diagnosis of DM is not difficult once the disease is considered. However, the true problem may be masked because symptoms can begin at any age, can be mild or severe, and can occur with a wide variety of associated complaints. Diagnosis of DM begins with a careful medical history and a thorough physical exam to determine the distribution of symptoms and to rule out other causes. A family history of DM or unexplained weakness helps to establish the diagnosis.

A definitive diagnosis of DM1 and DM2 is done by genetic testing, usually by taking a small amount of blood. The DNA in the blood cells is examined, and the number of repeats in the *DMPK* gene is determined. Various other tests may be done to help establish the diagnosis, but only rarely would other testing be needed. An electromyogram (EMG) is a test used to examine the response of the muscles to stimulation. Characteristic changes are seen in DM that help distinguish it from other muscle diseases. Removing a small piece of muscle tissue for microscopic examination is called a muscle biopsy. DM is marked by characteristic changes in the structure of muscle cells that can be seen on a muscle biopsy. An electrocardiogram could be performed to detect characteristic abnormalities in heart rhythm associated with DM. These symptoms often appear later in the course of the disease.

Prenatal testing

Testing a pregnancy to determine whether an unborn child is affected is possible if genetic testing in a family has identified a *DMPK* mutation. This can be done at 10–12 weeks gestation by a procedure called chorionic villus sampling (CVS), which involves removing a tiny piece of the placenta and analyzing DNA from its cells. It can also be done by amniocentesis after 15 weeks gestation by removing a small amount of the amniotic fluid surrounding the baby and analyzing the cells in the fluid. Each of these procedures has a small risk of miscarriage associated with it, and those who are interested in learning more should check with their doctor or genetic counselor. Prenatal testing for DM2 is only available if the disease-causing mutation has already been identified in an affected individual.

Another procedure, called preimplantation diagnosis, allows a couple to have a child that is unaffected with the genetic condition in their family.

QUESTIONS TO ASK YOUR DOCTOR

- Please explain the genetic basis for myotonic dystrophy.
- How is myotonic dystrophy like muscular dystrophy, and how is it different?
- What are the stages in the progression of myotonic dystrophy over a period of years?
- What are the most serious long-term medical consequences associated with myotonic dystrophy?
- What are the similarities and differences between myotonic dystrophy type 1 and myotonic dystrophy type 2?

Treatment and management

Myotonic dystrophy cannot be cured, and no treatment can delay its progression. However, many of the symptoms it causes can be treated. Physical therapy can help preserve or increase strength and flexibility in muscles. Ankle and wrist braces can be used to support weakened limbs. Occupational therapy is used to develop tools and techniques to compensate for loss of strength and dexterity. A speech-language pathologist can provide retraining for weakness in the muscles controlling speech and swallowing.

Irregularities in the heartbeat may be treated with medication or a pacemaker. A yearly electrocardiogram is usually recommended to monitor the heartbeat. Diabetes mellitus in DM is treated in the same way that it is in the general population. A high-fiber diet can help prevent constipation. Sleep apnea may be treated with surgical procedures to open the airways or with nighttime ventilation. Treatment of sleep apnea may reduce drowsiness. Lens replacement surgery is available when cataracts develop. Pregnant woman should be followed by an obstetrician familiar with the particular problems of DM because complications can occur during pregnancy, labor, and delivery.

Wearing a medical bracelet is advisable. Some emergency medications may have dangerous effects on the heart rhythm in a person with DM. Adverse reactions to general anesthesia may also occur.

Prognosis

The course of myotonic dystrophy varies. When symptoms appear earlier in life, disability tends to become more severe. Occasionally people with DM may

require a wheelchair later in life. Children with congenital DM usually require special educational programs and physical and occupational therapy. For both types of DM, respiratory infections pose a danger when weakness becomes severe.

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"Myotonic Dystrophy." NORD. <https://rarediseases.org/rare-diseases/dystrophy-myotonic/> (accessed July 9, 2021).

ORGANIZATIONS

Muscular Dystrophy Association (MDA), 222 S. Riverside Plaza, Suite 1500, Chicago, IL 60606, (800) 572-1717, mda@mdausa.org, <http://www.mda.org>

Myotonic Dystrophy Family Registry (MDFR), (602) 435-7496, Coordinator@myotonicregistry.org, myotonicregistry.org

National Registry of Myotonic Dystrophy and FSHD Patients and Family Members, 601 Elmwood Ave., Box 673, Rochester, NY 14642, (888) 925-4302, (585) 273-1255, dystrophy_registry@urmc.rochester.edu

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Myotubular myopathy

Definition

Myotubular myopathy (MTM) belongs to a rare group of developmental disorders of voluntary muscle called congenital myopathies that present as a "floppy baby" syndrome. This is a genetically inherited disorder with various abnormalities in muscle fiber development, muscle tone, and contraction. MTM refers to the pathological finding of muscle fibers with centrally located nuclei resembling the myotubule stage of muscle development.

Description

This condition is also known as centronuclear myopathy (CNM), X-linked MTM (MTM1 or XLMTM),

pericentronuclear myopathy, or type I fiber hypotrophy with central nuclei. It is primarily caused by defective maturation of the muscle. Spiro first described this disorder in 1966. The *myotubularin* gene was identified in 1996.

Muscle fibers normally undergo a complicated series of maturational changes before becoming fully functional normal adult muscle fibers. The myotubule stage is an intermediate state in the fiber maturational process. It is seen normally only in an 8- to 20-week-old fetus and is characterized by central nuclei. In MTM, the maturation is arrested at this stage, and the protein machinery of the muscle fiber needed for contraction is not fully formed. Muscles of patients with MTM thus show an overabundance of immature, poorly functional myotubular fibers.

MTM has different modes of inheritance, resulting in a wide variability of symptom onset (birth to early adulthood) and rate of symptom progression. Some researchers classify CNM and MTM as two extreme ends of a spectrum, with CNM being the milder form. Disability arises due to weakness of voluntary muscles and respiratory difficulty, progressing to death.

Genetic profile

There are three types of MTM, based on the mode of inheritance.

X-linked MTM (MTM1)

This is the most common form and is inherited usually in an X-linked recessive fashion, although *de novo* (new) mutations can occur rarely. It is due to a mutation in the myotubularin, or *MTM1*, gene that occurs on the long arm of the X chromosome at locus Xq27.3-q28. Another related gene, called *MTMRI*, is also found on the X chromosome. About 150 types of myotubularin mutations have been identified, and depending on the type, the severity of disease expression varies. Mutations that truncate the gene lead to severe or lethal disease expression. Mutations that delete part of the gene or cause misreading of the gene cause less severe disease. The gene encoding for the myotubularin protein is widely expressed, not just in the muscle. The relationship between the gene product and the disease is still being investigated.

Each cell has one pair of sex chromosomes. The female has two copies of the X chromosome, one inherited from each parent, while the male has only one X chromosome inherited from the mother and the Y chromosome inherited from the father. A mother who carries one abnormal X chromosome containing the myotubularin mutation has a 50% chance of passing it to each of her offspring. If the daughter inherits the mutation, she may not exhibit any symptoms because she has an extra normal copy; this makes her a

carrier. However, a son who inherits the mutation will express the disease because he cannot compensate for the mutated gene carried on his single X chromosome. If an affected male child has other affected male siblings, about 90% of the time the abnormal gene has been inherited from the mother in an X-linked fashion. If there are no other affected male siblings, then it is most likely a *de novo* mutation. Father-to-son transmission is not possible in *MTM1*.

Carriers of X-linked MTM

Carriers are usually females who have an abnormal gene on one of their X chromosomes. They usually do not express the disease due to compensation from the normal copy. Skewed inactivation of the X chromosome containing the normal gene leads to milder disease expression.

Autosomal dominant MTM

In this mode of inheritance, one copy of another myotubularin gene (*MTMR2*, *MTMR3*) is abnormal on an autosome, chromosome 12. Each cell has two chromosomes 12 carrying the myotubularin gene, and there are two alternate forms (alleles) in which the gene can exist. Therefore, four possible combinations of alleles can exist for this gene. If a person has one normal and one abnormal allele and expresses the normal allele, the individual will have the autosomal dominant form of MTM. Both males and females are equally affected, and the disease is passed on from generation to generation. There will usually be one affected person in each generation, and each child has a 50% chance of inheriting the abnormal gene. Father-to-son transmission is possible.

Autosomal recessive MTM

This can occur in three ways. The affected person can have two abnormal alleles of the myotubularin gene or can have two different types of abnormal alleles. Finally, the affected person can have one normal and one abnormal allele and express the abnormal allele. Males and females are affected equally. Some ethnic predilections occur due to consanguinity where each parent of an affected child is a non-expressing carrier with both a normal and an abnormal allele. Therefore, each of their children has a 25% chance of being affected and a 50% chance of being a non-expressing carrier.

Demographics

MTM is a rare condition; accurate estimates are unavailable. Approximate estimates in 2014 for X-linked MTM were estimated to be 1 in 50,000 newborn males. Unlike other congenital myopathies, there is a relatively high incidence in Africans.

KEY TERMS

Allele—One of two or more different genes encoding specific and inheritable characteristics that occupy corresponding locations on a pair of chromosomes.

Amniotic fluid—Fluid contained in a sac within the uterus that surrounds and protects the fetus during its development.

Autosomal—Relating to any chromosomes besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Carrier—An individual who possesses an unexpressed abnormal gene of a recessive genetic disorder.

Contracture—An abnormal and usually permanent shortening and contraction of a muscle or tendon that causes a deformity or subnormal range of movement.

Creatine kinase (CK)—An enzyme that is normally found in the skeletal or voluntary muscle and cardiac muscle; very high levels in the blood usually indicate breakdown of either heart or voluntary muscle.

Cryptorchidism—Failure of descent of the testis from the abdominal cavity into the scrotum.

De novo—Latin term for “new.”

Dolicocephaly—Elongated and narrow skull shape due to premature closure of the sagittal suture that runs from the forehead to the back of the skull.

Electromyography—A test that assesses the activity of the muscles and the nerves that supply the muscles; one part of the test involves passing electrical current through the nerves and studying the response of the muscles to it, while the other part involves studying muscle activity by inserting a thin needle into it.

G-tube—A gastrostomy tube, which is inserted surgically into the stomach and used for feeding and for administering medications.

Hydrocephalus—The excess accumulation of cerebrospinal fluid around the brain, often causing enlargement of the head.

Hypotonia—Low or poor muscle tone, resulting in floppy limbs.

Linkage analysis—A method of finding mutations based on their proximity to previously identified genetic landmarks.

Lordosis—An abnormal curvature of the spine in which the lumbar, or lower section, is excessively curved (also known as pigeon chest).

Myopathy—Any abnormal condition or disease of the muscle.

Myotubule—An intermediate stage in muscle fiber development, where the fiber is tubular with a centrally placed nucleus, instead of a peripheral eccentric nucleus.

Polyhydramnios—A condition in which there is too much fluid around the fetus in the amniotic sac.

Ptosis—Drooping of the upper eyelid.

Pulmonologist—A physician who specializes in lung diseases.

Scoliosis—Abnormal curvature of the spine, usually defined as greater than ten degrees to the right or left as the doctor faces the patient.

Skewed inactivation—Random inactivation of either the paternally or maternally derived X chromosome in the female, also called lyonization, occurring early in embryonic development.

Spherocytes—Abnormal spherically shaped red blood cells caused by a disorder in the cell membrane; normally, the red blood cell is biconcave in shape.

Stent—A tubular device made of metal or plastic that is inserted into a body duct or tube to prevent collapse, blockage, or overgrowth.

Tendon reflex—Reflex contraction of the muscle that is observed by tapping on its tendon.

Tracheostomy—An opening surgically created in the trachea (windpipe) through the neck to improve breathing.

Signs and symptoms

There is a wide spectrum of clinical features seen in MTM depending on the mode of inheritance, but the basic problem arises from poor muscle tone interfering with posture, locomotion, and muscle strength. In general, the earlier the symptoms present, the more severe and progressive the disorder.

X-linked MTM

This is the most severe and most studied form, which presents at birth or even prior to birth, typically occurring in males. Mothers who are pregnant with affected boys experience polyhydramnios, which is an excessive amount of amniotic fluid due to decreased fetal swallowing of the fluid. Affected boys also exhibit decreased

movements in utero. Fetal cardiac rhythm disturbances can also occur. Newborn males with MTM have a weak cry, are floppy at birth, have difficulty suckling and swallowing, exhibit severe generalized muscle weakness, and have serious respiratory difficulty. Life-threatening difficulties are caused by respiratory and swallowing problems. In very severe cases, the infants succumb to the disease quite early in the absence of adequate respiratory support, and death can occur within a few days of birth. Intermediate form of X-linked MTM occurs in adolescents who develop severe muscle weakness and become non-ambulatory between early and middle life. Mild forms can present in early adulthood with facial weakness, eye muscle weakness, and mild gait difficulty.

Affected boys have a long slender body with long fingers and toes and appear frail. Length is disproportional to body weight as skeletal growth surpasses muscle growth. This is thought to be a result of endocrine dysfunction leading to rapid skeletal growth. The head can be dolichocephalic (elongated) or enlarged due to hydrocephalus. Other facial features, such as high arched palate, dental abnormalities, puffy or droopy eyelids (ptosis) due to eye muscle weakness, and squint, occur. Poor muscle tone leads to decreased blinking during the day and incomplete eye closure during sleep, causing eye irritation. Speech is soft and nasal. The affected children adopt a frog-leg posture due to hypotonia (decreased muscle tone). Skeletal deformities, such as pigeon-chest, scoliosis, and joint dislocations, also occur due to hypotonia. Tendon reflexes are absent. Over time, contractures occur in the hip, knee, and ankle joints, making walking difficult. Swallowing difficulty leads to drooling with aspiration of oral secretions into the lungs that can result in pneumonia. Intelligence and cognitive development is usually normal unless there has been a significant birth injury or respiratory distress with prolonged lack of oxygen.

Other associated medical problems include spherically shaped abnormal red blood cells (spherocytes), anemia, enlarged spleen, and gallstones. Peliosis hepatis is a disorder in which the liver has large blood-filled cysts that can rupture into the abdominal cavity and cause massive bleeding and death. Some patients have a vitamin K responsive bleeding disorder. Other genital and urinary problems like undescended testes (cryptorchidism) and kidney stones also occur. Constipation can be a result of poor gut motility or overall physical immobility. Hearing and vision are unaffected.

Autosomal dominant MTM

This is the least severe form and tends to affect males twice as often as females. It presents in late childhood or early adulthood and progresses slowly. It is less common

than X-linked MTM. The major problem is proximal muscle weakness in the shoulders and hips with leg cramps. Ptosis, joint contractures, and a mild tremor can also be seen.

Autosomal recessive MTM

This can begin at birth, in late infancy, or in early adulthood, but it is much less severe than X-linked MTM. Females are slightly more affected than males. Common features include weakness of eye muscles and face; thin face with a high, arched palate; hypotonia; mild generalized weakness, including neck, trunk, shoulder, and hip muscles; delayed motor milestones; and respiratory distress. Affected individuals develop a waddling gait due to hip muscle weakness and have lordosis and clubfeet. Infants have a slowly progressive paralysis of eye muscles, loss of facial expression, and continuing limb weakness as they grow. Seizures or blackout spells can occur. Intelligence can be normal, or mental deficiency can occur. This condition progresses slowly and eventually leads to loss of ambulation. Many children are never able to run or participate in games with their peers.

Carriers

These are usually women, and they present with mild facial weakness, spinal deformities such as scoliosis, flat feet, mild muscle weakness, and gait difficulty.

Diagnosis

There is a considerable overlap in symptom severity among the three forms of MTM in affected males. Thus, in a family with a single affected male child, reliance on clinical features alone to diagnose the pattern of inheritance, to predict its prognosis, and to counsel the family regarding the chance of having another affected child becomes difficult. Detailed and thorough family history should be obtained to detect other family members with possible MTM. There is no absolute biochemical, DNA, or pathology test that can tell conclusively the pattern of inheritance in an isolated case. A history of spontaneous abortions or death of male infants in the neonatal period is a clue to X-linked transmission.

Creatine kinase (CK) is an enzyme that indicates muscle breakdown and can be normal or slightly increased. Electromyography (EMG), which involves needle testing of muscle activity, can point to a myopathy without being specific for MTM. Muscle biopsy is diagnostic, whereby a piece of muscle from the thigh or arm is taken and studied under the microscope to highlight the typical central plump nuclei in muscle fibers. The diagnosis depends on demonstrating a large number of muscle fibers with centrally placed nuclei. In X-linked

MTM, all muscles are equally affected and about 50%–80% of the muscle fibers are abnormal. Muscle biopsy can detect 50%–70% of female carriers of X-linked MTM, but the biopsy can also be normal.

Genetic testing can be done in specialized laboratories to detect the common types of myotubularin gene mutations. If no mutation is found on the X chromosome, this means that either the mutation is transmitted autosomally or that it is a mutation that cannot be detected by currently available methods. The mother of a child with X-linked MTM can be tested genetically to see if she is a carrier, as this helps predict the chances of recurrence in a future pregnancy. Testing for X-linked MTM is available on a commercial basis, but testing for autosomal forms is only available through a research study.

Prenatal diagnosis is possible for detecting X-linked MTM by tracing the family history of the disease by a process of linkage analysis, which works only if there is more than one affected male member in the family. This can be done even if the exact type of genetic mutation is not known. Pre-implantation genetic diagnosis (PGD) is a technique whereby testing is done on the embryo and only unaffected embryos are placed back in the uterus for continuation of pregnancy.

Treatment and management

There is no proven treatment to cure or stop progression of MTM, but aggressive supportive measures for swallowing and breathing are warranted to preserve good functional ability, as these have been shown to prolong life expectancy. A team approach, including a neurologist, pulmonologist, orthopedic surgeon, physiatrist, physical therapist, occupational therapist, and geneticist, ensures the best possible therapy.

Tracheostomy tubes and ventilators help with breathing. In some cases, the muscles become stronger with time, and the tubes can be removed. Stents can be used to widen and support floppy airways. Lung infections can be treated with antibiotics. Chest physiotherapy helps to periodically clear lung secretions and decrease the incidence of pneumonia. Nutrients can be fed via oral feeding tubes and G-tubes. There are no special ingredients to be incorporated in the diet, as no supplement has been consistently proven to improve muscle strength and build muscle bulk. Caloric intake should be tailored to the requirements of each individual child.

Physical therapy plays a very important part in maintaining and improving muscle strength, joint flexibility, range of motion, and gait. Care should be taken not to overexert and fatigue the already weak muscles, and a regular exercise program should be devised. Passive stretching, bracing, and surgical-release procedures are

QUESTIONS TO ASK YOUR DOCTOR

- What support for myotubular myopathy can be provided to my child?
- If a genetic disorder seems to run in my family, what are the chances that future children will have this disorder?
- Is genetic testing available to determine my and my partner's genetic carrier status?
- Can it be determined if a current pregnancy has myotubular myopathy?

done to prevent tendon and joint contractures. Bracing or surgery may be needed to correct spinal deformities. The occupational therapist can help in devising adaptive equipment for walking and for other daily activities.

Speech therapy is important to overcome problems with speaking due to poor phonation and articulation. Passy-Muir speaking valves can be used in patients who have a tracheostomy tube. Orthodontic services are needed to correct dental malocclusion. Some children can learn to communicate using sign language, communication assist devices, or high-tech computerized devices. Intelligence is not affected, and therefore these children may even be able to attend regular schools. Artificial tears should be used to prevent dry eyes. Yearly blood tests and liver function tests should be done to monitor the development of anemia and liver malfunction. Folic acid is used when the child has anemia and spherical red blood cells. Appropriate precautions should be taken to avoid bleeding during any major surgery.

Genetic counseling should be sought after a child has been diagnosed with MTM to discuss the prognosis for the child, to help the couple with future reproductive planning, and to help with prenatal diagnosis. The probability of having another affected child varies with the specific mode of inheritance.

Prognosis

Only males are severely affected by X-linked MTM, and prognosis has been historically poor due to early respiratory failure. The children lack enough strength and endurance in the respiratory muscles to withstand respiratory complications such as infections and lung collapse. Death used to occur within one to two years of life, with a mean of five months. Respiratory weakness and frequent pneumonias indicate poor prognosis. Today, with interventions like ventilators and tracheostomy tubes, these complications are

delayed and survival is prolonged. Currently, more than two-thirds of children with MTM survive past the first year of life. In X-linked MTM, contrary to prior thinking, the muscle weakness does not appear to be progressive. Children with autosomal recessive MTM usually survive past infancy. Those with autosomal dominant MTM even survive into late adulthood, and the disease is compatible with a normal life expectancy.

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ORGANIZATIONS

- Genetic Alliance, 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008-2369, (202) 966-5557, (202) 966-8553, info@geneticalliance.org, <http://www.geneticalliance.org>
- Joshua Frase Foundation, PO Box 2041, Ponte Vedra Beach, FL 32004, (904) 607-1358, (904) 273-9818, info@joshuafrase.org
- Muscular Dystrophy Association (MDA), 222 S. Riverside Plaza, Suite 1500, Chicago, Illinois 60606, (800) 572-1717, mda@mdausa.org, <http://www.mda.org>

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Nail-patella syndrome

Definition

Nail-patella syndrome is a genetic disease of the connective tissue that produces defects in the fingernails, knee caps, and kidneys.

Description

Nail-patella syndrome is also known as Fong disease, Hereditary Onycho-Osteodysplasia (H.O.O.D.), Iliac Horn Disease, and Turner-Kieser syndrome. Patients who have nail-patella syndrome may show a variety of physical abnormalities. The hallmark features of this syndrome are poorly developed fingernails, toenails, and patellae (kneecaps). Other common abnormalities include elbow deformities, abnormally shaped pelvis bone (hip bone), and kidney (renal) disease.

Less common medical findings include changes in the upper lip, the roof of the mouth, and unusual skeletal abnormalities. Skeletal abnormalities may include poorly developed scapulae (shoulder blades), sideways bent fingers (clinodactyly), clubfoot, scoliosis, and unusual neck bones. There are also other effects, such as thickening of the basement membrane in the skin and of the tiny clusters of capillaries (glomeruli) in the kidney. Scientists have recognized an association between nail-patella syndrome and colon cancer. Nail-patella syndrome is associated with open-angle glaucoma, which, if untreated, may lead to blindness. Patients may also have cataracts, drooping eyelids (ptosis), or corneal problems such as glaucoma.

People with nail-patella syndrome may display only a few or many of the recognized signs of this disease. Symptoms vary widely from person to person. Signs even vary within a single family with multiple affected members.

Genetic profile

Nail-patella syndrome has been recognized as an inherited disorder for over 100 years. It is caused by

mutations in a gene known as LIM homeobox transcription factor 1-beta (*LMX1B*), located on the long arm of chromosome 9.

The *LMX1B* gene codes for a protein that is important in organizing embryonic limb development. Mutations in this gene have been detected in many unrelated people with nail-patella syndrome. Scientists have also been able to interrupt this gene in mice to produce defects similar to those seen in human nail-patella syndrome.

Nail-patella syndrome is inherited in an autosomal dominant manner. This means that possession of only one copy of the defective gene is enough to cause disease. When a parent has nail-patella syndrome, each of their children has a 50% chance to inherit the disease-causing mutation.

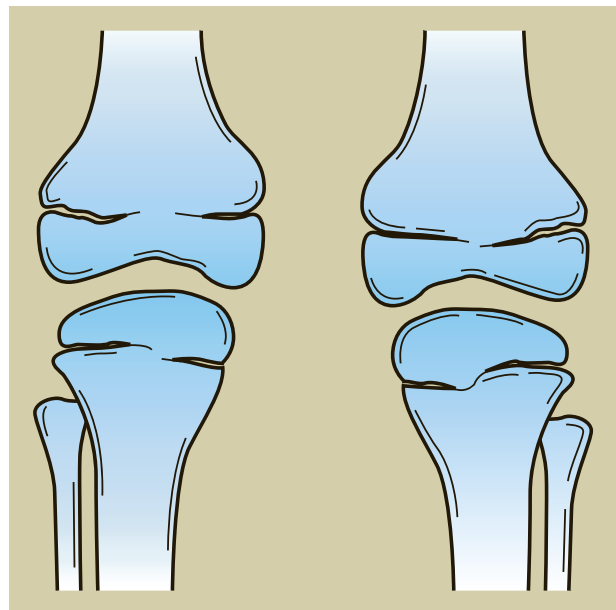


Diagram of two legs affected by nail-patella syndrome. Note the absence of the patella in this image of knees. (Gale)

A new mutation causing nail-patella syndrome can occur in a person with no family history. This is called a sporadic occurrence and accounts for approximately 20% of cases of nail-patella syndrome. The children of a person with sporadic nail-patella syndrome are at a 50% risk of developing signs of the disorder.

Demographics

The incidence of nail-patella syndrome is approximately 1 in 50,000 births. This disorder affects males and females equally. It is found throughout the world and occurs in all ethnic groups. The strongest risk factor for nail-patella syndrome is a family history of the disease.

Signs and symptoms

Medical signs of nail-patella syndrome vary widely between patients. Some patients with this disorder do not display symptoms. These patients are discovered to have nail-patella syndrome only when genetic studies trace their family history. Scientists are now working to learn what causes different people to display such different symptoms of nail-patella syndrome.

The most obvious signs associated with nail-patella syndrome is absent, poorly developed, or unusual fingernails. Fingernail abnormalities are found in over 80% of patients with this disorder. Abnormalities may be found in one or more fingernails. Only rarely are all fingernails affected. This disease most commonly affects the fingernails of the thumbs and index fingers. The pinky fingernail is least likely to be affected. Fingernails may be small and concave with pitting, ridges, splits, and/or discoloration. Toenails are less often affected. The lunulae, or light-colored crescent moons, at the base of the fingernail bed next to the cuticle are sometimes triangular-shaped in people with nail-patella syndrome.

Kneecap abnormalities are the second most common sign associated with this disorder. Either or both kneecaps may be missing or poorly formed. If present, kneecaps are likely to be dislocated. The knees of people with nail-patella syndrome may have a square appearance. Besides the kneecap, other support structures including bones, ligaments, and tendons may be malformed. These support structures stabilize the knee, therefore patients with some leg malformations may have difficulty in walking.

The hip bones of approximately 80% of patients with nail-patella syndrome have unusual bony projections called posterior iliac horns. These bony projections, or spurs, are internal and not obvious unless they are detected on x-ray. This unusual pelvic anatomy is not associated with any other disease.

KEY TERMS

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the early fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Glomeruli—Tiny clusters of capillaries in the kidney.

Hematuria—The presence of blood in the urine.

Patella—The kneecap.

Proteinuria—Excess protein in the urine.

Kidney disease is present in 30% to 50% of people with nail-patella syndrome. Biopsy shows lesions that resemble those of inflammation of the clusters of capillaries in the kidneys (glomerulonephritis) but without any infection present. Kidney failure is the most dangerous consequence of nail-patella syndrome. It occurs in about 30% of patients who have kidney involvement. An early sign of kidney involvement is the presence of protein or blood in the urine (chronic, benign proteinuria and hematuria). Kidney involvement is progressive, so early diagnosis and treatment of renal disease is important. Kidney disease has been reported in children with nail-patella syndrome, but renal involvement more commonly develops during adulthood.

Various skeletal symptoms may occur. Patients with nail-patella syndrome may not be able to fully straighten their arms at the elbow. This may create a webbed appearance at the elbow joint. Patients may have sideways bent fingers, poorly developed shoulder blades, clubfoot, hip dislocation, unusual neck bones, or scoliosis.

Eye problems may be present and vary from person to person. Nail-patella syndrome is associated with open angle glaucoma. Open angle glaucoma is caused by fluid blocked into the front chamber of the eye. This blocked fluid builds increasing pressure into the eye. If untreated, this increased pressure may lead to permanent damage of the optic nerve and irreversible blindness. Some patients with nail-patella syndrome have ptosis, or drooping eyelids. Nail-patella syndrome has also been associated with abnormalities of the cornea, cataracts, and astigmatism. Additionally, the irises of the eye may be multicolored, possibly displaying a clover-shaped pattern of color.

QUESTIONS TO ASK YOUR DOCTOR

- On what basis does a physician diagnose a person with nail-patella syndrome?
- Is nail-patella a life-threatening condition, and if not, what are its most serious medical consequences?
- Should my child be monitored on an ongoing basis for his nail-patella syndrome, and if so, what tests are recommended?

Diagnosis

Genetic testing for nail-patella syndrome is available only through research institutions that are working to further characterize this disorder. Genetic testing cannot predict which signs of the disease will develop, nor can genetic testing predict the severity of disease symptoms. Improved genetic testing for nail-patella syndrome is anticipated in the future.

Diagnosis of this disease is most often made on visual medical clues such as the characteristic abnormalities of the fingernails and kneecaps. Diagnosis is confirmed by x-ray images of the affected bones and, when indicated, kidney biopsy. The bony pelvic spurs found in 80% of patients with nail-patella syndrome are not associated with any other disease.

Prenatal diagnosis for nail-patella syndrome by third-trimester ultrasound was first documented in 1998. Prenatal diagnosis via genetic testing of cells obtained by chorionic villus sampling was first reported the same year. Prenatal genetic testing for nail-patella syndrome is not yet widely available. There is controversy surrounding the use of prenatal testing for such a variable disorder. Prenatal testing cannot predict the extent of an individual's disease.

Treatment and management

Treatment is usually not necessary. Treatment, when required, depends on each patient's specific symptoms. Severe kidney disease is treated with dialysis or a kidney transplant. Patients receiving kidney transplant do not develop nail-patella type renal complications in their new kidney.

A wheelchair may be required if walking becomes painful due to bone, tendon, ligament, or muscle defects. Orthopedic surgery may be necessary for congenital club-foot deformity. Manipulation or surgery may be required

to correct hip dislocation. Cataracts are also surgically treated. Medical treatment at early signs of glaucoma prevents progression of the disease to blindness.

Genetic counseling is offered to persons who have the disease. Parents with this disease have a 50% chance of passing it to each of their children. Current genetic testing technology cannot predict the severity or scope of an individual's symptoms.

Because many possible manifestations of nail-patella syndrome exist, patients are advised to pursue extra medical care including regular urinalysis and special eye exams. Children with nail-patella syndrome should be screened for scoliosis.

Prognosis

Survival among patients with nail-patella syndrome is not decreased unless they exhibit renal complications. It is estimated that 8% of individuals with nail-patella syndrome who seek medical attention eventually die of kidney disease.

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ORGANIZATIONS

- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

John Thomas Lohr
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Naito-Oyanagi disease see **Dentatorubral-pallidoluysian atrophy**

Nance-Insley syndrome

Definition

Nance-Insley syndrome is a craniofacial anomaly that is caused by a gene mutation interfering with prenatal bone development. The observable results are a short physique, flattened face, and overgrowth at joints. Another name for this condition is otospondylomegaepiphyseal dysplasia, derived from the Greek words “oto” (referring to the eyes), “spondylos” (referring to the spine), and “epiphyseal” (referring to the formative areas of the bones). The Greek word “dysplasia” refers to abnormal tissue formation. Nance-Insley is related to Stickler syndrome but is distinct from it. Nance-Insley is more severe in shared symptoms and involves hearing disabilities instead of the visual disability of Stickler.

Description

This disorder is caused by a mutation on the gene *COL11A2* responsible for producing collagen XI, an organic gel that influences the development of bones and cartilage in the skeletal system. People with Nance-Insley are affected mostly in their bone development and structure. The distinct facial features are due to weak bone structures under the face. There is no effect on intellectual function.

The distinct facial features of an affected person include an abnormally small lower jaw and an underdeveloped midface. The underdeveloped midface is noted by a small nose and flat nasal bridge. In addition to the facial features, the most notable feature of Nance-Insley is the relatively short stature of those affected. Other observable features include an abnormal skeletal framework and wide-set eyes. Almost all affected individuals have a cleft palate.

Expected characteristics include the following:

- Shortened limbs
- Short hands and feet
- Enlarged joints
- Flattened vertebrae
- Early onset of arthritis
- Hearing loss
- Joint pain
- Uprturned nose

Some of the common problems throughout the lifespan include pain in the joints and continually diminishing hearing. Many people with Nance-Insley syndrome suffer from the early onset of osteoarthritis.

KEY TERMS

Cartilage—The stiff yet flexible connective tissue found in many areas in the body, which grows and repairs more slowly than other connective tissue.

Fluorescence in-situ hybridization (FISH)—A method of analyzing the structures of human genetics that uses fluorescent probes designed to link to specific genetic particles such as proteins, genes, or chromosomal material.

Osteoarthritis—A group of diseases and mechanical abnormalities involving degradation of joints.

Type XI collagen—A type of collagen that produces an organic gel that helps cartilage to convert into bone and helps bone growth in the developing fetus.

Genetic profile

Nance-Insley syndrome is caused by a mutation on the gene *COL11A2* on chromosome 6. This gene is responsible for production of the type XI collagen. This collagen produces an organic gel that contributes to the systematic conversion of cartilage into bone and the orderly growth of bone in the developing fetus. Without type XI collagen, there is an overgrowth at the end of long bones contributing to stiff, inflexible joints. Another effect of the lack of type XI collagen is a decrease in bone growth.

Demographics

This condition is very rare. There is an extremely limited number of reports in the literature. No prevalence data were available as of 2015. The gene responsible for this disorder has been determined to be autosomal, which means that males and females are equally affected. The trait is dominant in some cases and recessive in others. Some cases have been shown to be due to a sporadic mutation.

Signs and symptoms

A child born with Nance-Insley syndrome will have abnormal bone growth, which is manifested in the characteristic facial features such as a small nose, flat nasal bridge, and underdeveloped midface. Other bone problems include the overgrowth at joints and short limbs. Other symptoms occurring in this syndrome include wide-set eyes, hearing loss, and a cleft palate.

The mutation responsible for Nance-Insley syndrome can be inherited in three manners: as an autosomal

QUESTIONS TO ASK YOUR DOCTOR

- What corrective surgery should I expect?
- How do other people with Nance-Insley cope with daily living skills?
- Is genetic counseling important for my situation?
- What are the chances that a child of mine will be born with Nance-Insley?
- How often should I be physically evaluated?
- Will my condition get worse?

dominant trait; as an autosomal passive trait; and as a spontaneous mutation. In some cases, the trait is dominant, but in another it is recessive, which is strange but not extraordinarily unusual. If a child is born with Nance-Insley syndrome there is a chance that later siblings may have it also and that current siblings are carriers. The age of either parent has been determined to be inconsequential in the development of this disorder.

Diagnosis

Signs of this disorder are observable from birth. However, many of these signs are also symptoms of Stickler syndrome. Identifying this condition as Nance-Insley with its accompanying complications is only possible through a genetic test of a blood sample.

The main test for recognizing chromosomal disorders is the fluorescence in-situ hybridization (FISH). This method of analyzing the structures of human genetics relies on fluorescent probes designed to link to specific genetic particles such as proteins, genes, or chromosomal material. If the correlating probe cannot link to the material for which it is designed, then the result is accepted as an absence of the material. In testing for Nance-Insley syndrome, the probes specific to the *COL11A2* gene on chromosome 6 would be injected into genetic material from the affected person. If examination of the probes does not detect a continuous pattern, then the person definitely has a mutation on this gene.

The condition can also be detected prenatally through amniocentesis. If a parent suspects that he or she is a carrier for Nance-Insley syndrome, an amniocentesis is able to detect the presence of the mutations. However, a test for Nance-Insley syndrome is complicated, so it is not usually done in amniocentesis analysis. The distinct characteristics, observable at birth, are not usually observable through the prenatal ultrasound. The problem with an ultrasound picture of the developing fetus is that

as of 2015, ultrasound was not powerful enough to detect the subtle features that would suggest the child has Nance-Insley syndrome.

Treatment and management

As noted above, the presence of the mutation can be detected through a prenatal test such as amniocentesis. Detecting the mutation is not usually a goal of typical amniocentesis because the condition is so rare. Prenatal counseling is recommended for a couple when one or both are carriers of the mutated gene. Information on this disorder and others that can arise through spontaneous mutations is recommended for parents during pregnancy.

There is no cure for the underlying condition of the mutation. The damage that is done prenatally remains for a lifetime. The various treatments for Nance-Insley syndrome are concerned with alleviating associated disabilities and delaying any perceived deterioration.

Traditional treatment

The usual treatment for children involves continuous evaluations of all related conditions. Orthopedic surgery may be necessary at times. Physical therapy and adaptive devices may help alleviate some of the problems. The cleft palate needs to be repaired in childhood, as well as any condition of the ears. If there is no chance for correcting the problems with the ears, therapy designed to help the patient adapt to a loss of hearing is required.

Some problems are less severe with age. However, joint pain and loss of hearing require assessment and treatment throughout the lifespan. Joint replacement may be required at a relatively young age.

Alternative treatment

The popularity of human growth hormone therapy may lead someone with Nance-Insley to consider it as an acceptable therapy for this condition. However, the short stature of the Nance-Insley patient is due to bone malformations. Such disorders do not respond well to growth hormone therapy.

Prognosis

There is no cure for Nance-Insley syndrome. Some of the initial bone structure problems may be alleviated with age. However, the early onset of osteoarthritis is fairly certain, as is lifetime hearing problems. Those affected with this syndrome have intellectual skills in the normal range and can learn adaptive skills well. Also, there is nothing inherent in this disorder to suggest less than average life expectancy.

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ORGANIZATIONS

- Human Growth Foundation, 997 Glencove Ave., Suite 5, Glenhead, NY 11545, (800) 451-6434, hgf1@hgfound.org, <http://www.hgfound.org>
- Little People of America, LPA National Headquarters, 250 El Camino Real, Suite 211, Tustin, CA 92780, (888) LPA-2001, info@lpaonline.org, <http://www.lpaonline.org>

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Nanocephalic dwarfism see **Seckel syndrome**

Narcolepsy

Definition

Narcolepsy is a lifelong disorder marked by excessive daytime sleepiness, uncontrollable sleep attacks, and interrupted nighttime sleep. There are two types of Narcolepsy: Type 1 (NT1) and Type 2 (NT2). Both types share many of the same symptoms. One major difference is that people with NT1 have cataplexy, while people with NT2 do not. Cataplexy is a sudden loss of muscle tone, that can last up to 30 minutes. Individuals with NT1 also have a dramatic decrease in the neuro-hormone hypocretin (orexin), which regulates sleep/wake cycles and eating behavior. Individuals with NT2, on the other hand, have normal levels.

Description

Narcolepsy usually starts in adolescence, but it can have an onset in childhood. It is the second-leading cause of excessive daytime sleepiness after obstructive sleep



Narcolepsy causes affected individuals to suddenly fall into a deep sleep, even in the middle of an activity. (A and N photography/Shutterstock)

apnea. People with narcolepsy suffer from sleep attacks in which they unwillingly fall asleep during their daily activities. Sleep attacks can last from a few seconds to more than an hour. Depending on where they occur, they may be mildly inconvenient or even dangerous. Contrary to what one may think, individuals with a narcolepsy disorder do not get more sleep than those without narcolepsy.

Narcolepsy also affects nighttime sleep. Most people with narcolepsy are unable to sleep more than a couple of hours at night. They may experience hallucinations when falling asleep and waking up and vivid dreams that cause them to move around excessively and talk in their sleep. It is also common for them to become paralyzed when falling asleep or waking up. Narcolepsy can affect rapid eye movement (REM) sleep. Our brain is the most active during REM sleep, and this is when dreams usually occur. People with narcolepsy often go directly into REM sleep. Healthy people, on the other hand, usually first have 90 minutes of non-REM sleep which is followed by REM sleep. People with narcolepsy can also experience REM sleep throughout the day.

People with Type 1 Narcolepsy (NT1) can experience cataplexy, where they have a sudden weakness of their muscles. This weakness can cause them to collapse or fall, which can sometimes result in injury. Cataplexy can be triggered by emotions like laughter, surprise, or anger.

Genetic profile

Narcolepsy is a complex disease caused by both genetic and environmental risk factors. It is likely that narcolepsy has different causes in different individuals. The disorder sometimes runs in families, but most people with narcolepsy have no relatives with the disorder. Both

identical twins have narcolepsy in about one in four (25%) cases. This suggests that, in many cases, environmental factors play a role in triggering the disorder. More is known about the genetics of NT1 than NT2.

Immune System Genes

Most of the genetic variations known to be associated with NT1 are related to the immune system. Across ethnicities, 88% to 98% of patients affected by NT1 share the HLA type *HLA-DQB1*0602*. The *HLA* gene family provides instructions for making a group of proteins known as the human leukocyte antigen (HLA) complex, which helps the immune system distinguish the body's own proteins from proteins made by foreign invaders such as viruses and bacteria.

It is likely that narcolepsy has an autoimmune component. Autoimmune reactions happen when the immune system attacks the body by mistake. NT1 may result from an autoimmune reaction in individuals with a susceptible HLA type that is triggered by infections. A number of lines of evidence support this theory:

- The onset of NT1 is often in the late spring, which suggests that it might be triggered by infections in the winter.
- NT1 has been associated with streptococcus infections.
- An increased risk of NT1 is associated with the H1N1 vaccine, Pandemrix.
- An increased risk of NT1 was found in children with the HLA type *HLA-DQB1*0602* following the H1N1 2009-2010 pandemic.

Orexin deficiency

Orexin is undetectable in the cerebrospinal fluid (CSF) of approximately 90% of patients with NT1. This protein is produced by the nerve cells (neurons) and regulates sleep/wake cycles and eating behavior. There has been one, early onset, severe case of NT1 that was associated with a variation (mutation) in the orexin gene. Most cases, are not caused by variations in that gene. It is possible that in some cases, NT1 is caused by the loss of the neurons that produce orexin. This might happen as the result of an autoimmune reaction where the body attacks the orexin producing neurons. This process, in turn, reduces, or even eliminates, orexin in the CSF.

Other genes.

Several additional gene loci have been identified to be associated with the development of narcolepsy, including the *TRAC*, *TNFSF4*, *CTSH*, *P2RY11*, *EIF3G*, *ZNF365*, *TCRB*, *IL10RB-IFNAR1*, and *CCR1/CCR3* gene loci.

KEY TERMS

Agonist—A chemical or biological agent that binds to a receptor and activates the receptor to produce a biological response.

Autoimmune reaction—When the body attacks itself, thinking it is being invaded by a foreign body like a bacteria.

Cataplexy—A symptom of narcolepsy in which there is a sudden episode of muscle weakness triggered by emotions. The muscle weakness may cause the person's knees to buckle, or the head to drop. In severe cases, the patient may become paralyzed for a few seconds to a few minutes.

Hypnagogic hallucinations—Dream-like auditory or visual hallucinations that occur while falling asleep.

Hypocretin—A neuro-hormone involved in the regulation of sleep, wakefulness, and eating behaviors, also known as orexin.

Hypothalamus—A part of the forebrain that controls heartbeat, thirst, hunger, body temperature and pressure, blood sugar levels, and other functions.

Sleep paralysis—An abnormal episode of sleep in which the patient cannot move for a few minutes, usually occurring on falling asleep or waking up. Often found in patients with narcolepsy.

Demographics

According to the National Institute for Neurological Disorders and Stroke (NINDS), narcolepsy is an under-recognized and under-diagnosed condition in the United States. The disorder occurs worldwide in every racial and ethnic group, affecting males and females equally. The prevalence of NT1 is 0.03%–0.05% as determined by several population studies conducted across the world. The prevalence of NT2 is approximately 36% lower than NT1. First-degree relatives (e.g., children, parents and siblings) of people with NT1 have approximately a 10- to 40-fold increased risk of narcolepsy. The age of onset is typically 10 to 20 years.

Signs and symptoms

While the symptoms of narcolepsy usually appear during adolescence, they can occur at any age, and the disease might not be diagnosed for many years. It is not progressive, and it is not fatal, but it is chronic. Most often, the first symptom is an overwhelming feeling of

QUESTIONS TO ASK YOUR DOCTOR

- Are my symptoms of sleepiness caused by narcolepsy?
- How will you determine whether I have narcolepsy?
- Will my symptoms get worse, and are there other symptoms that I could develop?
- What treatments are available for my symptoms, and what interactions could occur with medications I already take?
- Are there nonpharmacological approaches I can use to treat the symptoms of narcolepsy?
- Are there certain activities I should avoid?
- How can I keep others and myself safe if I have a sudden sleep attack or muscle weakness?

fatigue. After several months or years, cataplexy and other symptoms may appear.

Cataplexy is the most dramatic symptom of narcolepsy. It affects 75% of people with the disorder. During attacks, the loss of muscle control can range from a weak response, including buckling of the knees or neck muscles going slack, to severe, such as a complete body collapse. This loss of muscle tone is temporary, lasting from a few seconds to half an hour, but it is frightening. The attacks can occur at any time but are often triggered by strong emotions, such as anger, joy, or surprise.

Other symptoms of narcolepsy include the following:

- Sleep attacks: short, uncontrollable sleep episodes throughout the day
- Sleep paralysis: a frightening inability to move shortly after awakening or dozing off
- Auditory or visual hallucinations: intense, sometimes terrifying experiences at the beginning or end of a sleep period
- Disturbed nighttime sleep: tossing and turning, nightmares, and frequent awakenings during the night

Diagnosis

Narcolepsy is a complex disorder, and it is often misdiagnosed. It takes 14 years, on average, for an individual to be correctly diagnosed. If a person experiences both excessive daytime sleepiness and cataplexy, a diagnosis of NT1 may be made on patient history alone. Laboratory

tests, however, can confirm a diagnosis. They may include an overnight polysomnogram—a test in which sleep is monitored with electrocardiography, video, and respiratory parameters. A Multiple Sleep Latency Test, which measures sleep latency (onset) and how quickly REM sleep occurs, may be used. People who have narcolepsy usually fall asleep in less than five minutes. The absence of orexin in the cerebrospinal fluid can help confirm a diagnosis of NT1.

NT2 is more difficult to diagnose. It is suspected in patients who do not have cataplexy, have normal orexin levels in their CSF, and who have two or more abnormal sleep onset REM periods during a sleep test.

Treatment and management

There is no cure for narcolepsy. The symptoms can be managed with medication or lifestyle adjustment. Amphetamine-like stimulant drugs are often prescribed to control drowsiness and sleep attacks. Patients who do not like taking high doses of stimulants may choose to take smaller doses and “manage” their lifestyles, such as by napping every couple of hours to relieve daytime sleepiness. Antidepressants are often effective in treating symptoms of abnormal REM sleep. Sodium oxybate is a liquid medication that can help treat daytime sleepiness and cataplexy. It is taken before bedtime and two to four hours later.

Approximately 20% of patients with NT1 have abnormally low levels of acylcarnitine. Acylcarnitine is involved in regulating sugar and fat metabolism. Treating with L-carnitine seems to reduce the symptoms of narcolepsy in some people with NT1 and NT2.

Researchers are investigating novel therapies such as orexin replacement therapy, agonists of the hypocretin receptor, and even gene therapy for treatment and prevention of narcolepsy.

Prognosis

Narcolepsy is not a degenerative disease, and patients do not develop other neurologic symptoms. However, narcolepsy can interfere with a person's ability to work, play, drive, and perform other daily activities. In severe cases, the disorder prevents people from living a normal life, leading to depression and a loss of independence.

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ORGANIZATIONS

- Narcolepsy Network, 46 Union Drive, #A212, North Kingstown, RI 02852, (888) 292-6522, (401) 667-2523, (401) 633-6567, NarNet@narcolepsynetwork.org, <http://www.narcolepsynetwork.org>.
- National Heart, Lung, and Blood Institute (NHLBI), P.O. Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbiinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov>.
- National Institute for Neurological Disorders and Stroke (NINDS), P.O. Box 5801, Bethesda, MD 20824, (301) 496-5751, (800) 352-9424, <http://www.ninds.nih.gov>.
- National Sleep Foundation, 1010 N. Glebe Road, Suite 310, Arlington, VA 22201, (703) 243-1697, nsf@sleepfoundation.org, <http://www.sleepfoundation.org>

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Nephrogenic diabetes insipidus

Definition

Nephrogenic diabetes insipidus (NDI) is a kidney disorder characterized by the organ's inability to respond to the antidiuretic hormone (ADH), also called arginine vasopressin (AVP), produced in the hypothalamus, a structure of the brain. NDI involves an abnormality in the kidney tubules that prevents the proper amount of water from being reabsorbed from the kidneys back into the body. Instead, the water is excreted in large amounts as diluted urine.

Description

There are two categories of nephrogenic diabetes insipidus: inherited and acquired. Within the inherited

group, there are three types of NDI: X-linked, autosomal recessive, and autosomal dominant. Unlike the more common diabetic disorder diabetes mellitus, NDI is not related to insulin production or levels of sugar in the blood and urine.

Ninety percent of inherited NDI is X-linked, meaning it is caused by an alteration in a gene carried on the X chromosome. Since women have two X chromosomes and men have only one, an X-linked recessive condition is expected to affect men since they do not have a second X chromosome with a normal copy of the gene to produce the needed substance. Autosomal recessive NDI is rarer and equally affects males and females. Autosomal dominant NDI is the rarest of the three and affects both males and females.

Inherited NDI is present from birth, and symptoms usually manifest within the first several days of life. If the disorder is not diagnosed and treated early, it will cause the body to lose too much water. This dehydration can lead to brain damage and eventually death. With early diagnosis and treatment to avoid severe dehydration, however, the person can live a normal lifespan without any mental impairment.

Acquired NDI is the most common type of the disease and can be acquired at any age. It is most frequently acquired through the long-term use of certain prescription medicines, including demeclocycline, methicillin, foscarnet, and some anticancer drugs. In rare instances, it can be caused by an underlying disease or disorder, such as sickle cell anemia, chronic kidney failure, sarcoidosis, amyloidosis, Fanconi syndrome, and Sjögren's syndrome. Other rare causes of acquired NDI are low blood levels of potassium and abnormally high blood calcium levels. Pregnancy can also result in temporary acquired NDI. However, most cases of acquired NDI are caused by long-term use of the prescription drug lithium, which is used to treat bipolar disorder (manic depression).

NDI, also called gypsy's curse, is caused by the kidneys' inability to respond to the water-saving hormone (ADH), a natural chemical that is manufactured in the brain but that works in the kidneys. The body's two kidneys make urine, which is then sent to the bladder, and help to maintain the balance of water, salt, and minerals. A majority of the water is reabsorbed from nephrons in the kidneys into surrounding inner tissue. Each kidney contains hundreds of thousands of nephrons, microscopic tubes that filter the water flowing into the kidneys. The water that is not absorbed becomes urine.

The first references to NDI appeared in medical literature in the 1880s, but it wasn't until the 1940s that

detailed observations and studies were done. In a landmark 1946 study published in the *American Journal of the Diseases of Children*, authors A. J. Waring, L. Kajdi, and V. Tappan summarized the main clinical and pathophysiological aspects of the disorder. “The presenting complaints were unexplained fever, failure to gain weight, and constipation. The bouts of dehydration are usually not associated with acidosis. The thirst of one of the patients studied was satisfied only when five to six times the normal requirement of fluid was offered. The levels of (blood) serum sodium and chloride decreased to normal and the infant remained free from fever on this high fluid intake.”

Genetic profile

Genes are the blueprint for the human body and direct the development of cells and tissue. Mutations in some genes can cause genetic disorders such as inherited nephrogenic diabetes insipidus. Every cell in the body has 23 pairs of chromosomes, 22 pairs of which are called autosomes and contain two copies of individual genes. The chromosomes in the 23rd pair are called the sex chromosomes because they determine a person’s sex. Men have an X and a Y chromosome, while women have two X chromosomes. X-linked nephrogenic diabetes insipidus is caused by a defect in the vasopressin-2 receptor (*AVPR2*) gene in the X chromosome that renders the kidneys unresponsive to ADH.

Since inherited NDI is usually inherited as an X-linked condition, almost all persons with the disorder are male. Females have two X chromosomes, which means they have two copies of each gene. Males have only one X chromosome and one copy of each gene. If a male has an altered *AVPR2* gene, he will have NDI. If a female has one altered gene, she will be a carrier and will be at risk to pass the altered gene on to her children. If her son inherits the altered gene, he will be affected. If her daughter inherits the affected gene, she will be a carrier like her mother. If her son does not inherit the altered gene, he will not be affected and will not pass the altered gene on to his children. If a daughter does not inherit the altered gene, she will not pass it on to her children. If an affected male has children, all of his daughters will be carriers but none of his sons will be affected.

Women who have the abnormal *AVPR2* gene may have milder symptoms of NDI than males. This is because early in development, one X-chromosome in each cell of a female is “turned off” at random. If by chance a woman has more than half of the X chromosomes that carry the normal *AVPR2* gene turned off, she

may have mild symptoms of NDI. Approximately 90% of people with inherited NDI have it as a result of this X-linked gene.

The gene that produces aquaporin-2 (*AQP2*) can cause autosomal recessive and autosomal dominant NDI when altered. The *AQP2* gene produces a protein that helps the kidneys reabsorb water into the body and concentrate urine. Since the *AQP2* gene is carried on chromosome 12, a nonsex chromosome, it is carried in both males and females. Also, an abnormal *AQP2* gene is recessive, meaning that if only one of the person’s two *AQP2* genes is abnormal, it will not cause NDI. If both genes are abnormal, then that person will have NDI. A child born to parents who are both carriers of autosomal recessive NDI has a 25% chance to be affected since the child is at risk to receive a copy of the altered gene from his or her mother and father. In autosomal dominant NDI, either parent may be affected and may pass the altered gene to the child. Also, only one altered gene is necessary to be present for the condition to manifest. Acquired NDI is not hereditary and cannot be genetically passed on from parents to their offspring.

Demographics

In general, the various types of NDI appear to affect people regardless of age, race, or ethnicity. However, in X-linked NDI, the predominance of cases is among males. The exact number of people with NDI is not known. Estimates range from 1 in every 500,000 to 5 in every 100,000. In acquired NDI, one of the diseases that can cause it is sickle cell anemia, which occurs primarily in people of African descent.

Signs and symptoms

The primary symptoms for all types of NDI are generally the same: polyuria (excreting large amounts of dilute urine) and polydipsia, drinking excessive amounts of water, from 3–10 gal (12–38 L) per day. In infants born with NDI, symptoms begin to occur within a few days after birth. However, since a child cannot verbally communicate its need for greater than normal amounts of water, parents, physicians, and other caregivers must be alert to other signs of the disorder. Overt signs include fever, irritability, and constipation, all of which may indicate dehydration. The child may also vomit often, be anorexic, and prefer water to milk. Other signs include rapid and severe dehydration if fluids are restricted or withheld, high levels of sodium and chloride in the blood, and urine that does not have a high specific gravity.

KEY TERMS

Acidosis—A condition of decreased alkalinity resulting from abnormally high acid levels (low pH) in the blood and tissues. Usually indicated by sickly sweet breath, headaches, nausea, vomiting, and visual impairments.

Alzheimer's disease—A degenerative disease of the central nervous system characterized by premature senility and other mental deterioration.

Amyloidosis—Accumulation of amyloid deposits in various organs and tissues in the body such that normal functioning of an organ is compromised.

Dehydration—An extreme loss of water in the body, which, if untreated, can lead to brain damage and death.

Electrolyte—A solution or a substance in a solution consisting of various chemicals that can carry electric charges. Electrolytes exist in the blood as acids, bases, and salts, such as sodium, calcium, potassium, chlorine, and magnesium.

Fanconi syndrome—A reabsorption disorder in the kidney tubules.

Kidney tubules—A portion of the kidneys that causes water to be excreted as urine or reabsorbed into the body.

Nephrons—Microscopic tubes that filter the water that flows into the kidneys.

Osmolarity—The concentration of an osmotic solution, especially when measured in osmoles or milliosmoles per liter of solution.

Osmotically—Referring to the movement of a solvent through a semipermeable membrane (as of a living cell) into a solution of higher solute concentration that tends to equalize the concentrations of solute on the two sides of the membrane.

Sarcoidosis—A chronic disease characterized by nodules forming in the lymph nodes, lungs, bones, and skin.

Sickle cell anemia—A chronic, inherited blood disorder characterized by sickle-shaped red blood cells. It occurs primarily in people of African descent and produces symptoms including episodic pain in the joints, fever, leg ulcers, and jaundice.

Sjögren's syndrome—A chronic inflammatory disease often associated with rheumatoid arthritis.

Elderly people, usually those with acquired NDI, may need close monitoring for symptoms, especially if they are unable to communicate their need for a large amount of water, such as patients with Alzheimer's disease or other mental deterioration. Also, elderly persons may be less sensitive to their need for water. Because of this, elderly persons with NDI can be more prone to dehydration, leading to such problems as infection, kidney failure, confusion, lethargy, and constipation.

For acquired NDI, close medical monitoring should be done for people at high risk for the disorder. These include people undergoing long-term treatment with lithium and people with sickle cell anemia, chronic kidney failure, other kidney problems, very low blood levels of potassium and protein, and high blood levels of calcium.

Diagnosis

NDI is one of four types of diabetes insipidus (DI). In all four types, the basic symptoms are extreme thirst and excessive urination. Depending on other symptoms and conditions present in the patient, it can often be easy

for a physician to suspect NDI. However, additional tests are required to confirm it. These include a test of urine concentration to measure the ratio of osmotically active particles (such as sodium) to body water, a blood test to determine plasma concentrations, measuring urine volume, and a test to determine the level of the antidiuretic hormone AVP in blood plasma.

Sometimes physicians will have the patient take a water deprivation test to help determine the type of NDI present. In this test, the patient goes without water or other liquids for up to six hours. The blood plasma concentrations and urine volume are then measured. Even though a patient with NDI will become dehydrated during this test, the doctor monitors the patient's body weight and blood plasma osmolarity levels to ensure that the patient remains within safe parameters. At the end of the test, the patient is generally diagnosed with NDI if he or she has high levels of osmotically active particles in the blood and low levels of osmotically active particles in the urine.

The patient is also given desmopressin acetate (DDAVP), a synthetic version of AVP, to determine if he or she has a different form of DI called pituitary

QUESTIONS TO ASK YOUR DOCTOR

- Please describe the internal body changes that take place in a child with nephrogenic diabetes insipidus.
- What information about this disorder can a genetic counselor provide?
- Are there medications, tests, or other procedures that should be considered when treating a child with nephrogenic diabetes insipidus?
- How will nephrogenic diabetes insipidus affect the kind of life my child will be able to live?

diabetes insipidus, also known as central diabetes insipidus. In addition, the physician measures heart rate and diastolic blood pressure to help determine whether the NDI is caused by defective *AVPR2* genes or defective *AQP2* genes.

Treatment and management

Although there is no cure for NDI, all forms of the disorder are treatable. Drinking plenty of water is the first and foremost treatment. Regardless of the age of the patient, water must be available at all times. However, it is important for a child to maintain control of NDI with medication so that he or she can eat, drink, and grow normally.

Medications used to treat NDI include one or a combination of indomethacin (Indocin), amiloride (Mida-mor), the thiazide diuretics hydrochlorothiazide (HydroDIURIL) or chlorothiazide (Diuril), and occasionally desmopressin.

Management of NDI is also accomplished through restricting the intake of sodium and sometimes protein. Thiazide diuretics can reduce a patient's urine output, but they may also cause potassium depletion. Potassium supplements may be required. NDI that occurs during pregnancy usually goes away after delivery of the child. NDI caused by diet abnormalities is usually reversible once the diet becomes balanced. Acquired NDI caused by electrolyte imbalances such as low levels of calcium in the blood plasma or high levels of potassium in the blood plasma can be reversed once the imbalance is corrected.

In patients with lithium-induced NDI, thiazide diuretics are used cautiously since they reduce the kidneys' ability to excrete lithium. In many, but not all, cases,

people with lithium-induced NDI can improve when the dosage is decreased or stopped. In some cases, the lithium-induced NDI is irreversible.

Prognosis

Infants and children with inherited NDI can live a normal lifespan provided they are diagnosed correctly, treated early, and properly manage the disorder. Without early diagnosis and treatment in infancy, NDI can lead to intellectual disability and even death. Infants and children with NDI tend to be slightly smaller and weigh less than children without NDI. As children with NDI mature into adults, they tend to be slightly shorter than their parents, but with a normal weight. With appropriate treatment and management, NDI should not interfere with activities such as school, work, or sports.

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ORGANIZATIONS

Genetic Disease Foundation, 1425 Madison Ave., Box 1498, New York, NY 10029, <http://www.geneticdiseasefoundation.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Ken R. Wells

Nephrotic syndrome 2 see **Steroid-resistant nephrotic syndrome type 2/Galloway-Mowatt syndrome**

Neu-Laxova syndrome

Definition

Neu-Laxova syndrome (NLS) is a rare disorder characterized by onset of severe growth delay during pregnancy, multiple birth defects, and abnormal physical development of the brain. Affected infants typically die shortly after delivery or are stillborn.

Description

In 1971, Dr. Richard Neu published the first report of a family that included three children with a unique pattern of multiple birth defects. Each child had an unusually small head (microcephaly) and abnormalities of the arms, legs, skin, and external genitalia. The two affected daughters were each stillborn, while the affected son only lived for seven weeks. In 1972, Dr. Renata Laxova described a different family whose children had birth defects similar to those first described by Dr. Neu. The parents in this second family were first cousins to one another. Taken together, these two families were considered evidence of a previously unrecognized genetic syndrome. The disorder was named Neu-Laxova syndrome in honor of these two physicians.

NLS has since become known as a rare, lethal inherited condition characterized by a specific pattern of facial, brain, and limb abnormalities. Other associated abnormalities often include dry, scaly skin; generalized swelling of body tissues (edema); and extremely slow growth.

Genetic profile

NLS is inherited as an autosomal recessive condition. Males and females are equally likely to be affected. It has been reported in a variety of ethnic groups. Proof of autosomal recessive inheritance includes the birth of more than one affected child to normal parents and the observed incidence of infants with NLS among the children of two blood relatives. Consanguinity, or the mating of two biologically related individuals, increases the possibility of having a child with a genetic disorder. Since any two relatives will share a portion of their genes in common, they are more likely to each be a carrier of the same autosomal recessive gene.

In order to be affected with NLS, an individual must inherit two copies of the *NLS* gene or one copy from each carrier parent. A carrier has one *NLS* gene and one normal gene; as such, an NLS carrier appears completely normal. However, two carriers face a risk of 25%, or a 1 in 4 chance, of having a child with NLS. Conversely, they also have a 75% chance of having an unaffected child. These risks apply to each of their pregnancies together.

KEY TERMS

Agenesis of the corpus callosum—Failure of the corpus callosum to form and develop. The corpus callosum is the band of nerve fibers located between the two sides, or hemispheres, of the brain.

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light, resulting in blurry vision. Surgery may be performed to remove the cataract.

Cerebellum—A portion of the brain consisting of two cerebellar hemispheres connected by a narrow vermis. The cerebellum is involved in control of skeletal muscles and plays an important role in the coordination of voluntary muscle movement. It interrelates with other areas of the brain to facilitate a variety of movements, including maintaining proper posture and balance, walking, and running, and fine motor skills, such as writing, dressing, and eating.

Cleft lip—A separation of the upper lip that is present from birth but originates early in fetal development. A cleft lip may appear on one side (unilateral) or both sides (bilateral) and is occasionally accompanied by a cleft palate. Surgery is needed to completely repair cleft lip.

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Dandy-Walker malformation—A complex structural abnormality of the brain frequently associated with hydrocephalus, or accumulation of excess fluid in the brain. Abnormalities in other areas of the body may also be present. Individuals with Dandy-Walker malformation have varying degrees of mental handicap or none at all.

Placenta—The organ responsible for oxygen and nutrition exchange between a pregnant mother and her developing baby.

Stillbirth—The birth of a baby who has died sometime during the pregnancy or delivery.

Infants with NLS have also been born to non-consanguineous, or unrelated, couples. Any time a child with NLS is born, the parents must be obligate, or mandatory, carriers of one *NLS* gene. As such, they face an increased risk in future pregnancies together of having another affected child.

The gene for NLS has not yet been identified. Thus, it is not possible to perform direct genetic testing to determine carrier status, confirm a clinical diagnosis, or provide accurate prenatal diagnosis.

Demographics

Adequate data are not available to provide a specific statistic regarding the frequency of NLS. The condition is very rare. As of 2015, about 60 cases of Neu-Laxova syndrome had been reported.

Signs and symptoms

Stillborn or newborn infants with NLS have a characteristic pattern of internal and external abnormalities. Not all affected infants will have all of the features listed, and some anomalies are slightly more common than others.

Infants with Neu-Laxova syndrome often have unusual facial features. Their heads are very small, and their foreheads appear to slant backward. The distance between the eyes is wider than normal (hypertelorism), and the eyes are prominent or bulging. Cataracts may be present. The eyelids are typically absent. The bridge of the nose is wide and slightly flattened. The ears are abnormally shaped. The lower jaw appears recessed as compared to the upper jaw (retrognathia), and the mouth itself is usually open with abnormally thick lips. Cleft lip may be present, with or without cleft palate.

The external features of the head and face are a reflection of severe physical abnormalities of the brain. It is not unusual for an infant with NLS to have an underdeveloped cerebellum or even lissencephaly, a more serious malformation characterized by a smooth brain surface. Normal development of the brain includes an intricate pattern of grooves, or gyri, on its outer surface. A lack of these grooves leads to profound intellectual disability among survivors and an increased frequency of medical complications, such as seizures. Other reported brain malformations include agenesis of the corpus callosum and Dandy-Walker malformation.

A variety of limb abnormalities have also been described in NLS. Affected individuals often have shortened arms and legs that are held out from the body in an unusual, fixed position. This positioning is often referred to as flexion contractures. The fingers and toes may appear underdeveloped (hypoplastic) and/or fused together (syndactyly). The heels of the feet are often rounded (rocker-bottom feet), and the neck is short.

Other abnormalities more common to NLS include markedly limited physical growth. This typically begins during pregnancy and, as such, is referred to as

QUESTIONS TO ASK YOUR DOCTOR

- Can Neu-Laxova syndrome be diagnosed prenatally, and if so, how reliable is that diagnosis?
- What information can a genetic counselor give us about this disorder?
- What medical conditions are typically associated with Neu-Laxova syndrome?
- Can you recommend a source for further information about Neu-Laxova syndrome that will help us understand more about this disorder?

intrauterine growth restriction (IUGR). Edema, or an excessive amount of fluid in the tissues of the body, is a hallmark of NLS. The edema may either be generalized and very severe throughout the body or limited only to the face or scalp. The skin is often extremely dry and scaly, a medical condition called ichthyosis. The lungs are often hypoplastic (underdeveloped), even when delivery occurs at term. The external genitalia are often abnormal, but this is more obvious in males than in females since males typically have a small, underdeveloped penis.

Finally, in addition to IUGR during pregnancy, an excessive volume of amniotic fluid (polyhydramnios) often develops. This is due to a combination of abnormal fluid production and impaired fetal swallowing from the associated nervous system abnormalities. The placenta is also usually abnormal in appearance and function.

Diagnosis

Many infants with NLS have been born into families with no previous history of the disorder and/or ones in which the parents are unrelated. Thus, an exact diagnosis of NLS during pregnancy may be very difficult, particularly for a couple with no apparent risk factors. Direct genetic testing for NLS will not be possible until the responsible gene has been identified. Some non-specific prenatal findings should, however, alert the physician that additional prenatal evaluation is warranted. These include IUGR and polyhydramnios. Both findings often lead to an obvious difference in the size of a pregnant woman's uterus and her estimated weeks of pregnancy. A woman whose fetus has severe IUGR and normal amniotic fluid often appears less pregnant than she actually is. In contrast, a woman with polyhydramnios often appears more pregnant, or larger. A detailed prenatal ultrasound test may be used to obtain pictures of abnormalities of the fetus as well as possible abnormalities of the placenta

whenever there is an apparent discrepancy in a woman's size and her dates.

Two groups have separately reported diagnosis of NLS using ultrasound. However, in both cases, the diagnosis was formally established only after delivery. A number of the physical findings associated with NLS, particularly those involving the face, limbs, and brain, may be apparent following a detailed ultrasound later in pregnancy. In experienced hands and with the knowledge of a previous affected infant, some of these findings may be observed earlier.

In one of the published cases, a diagnosis of NLS was helped by the physical findings of an ultrasound exam at 32 weeks of pregnancy. The fetus was found to have many of the abnormalities associated with NLS. In the second report, ultrasound was used to assess fetal movement patterns at 34 weeks of pregnancy. Abnormal fetal movement is indicative of abnormal brain development. The authors were able to document a lack of normal fetal activity, such as breathing movements, sucking, swallowing, hiccups, and movements of the arms and legs in a fetus diagnosed with NLS after birth.

Accurate diagnosis of this condition is difficult before birth for those couples in which no *NLS* gene has been identified and no family history of NLS is known. While the combination of abnormal physical development and possibly abnormal fetal activity is highly indicative of a severe genetic condition, both would not be specific enough to pinpoint NLS as the cause in all cases. Other genetic syndromes would be under consideration, pending a clinical examination after delivery.

For this reason, a careful physical evaluation after birth is critical in establishing a diagnosis of NLS. For those infants who are stillborn and for those who die after delivery, an autopsy is also helpful in documenting all of the associated internal abnormalities. A precise diagnosis facilitates accurate genetic counseling, including prognosis for an affected child and the risk of recurrence for future pregnancies.

Treatment and management

For those couples who have had a previous child with NLS, serial prenatal ultrasound evaluations should be offered to monitor fetal growth, screen for physical abnormalities, and assess fetal well-being later in pregnancy given the increased risk for stillbirth. Ultrasound diagnosis of any of the structural birth defects associated with NLS in these families should be considered evidence of the disorder. Since some of these findings may not become evident until later in pregnancy, termination of the pregnancy may not be an option for some couples. Plans for the remainder of the pregnancy as well as

delivery can, however, be discussed. Given the serious prognosis associated with NLS, some parents may find a noninterventionist approach during labor and delivery, such as no fetal monitoring or Cesarean section delivery, acceptable. A clinical examination after birth is recommended.

Most infants with NLS have either been stillborn or died very shortly after delivery. However, there is one reported case of an affected Japanese infant who lived for 134 days. Humane medical care is therefore appropriate in survivors, although the prognosis would still be extremely poor.

An autopsy is recommended on all affected infants to document and confirm all of the associated physical abnormalities. While this acts as a way to confirm the diagnosis, it is also a useful way to continue to add to the knowledge about the syndrome and its physical effects.

Prognosis

The number of infants described with NLS is small. However, with the exception of the reported infant who lived 134 days, all affected children have either died before delivery or shortly thereafter. NLS is a serious genetic condition whose anomalies prevent long-term survival.

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ORGANIZATIONS

Compassionate Friends, PO Box 3696, Oak Brook, IL 60522, (630) 990-0010, (877) 969-0010, (630) 990-0246, <https://www.compassionatefriends.org/home.aspx>

March of Dimes, 1275 Mamaroneck Ave., White Plains, NY 10605, (914) 997-4488, <http://www.marchofdimes.org>

Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

Terri A. Knutel, MS, CGC

Neural tube defects

Definition

Neural tube defects are severe birth defects in which there is an opening in the spine or skull that exposes the brain or spinal cord. This exposure can result in damage to the brain or spinal cord.

Description

Neural tube defects are among the most common serious birth defects, and they vary considerably in their severity. Neural tube defects happen during the fourth week of pregnancy, if the soft and bony tissue protecting the spine and brain do not form properly. Openings may occur anywhere in the midline of the head or spine. In some cases, the brain or spinal cord is completely exposed or protected by a tough membrane (meninges) and in other cases covered by skin.

Spina bifida, which results from an opening in the spine, accounts for about two-thirds of all neural tube defects. The spine defect may appear anywhere from the neck to the buttocks. In its most severe form, termed “spinal rachischisis,” the entire spinal canal is open, exposing the spinal cord and nerves. More commonly the defect appears as a localized mass on the back that is covered by skin or by the meninges.

Anencephaly is the second most common neural tube defect and accounts for about one-third of cases. Two major subtypes of anencephaly occur. In the most severe form, all of the skull bones are missing, and the brain is entirely exposed. In the second form, called “meroacrania,” only a part of the skull is missing, and a portion of the brain is exposed.

Encephaloceles are the rarest form of neural tube defects. With encephaloceles, a portion of the skull bone is missing, leaving a bony hole through which the brain and its coverings herniate (protrude). Encephaloceles can occur anywhere from the front top half of the skull to the back of the skull near the neck. Encephaloceles on the back of the skull (occipital) are the most common. As with spina bifida, the severity varies greatly. In its mildest form, an encephalocele may appear as only a small area of faulty skin development, with or without any underlying skull defect. At the severe end of the

KEY TERMS

Embryo—The earliest stage of development of a human infant; used to refer to the first eight weeks of pregnancy. The term “fetus” is used from roughly the third month of pregnancy until delivery.

Hydrocephalus—The excess accumulation of cerebrospinal fluid around the brain that often causes enlargement of the head.

Meninges—The two-layered membrane that covers the brain and spinal cord.

Midline—An imaginary line that divides the body into right and left parts.

spectrum, most of the brain may be herniated outside of the skull into a skin-covered sac.

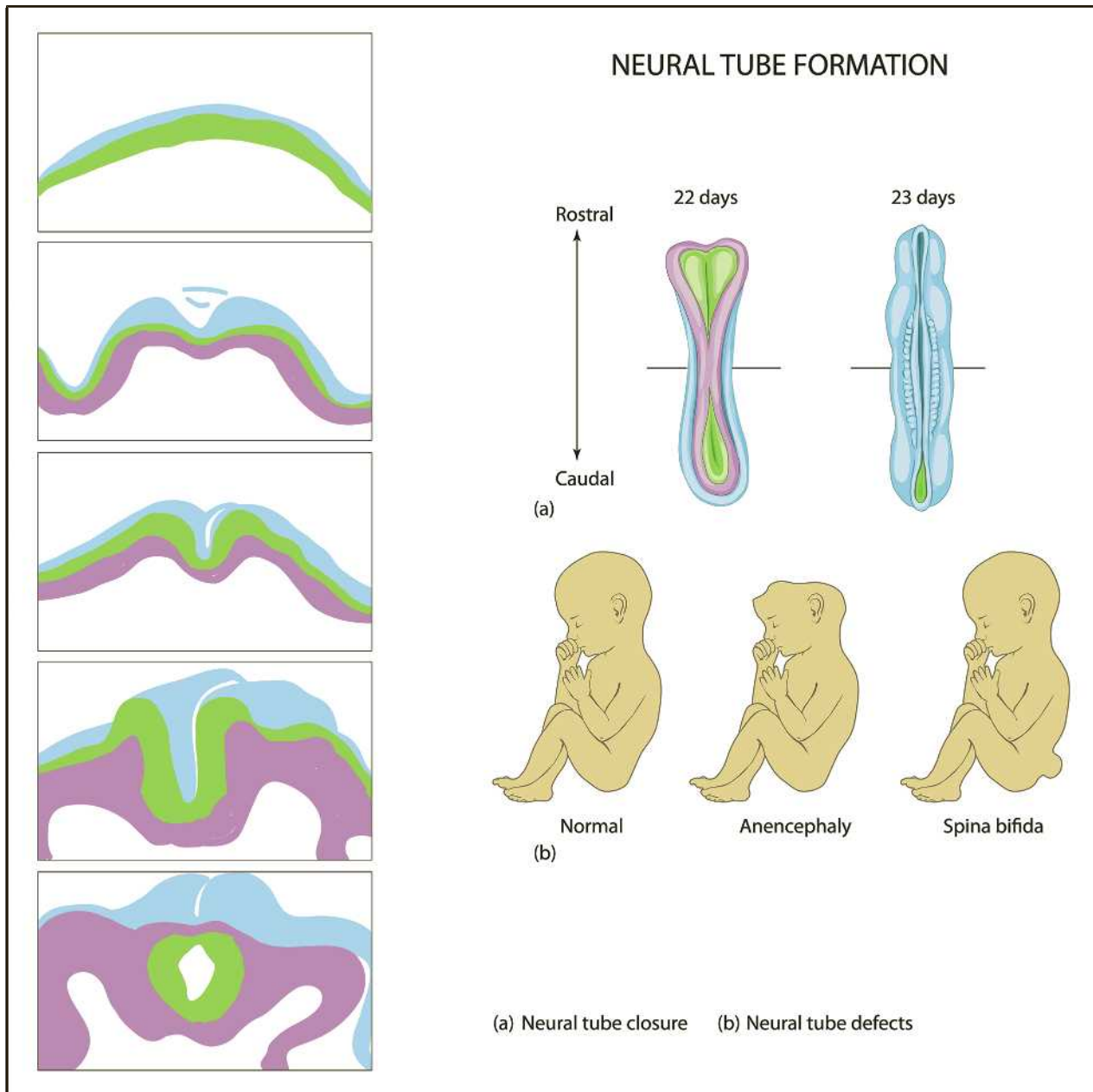
Genetic profile

Most neural tube defects (80% to 90%) occur without a family history of the condition. They can have different causes and can result from both genetic and environmental factors. Neural tube defects are also found in disorders where people have an extra chromosome. Chromosomes are inherited from the parents and contain their DNA.

The risk of neural tube defects can be increased as the result of environmental exposures during pregnancy. For example, the risk of neural tube defects in the baby can be increased if during the pregnancy the mother:

- has insulin-dependent diabetes
- is obese
- uses certain antiseizure medications that interfere with folic acid metabolism
- uses opioids in the first two months of pregnancy
- has a high body temperature early in pregnancy
- drinks a lot of tea early in pregnancy
- has folic acid deficiency
- has vitamin D deficiency
- has vitamin B12 deficiency
- smokes cigarettes

Maternal folic acid deficiency may be the most common cause of neural tube defects. About 50% to 70% of neural tube defects can be prevented with maternal folic acid supplements during pregnancy. In some cases, the maternal folic acid deficiency may be due to a genetic defect in the pathway involved in the breaking down and converting of folic acid for use by the body (metabolism).



Neural tube defects. (Shutterstock/Vasilisa Tsouy)

Neural tube defects can have a genetic component. Some evidence that there is a genetic component is that the chance of having another child with neural tube defects is increased and that both identical twins are more likely to have a neural tube defect than are non-identical twins. After a couple has one infant with a neural tube defect, the recurrence risk is 3% to 5%. After the birth of two NTD-affected infants, the risk increases to 8% to 10%. This recurrence risk is lower than the 25% to 50% recurrence risk that is typically seen in disorders caused by variations in one major gene, which suggests that while there are genetic factors that predispose someone

to neural tube defects, in many cases an environmental trigger is also required.

Most of the variations in genes (mutations) that contribute to the development of neural tube defects are not known. Key genes that are being studied are those that influence the metabolism of folic acid and those that affect the organization of cells that form the spinal cord (planar cell polarity).

Pathogenic variants (mutations) in the *Vang2* gene, which is involved in development of the spinal column, can cause neural tube defects. In some rare cases, this

QUESTIONS TO ASK YOUR DOCTOR

- What symptoms can I expect if my child is born with an NTD?
- What treatments are available if my child is born with an NTD?
- What programs are available to assist in managing NTD?
- I am planning to become pregnant; what should I do to prevent NTD?

variant can be inherited, but in most cases, it happens when the embryo is developing. A baby can even develop a neural tube defect if only some of the cells have a variant in the *Vang2* gene. When some cells have a normal gene, and some have a variant, it is called mosaicism.

Demographics

Neural tube defects occur worldwide. It appears that the highest prevalence (about one in 100 pregnancies) occurs in certain northern provinces in China. An intermediate prevalence (about one in 300 to 500 pregnancies) has been found in Ireland and in Central and South America, and the lowest prevalence (fewer than one in 2,000 pregnancies) has been found in the Scandinavian countries. In the United States, the highest prevalence has occurred in the Southeast. Worldwide, there has been a steady downward trend in prevalence rates over the past 50 to 70 years, possibly due to better quality of life, nutrition, and access to medical care in most parts of the world.

Signs and symptoms

Because of the faulty development of the spinal cord and nerves, the nerves below the level of the defect fail to function and result in paralysis and loss of sensation below the spinal lesion. Since most defects occur in the lumbar region, the lower limbs are usually paralyzed and lack normal sensation. Furthermore, the bowel and bladder have inadequate nerve connections, causing inability to control organ function. Sexual function is likewise impaired. An abnormal buildup of spinal fluid (hydrocephaly) develops in most infants either before or after surgical repair of the spine defect.

In anencephaly, the brain is destroyed by exposure during intrauterine life. Most infants with anencephaly are stillborn or die within the initial days or weeks after birth.

Infants with encephaloceles have variable neurologic impairments, depending on the extent of brain involvement. When only the brain covering is involved, the individual may escape any adverse effects; however, when the brain is involved in the defect, impairments of the special senses, such as sight, hearing, and cognitive thinking, commonly result.

Diagnosis

At birth, the diagnosis is usually obvious, based on external findings. Prenatal diagnosis may be made with ultrasound examination after 12 to 14 weeks of pregnancy. Screening pregnancies can be carried out at 16 weeks by testing the mother's blood for the level of alpha-fetoprotein, which is made by the fetus. Open neural tube defects leak this fetal chemical into the surrounding amniotic fluid, a small portion of which is absorbed into the mother's blood and can be measured.

Treatment and management

No treatment is available for anencephaly. Aggressive surgical and medical management has improved survival and function of infants with spina bifida. Surgery closes the defect, providing protection of the spinal cord against injury and infection. One common complication that may occur before or after surgical correction is the accumulation of excessive cerebrospinal fluid (hydrocephaly) in the major cavities (ventricles) within the brain. Hydrocephaly is usually treated with the placement of a mechanical shunt, which allows the cerebral spinal fluid from the ventricles to drain into the circulation or another body cavity. A number of medical and surgical procedures have been used to protect the urinary system as well. Walking may be achieved with orthopedic devices. Encephaloceles are usually repaired by surgery soon after birth. The success of surgery often depends on the amount of brain tissue involved in the encephalocele. In some cases, surgical repair can be done before the baby is born.

It has been found that taking 400 micrograms of folic acid two to three months prior to conception, and two to three months following conception, protects against neural tube defects. While there are a number of foods (green leafy vegetables, legumes, liver, and orange juice) that are good sources of natural folic acid, synthetic folic acid supplementation is recommended, since it can be difficult to get enough folic acid from natural sources.

Prognosis

Infants with anencephaly are usually stillborn or die within the initial days of life. Eighty to ninety percent of infants with spina bifida can survive with surgery.

Paralysis below the level of the defect, including an inability to control bowel and bladder function, and hydrocephaly are complications experienced by most survivors. Intellectual function is normal in most cases.

The prognosis for infants with encephaloceles varies considerably. Small encephaloceles may cause no disability whether surgical correction is performed or not. Infants with larger encephaloceles may have residual impairment of vision, hearing, nerve function, and intellectual capacity.

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ORGANIZATIONS

March of Dimes Birth Defects Foundation, 1275 Mamaroneck Avenue, White Plains, NY 10605, (914) 997-4488, <http://www.marchofdimes.org>.

National Birth Defects Prevention Network, 1321 Upland Drive, Suite 1561 Houston, TX 77043, nbdpn@nbdpn.org, <http://www.nbdpn.org>

Shriners Hospitals for Children, International Shrine Headquarters, 2900 Rocky Point Drive, Tampa, FL 33607-1460, (813) 281-0300, <http://www.nbdpn.org>

Spina Bifida Association of America, 4590 MacArthur Boulevard NW, Suite 250, Washington, D.C. 20007-4226, (202) 944-3285, (800) 621-3141, (202) 944-3295, <http://spinabifidaassociation.org>

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Neurofibromatosis

Definition

Neurofibromatosis (NF) are a group of three genetic disorders that cause tumors of the nervous system. These disorders cause tumors of the supporting cells of the nerve and myelin sheath (neurofibromas). The disorders occur as neurofibromatosis type 1 ([NF1] or von Recklinghausen disease), neurofibromatosis type 2 (NF2), and Schwannomatosis (NF3).



Neurofibromatosis is a genetic disorder that causes tumors to grow on nerves. (Pornsak Paewlumfaek/Shutterstock)

Description

Neural crest cells are primitive cells that exist during fetal development. These cells eventually turn into cells that form nerves throughout the brain, spinal cord, and body. Collectively, this system of nerve cells is called the nervous system, which coordinates movement and sensation. Some nerve cells carry impulses from the brain to muscles or other peripheral structures, hence the name peripheral nervous system. Another group of nerve cells called the central nervous system are capable of transmitting sensation back to the brain for interpretation (such as feeling cold or hot).

In neurofibromatosis, a genetic defect causes these neural crest cells to develop abnormally. This results in numerous tumors and malformations of the nerves, bones, and skin.

Genetic profile

Both forms of neurofibromatosis are caused by a defective gene. NF1 is due to mutations in the *NF1* gene (17q11.2) and rarely by 17q11 microdeletion (only 5%). This gene provides instructions for making a protein called neurofibromin, produced in many types of cells, including nerve cells and cells that surround nerves, forming myelin sheaths, the fatty layers that protect certain nerve cells. As of 2015, over 1,000 NF1 mutations had been identified.

NF2 results from mutations in the *NF2* gene on chromosome 22q. The *NF2* gene provides instructions for making a protein called merlin (or schwannomin). It is produced in the nervous system, particularly in Schwann cells, which surround and protect nerve cells in the brain and spinal cord. It is believed to act as a tumor suppressor, meaning that it



Reggie Bibbs, a man afflicted with neurofibromatosis, sits with his mother, Dorothy. The disorder is characterized by skin changes and bone deformities. (Marie D. De Jesus/Houston Chronicle/AP Images)

KEY TERMS

Chromosome—A microscopic thread-like structure found within each cell of the body and consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Mutation—An inherited or de novo change in the DNA sequence of the genome.

Neurofibroma—A soft tumor usually located on a nerve.

Schwannoma—A tumor that grows from the cells that line the nerves of the body (Schwann cells).

Tumor—An abnormal growth of cells. Tumors may be benign (noncancerous) or malignant (cancerous).

prevents uncontrolled cell growth. A lack of merlin allows Schwann cells to multiply excessively and form the tumors associated with NF2.

Both of these disorders are inherited as a dominant trait. This means that anybody who receives just one defective gene will have the disease. However, a family pattern of NF is only evident for about half of all cases of NF. The other cases of NF occur due to a spontaneous mutation (a spontaneous and permanent change in the structure of a specific gene). Once a spontaneous mutation has been established in an individual, it is then possible to pass the mutation on to any offspring. The chance of a person with NF passing on the *NF* gene to his or her child is 50%. There are different pathologic alleles (variations of the mutant gene). The frequency of spontaneous (new) mutations is very high; causes for this are still unknown.

Demographics

According to the National Institute for Neurological Disorders and Stroke (NINDS), an estimated 100,000 Americans have a neurofibromatosis. NF1 occurs in about 1 of every 3,000 to 4,000 births. Between 30% and 50% of new cases arise from a spontaneous mutation that can then be passed down. It is one of the most common genetic disorders that is dominantly inherited, and it represents the most common form of NF cases.

The incidence of NF2, a rare disorder, affects approximately 1 in 25,000 people. About 50% of patients inherit the disorder.

Schwannomatosis is a very rare form of NF that is both genetically and clinically different from NF1 and NF2. Only 15% of all cases are inherited.

Signs and symptoms

NF1 has a number of possible signs and can be diagnosed if any two of the following are present:

- The presence of café-au-lait (French for “coffee with milk”) spots. These are patches of tan or light brown skin, usually about 5 to 15 mm in diameter. Nearly all patients with NF1 display these spots.
- Multiple freckles in the armpit or groin area.
- Most patients with NF1 have tiny tumors called Lisch nodules in the iris (colored area) of the eye. Neurofibromas occur under the skin and are often located along nerves or within the gastrointestinal tract. They are small and rubbery, and the skin overlying them may be somewhat purple in color.
- Skeletal deformities, such as a twisted spine (scoliosis), curved spine (humpback), or bowed legs.
- Tumors along the optic nerve (the nerve cells that transmit a visual stimulus to the back part of the brain [the occipital lobe] for interpretation) cause vision disturbance and occur in about 20% of patients.
- The presence of NF1 in a patient’s parent, child, or sibling.
- Hypertension, or elevated blood pressure.

There are very high rates of speech impairment, learning disabilities, and attention deficit disorder in children with NF1. Other complications include the development of a seizure disorder (an abnormal firing of nerve cells in muscles, causing severe contractions, sometimes involving the whole body) or abnormal accumulation of fluid within the brain (a condition called hydrocephalus). A number of cancers are more common in patients with NF1. These include a variety of types of malignant brain tumors, as well as leukemia, and cancerous tumors of certain muscles (rhabdomyosarcoma), the adrenal glands (pheochromocytoma), or the kidneys (Wilms’ tumor).

NF2 patients have tumors along the eighth cranial nerve (vestibular schwannomas). The eighth cranial nerve has two branches: the acoustic nerves involved in hearing and the vestibular nerves involved in maintaining balance. Interfering with the function of these nerves results in a loss of hearing, dizziness, poor balance, and uncoordinated walking. Cataracts frequently develop at an unusually early age. As in NF1, the chance of brain tumors, gliomas, ependymomas (two types of tumors of the spinal cord), and meningiomas (tumors that grow in the protective layers surrounding the brain [meninges]) developing is unusually high. Peripheral neuropathy or

QUESTIONS TO ASK YOUR DOCTOR

- How do you inherit neurofibromatosis?
- What is the treatment for neurofibromatosis?
- Will I pass this condition to my children?

numbness in the extremities can occur as the tumors press on vital nerves or brain areas.

Schwannomatosis is a very rare form of NF that is both genetically and clinically different from NF1 and NF2. Only 15% of all cases are inherited. A mutation of the *SMARCB1/INI1* gene is associated with the familial form of the diseases. Characteristically these patients develop multiple schwannomas (tumors of the Schwann cells that are involved in the development of the protective myelin sheath that surrounds nerve cells) everywhere in the body except along the vestibular nerve. The main symptom is pain that occurs as the tumors press on the nerves and surrounding tissues.

Diagnosis

Diagnosis is based on the broad spectrum of clinical signs previously described, which usually can be detected by careful physical examination, ophthalmologic evaluation (visualizing the structures in the eye), and audiogram (test to measure hearing ability). Diagnosis of NF1 requires that at least two of the listed signs are present. Diagnosis of NF2 requires the presence of either a mass on the acoustic nerve or another distinctive nervous system tumor. An important diagnostic clue for either NF1 or NF2 is the presence of the disorder in a patient’s parent, child, or sibling. A test to detect a protein (the end-products of a gene) relevant to NF1 mutagenesis has been created, but accuracy for this procedure has not been established.

Monitoring the progression of neurofibromatosis involves careful testing of vision and hearing. X-ray studies of the bones are frequently indicated to detect for the development of deformities. CT scans and MRI scans are performed to track the development/progression of tumors in the brain and along the nerves. Auditory evoked potentials (the electric response evoked in the cerebral cortex by stimulation of the acoustic nerve) may be helpful to determine acoustic nerve involvement, and EEG (electroencephalogram, a record of electrical impulses in the brain) may be required for patients with suspected seizures. Regular blood pressure monitoring is also advised.

Treatment and management

There are no available treatments for the disorders that underlie either type of neurofibromatosis. To some extent, the symptoms of NF1 and NF2 can be treated individually. Skin tumors can be surgically removed. Some brain tumors and tumors along the nerves can be surgically removed or treated with chemotherapy or radiation therapy. Twisting or curving of the spine and bowed legs may require surgical treatment or the wearing of a special brace.

There is no known way to prevent the approximately 50% of all NF cases that occur due to a spontaneous change in the genes (mutation). New cases of inherited NF can be prevented with careful genetic counseling. A person with NF can be taught that each of his or her offspring has a 50% chance of also having NF. Special tests can be performed on the fetus during pregnancy to determine if the fetus will be born with this disorder. Amniocentesis (in which a needle is passed through the mother's abdomen into the amniotic sac, which contains the amniotic fluid and cushions the developing fetus) or chorionic villus sampling (a procedure involving extraction of a tissue sample from the placenta, the structure that connects the fetal blood with the mother, necessary for nutrient and waste exchange) are two techniques that allow small amounts of fetal DNA to be removed for analysis. The tissue can then be examined for the presence of the parent's genetic defect. Some families choose to use this information to prepare for the arrival of a child with a serious medical condition. Other families may choose not to continue the pregnancy.

Prognosis

Prognosis varies depending on the tumor type that develops. As tumors grow, they begin to destroy surrounding nerves and structures. Ultimately, this destruction can result in blindness, deafness, increasingly poor balance, and increasing difficulty with the coordination necessary for walking. Deformities of the bones and spine can also interfere with walking and movement. When cancers develop, prognosis worsens according to the specific type of cancer.

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Children's Tumor Foundation, 120 Wall St., 16th Floor, New York, NY 10005-3904, (212) 344-6633, (800) 323-7938, (212) 747-0004, info@ctf.org, [http://www.ctf.org](http://www.ctf.orghttp://www.ctf.org)

National Cancer Institute (NCI), BG 9609 MSC 9760, 9609 Medical Center Dr., Bethesda, MD 20892-9760, (800) 422-6237, <http://cancer.gov>

National Comprehensive Cancer Network, 275 Commerce Dr., Suite 300, Fort Washington, PA 19034, (215) 690-0300, (215) 690-0280, [http://www.nccn.org](http://www.nccn.orghttp://www.nccn.org)

National Institute for Neurological Disorders and Stroke (NINDS), PO Box 5801, Bethesda, MD 20824, (301) 496-5751, (800) 352-9424, <http://www.ninds.nih.gov>

Neurofibromatosis Network, 213 S. Wheaton Ave., Wheaton, IL 60187, (630) 510-1115, (800) 942-6825, (630) 510-8508, admin@nfnetwork.org, <http://www.nfinc.org>

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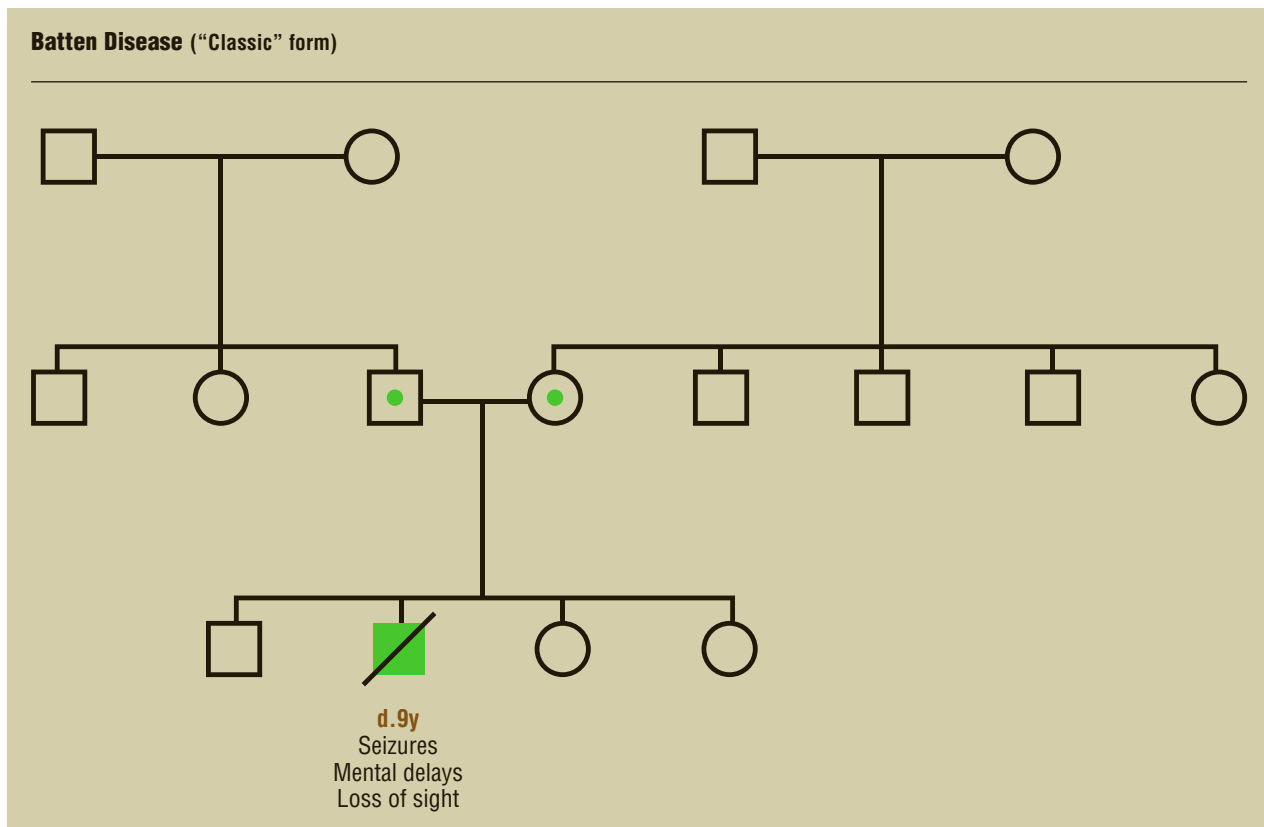
Neuronal ceroid lipofuscinoses

Definition

Neuronal ceroid lipofuscinoses (NCLs) are a family of about eight disorders affecting the nervous system. Most commonly they develop in infancy or childhood. Symptoms of the disorder include mental impairment, seizures, and the loss of sight and motor skills. These disorders result from an overaccumulation of lipopigments in neuronal cells and other bodily tissues. All mutations that are associated with NCLs are linked to genes that are involved in neural synapsis metabolism and the recycling of vesicle proteins.

Description

NCL is characterized by an abnormal build-up of lipopigments—substances made up of fats and proteins—in membrane-bound compartments within cells. The compartments are organelles called lysosomes



Batten disease: pedigree analysis chart (Gale)

and function in the breakdown of waste products and complex molecules produced by the cell. In NCL diseases, this process is disrupted, and lipopigments can accumulate. The accumulation of lipopigments can contribute to vision failure and the loss of mental and neurological functions beginning in early childhood.

NCL is the general term for a family of progressive neurological disorders. There are approximately eight disorders in the NCL family, although all of these disorders are often collectively referred to as Batten disease.

Genetic profile

The first notable description of NCL was in 1826 in Norway by Dr. Christian Stengel, who observed siblings that showed characteristics of the disease. The British pediatrician Frederick Batten performed clinical studies on several families in the early 1900s; the juvenile form of NCL was named after him. Batten also played an important role in defining the juvenile form of NCL as a different disorder from that of Tay-Sachs disease. NCLs are autosomal recessive disorders, which means that they occur when a child receives one copy of the abnormal gene from each parent.

Individuals with only one abnormal gene are known as carriers; they do not develop the disease but can pass the gene on to their own children. When both parents carry one abnormal gene their children have a one in four chance of developing an NCL disease.

Initially, NCL disorders were differentiated by the age of onset. These classifications included:

- Infantile NCL (Santavuori-Haltia)
- Late infantile NCL
- Juvenile NCL (Batten disease, Spielmeier-Vogt disease)
- Adult NCL (Kuf's disease, Parry's disease)

Now that the genes involved in the diseases have been identified, the associated genes classify the types of NCL. Mutations in eight genes have been found to contribute to NCL symptoms and also now serve as names for specific forms of NCL:

- CLN1 encodes an enzyme called palmitoyl-protein thioesterase 1 (PPT1). It is insufficiently active in infantile NCL.
- CLN2 produces an enzyme called tripeptidyl peptidase 1 (TPP1) that is an acid protease that degrades

proteins. The enzyme is insufficiently active in late infantile NCL.

- CLN3 is the major cause of juvenile NCL. *CLN3*, or battenin, is found in the membranes of the cell, most predominantly in lysosomes, and in related structures called endosomes. The protein's function is currently unknown.
- CLN5 causes variant late infantile NCL (vLINCL) and produces a lysosomal protein whose function has not been identified.
- CLN6 also causes late infantile NCL and encodes a protein called CLN6 or linclin. The protein is found in the membranes of the endoplasmic reticulum. Its function has not been identified.
- MFSD8 is a variant of late infantile NCL, also referred to as *CLN7*; it encodes the MFSD8 protein that is a member of a protein family called the major facilitator superfamily. Proteins in this superfamily are involved with transportation across the cell membranes. The precise function of MFSD8 has not been identified.
- CLN8 causes progressive epilepsy with intellectual disability. The gene encodes the *CLN8* protein, which is found in the endoplasmic reticulum and whose function has not been identified.
- CTSD is involved with congenital NCL (also referred to as *CLN10*) and encodes cathepsin D, a lysosomal enzyme. A deficiency of cathepsin D causes the disorder.

While not initially considered part of the NCL classification, northern epilepsy syndrome is a subtype of NCL that is reported only in people from northern Finland and those of Finnish descent. It is characterized by seizures that begin in early childhood and progress through adolescence. Intellectual disability is associated with the syndrome, and while the seizures may decrease with age, mental faculty does not return. In 1999, northern epilepsy syndrome was reclassified as an NCL disease when the missense mutation associated with the syndrome was found to occur in the *CLN8* gene. This mutation alters the lipid content of the brain, which affects brain function and produces the symptoms of the disease. Northern epilepsy syndrome is considered to be one of the milder forms of NCL disorders.

Demographics

NCLs are relatively rare, occurring in 2 to 4 of every 100,000 births in the United States. NCLs appear to be more common in children living in Northern Europe and Newfoundland, Canada. Although the disorder affects both genders equally on a genetic level, female patients show signs up to a year later than male patients and tend to die earlier from Batten disease.

KEY TERMS

Lipofuscin—Pigment granules that are produced from lysosomal degradation. Lipofuscin normally accumulates over time and with age.

Lipopigments—Substances made up of fats and proteins that can accumulate in different tissues of the body. They have a yellowish color to them under UV light. Lipopigments can result from oxidation of fatty acids and may be symptomatic of damage or aging.

Lysosome—A membrane-enclosed compartment in cells that contains many hydrolytic enzymes where large molecules and cellular components are broken down.

Neuronal ceroid lipofuscinoses—A family of eight genetically distinct progressive neurological disorders that are all a result of overaccumulation of lipopigments.

Signs and symptoms

Early symptoms of NCLs usually develop in early childhood at two or four years of age and include vision difficulties and seizures. There may also be personality and behavioral changes, slow learning, clumsiness, or stumbling by the time the child is between the ages of five and eight. Over time, the child can develop mental impairment or regression, worsening seizures, and the complete loss of vision and motor skills. NCL diseases are terminal and eventually lead to death in those who suffer from them.

Childhood forms of NCLs may first be suspected during an eye exam that displays a loss of certain cells. Because such cell loss can occur in other eye diseases, this sign alone cannot diagnose the disorder. An eye specialist who suspects an NCL disease may refer the child to a neurologist, who can analyze the medical history and information from various laboratory tests.

Diagnosis

Diagnostic tests used for NCLs include blood or urine tests that can detect abnormalities, skin or tissue sampling can measure the build-up of lipopigments in cells, electroencephalograms that display electrical activity within the brain that suggests a person has had seizures, electrical studies of the eyes that can further detect various eye problems common in childhood NCL, and brain scans can visualize changes in the brain's appearance. When the specific gene that causes the form

QUESTIONS TO ASK YOUR DOCTOR

- What physiological changes are associated with my child's NCL disease?
- What treatments are available to slow the progress of this condition?
- What treatments are available to make my child more comfortable and better adapted to this medical condition?
- What is the prognosis for this disorder?

of NCL is known, DNA testing can confirm the diagnosis. DNA analysis can also be used to identify unaffected family members as carriers when NCL is suspected. This analysis can be useful to those who are carriers in providing assistance in their own family planning.

Treatment and management

There is no widely used treatment to prevent or reverse the symptoms of NCLs. Anticonvulsant drugs are often prescribed to reduce or control seizures. Other medicines may be prescribed to manage other symptoms associated with the disorder. Physical and occupational therapies may also help people retain function for a longer period of time. There have been reports of the slowing of the disease among children who were given vitamins C and E and diets low in vitamin A. However, the fatal outcome of the disease remained the same.

In 1987, there was a small, phase I clinical study done at Cornell University using gene therapy to treat late infantile neuronal ceroid lipofuscinosis caused by the loss of the *CNL2* gene. An adeno-assisted virus 2 (AAV2) vector was used to introduce a normal copy of the *CNL2* gene into patients and showed that progression was slowed after treatment.

In 2006, stem cells were injected into the brains of six children who had NCL disease who, after six treatments, recovered speech and mobility. The study was a phase I clinical trial and focused on showing the safety of the procedure of transplantation and the use of stem cells in the treatment of neurological disorders. These patients were followed for 12 months after the treatment and showed normal progression of the disease.

Since 2010, research groups at the University of Rochester and Cornell University have been actively pursuing use of gene therapies in the treatment of Batten disease and other forms of NCL.

Prognosis

People with NCL disease may become blind, confined to bed, and unable to communicate. NCLs are typically fatal by the late teens or 20s. Some people with late-onset disease, however, can live into their 30s.

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ORGANIZATIONS

Battens Disease Support and Research Association, 1175 Dublin Rd., Columbus, OH 43215, (800) 448-4570, (866) 648-8718, <http://www.bdsra.org>

Children's Craniofacial Association, 13140 Coit Rd., Suite 517, Dallas, TX 75240, (214) 570-9099, (800) 535-3643, (214) 570-8811, contactCCA@ccakids.com, <http://www.ccakids.com>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Nevoid basal cell carcinoma

Definition

Nevoid basal cell carcinoma syndrome (NBCCS) is primarily a genetic skin cancer condition. The syndrome derives its name from the cancerous skin lesions that typically begin in the third decade of life. However, the name is not completely satisfactory as there are other manifestations of the syndrome.

Description

A condition that was first described in 1894, nevoid basal cell carcinoma syndrome has been found in mummies dating back to 1000 b.c. However, the condition was brought to the attention of the medical community by Dr. Robert Gorlin, and thus bears the alternative name Gorlin syndrome. Other names include Gorlin-Goltz syndrome and basal cell nevus syndrome.

While NBCCS often leads to cancer, it can also result in various other physical findings and birth defects. The most common cancer is that of the skin, known as basal cell carcinoma. However, medulloblastoma (brain cancer) and ovarian cancer are also possible. Also frequently present are cysts (fluid-filled sacs) of the skin and jaw, palmar and plantar pits (slight depressions on the surface of the skin), a non-cancerous growth on the heart known as a fibroma, macrocephaly, and various skeletal problems.

Genetic profile

NBCCS is caused by mutations in a gene known as “patched” (*PTCH*). *PTCH* is located on chromosome 9. It is believed to be a tumor suppressor gene. The normal role of such genes is to prevent the growth of tumors. They do this by controlling cell growth and division. It is the presence of uncontrolled cell growth that can lead to a tumor.

NBCCS is inherited in an autosomal dominant manner, meaning that only one of the two *PTCH* genes found in every cell of the body must be mutated in order to have NBCCS. If a person has a mutation in just one of their *PTCH* genes, the disease will be present. This will include some of the signs and symptoms of the condition.

In about 50% of cases, a mutation in the *PTCH* gene may be inherited from a parent with NBCCS. In the other 50% of cases, a mutation can also occur by chance, in an individual without a family history of NBCCS. If the mutated gene is inherited from a parent, the symptoms of the disorder may be very different than those present in the parent. Some individuals will be more severely affected than others, even if they are all from the same family.

Once an individual has a *PTCH* mutation, there is a 50% chance with each pregnancy that the mutated *PTCH* gene will be passed on. If inherited, that male or female will have NBCCS.

While an individual with NBCCS will have a mutation in one of their two *PTCH* genes, it is the development over time of a second *PTCH* mutation in skin cells that actually leads to the development of the basal cell carcinomas. This second mutation is believed to occur

by chance, with the exact factors leading to a second mutation not yet fully understood. A second mutation in other cells may also lead to the other types of growths that can occur in NBCCS, including cardiac and ovarian fibromas, as well as medulloblastoma.

Demographics

NBCCS occurs in an estimated 1 out of every 57,000 individuals worldwide. However, this may be an underestimation of the true prevalence. While NBCCS is seen in all ethnic groups, individuals of Caucasian descent tend to exhibit cases of skin cancer more frequently than individuals of African descent. Approximately 0.4% of all cases of basal cell carcinoma are caused by the NBCCS.

Signs and symptoms

The characteristics associated with NBCCS are variable. The most prevalent symptom of this condition is skin cancer. Small growths (1–10 mm [0.04–0.4 in.] in diameter) on the skin can occur during as early as two years of age. However, if not removed, these can develop into basal cell carcinomas by as early an age as puberty. The number of growths may vary from just a few to thousands.

Medulloblastoma, a type of brain cancer, occurs in 3%–5% of individuals with NBCCS. It typically presents around two years of life and occurs in males more commonly than females. Seizures have occasionally been seen as part of this condition but are not felt to be related to the presence of medulloblastoma.

An increased risk for other cancers has been proposed to be associated with this syndrome. However, as of the year 2015 this has not been proven.

Jaw cysts are another common sign of NBCCS. They typically first appear around 15 years of age. Although often large, they rarely cause symptoms other than tooth displacement. The number of cysts can vary greatly and they do have a tendency to recur after surgical removal.

Various birth defects are more common in NBCCS. These can include polydactyly, cleft lip, cleft palate, various eye abnormalities, minor kidney anomalies, rib problems, and spinal anomalies (such as unusually shaped bones of the spinal column). Interestingly, overall height in individuals with NBCCS is slightly higher than average.

There are many possible eye abnormalities, such as cataracts found at birth, unusually small eyeballs, cysts in the eye, failure of the eye to develop fully, shaky or jerky eye movements, and problems with the nerve connecting the eye to the brain.

Rib anomalies are found in 45%–60% of individuals with NBCCS. They generally do not cause any problems,

although can be a clue to the diagnosis. Different rib problems associated with NBCCS can include partially missing ribs, ribs that split into two (known as bifid ribs), and ribs that fuse together.

The kidney problems are not as common a symptom, occurring in 14% or less of individuals with NBCCS. The most serious condition is when both kidneys are fused together, known as a horseshoe kidney. Unusually shaped kidneys, cysts, a single missing kidney, and duplication of parts of the kidney can also occur. However, as many of these kidney problems do not tend to cause health issues, they are not always detected unless specifically looked for.

A small percentage of males will have undescended testicles, the loss of the ability to smell, unusual breast tissue development, and sparse facial and body hair. These can all be signs of hormonal or endocrine disturbance.

Other features often include macrocephaly and growths (fibromas) in the heart and ovaries. Finally, pits or lesions in the palms of the hands or soles of the feet are very common, harmless findings.

Diagnosis

To make a diagnosis of NBCCS an individual must have at least two major and one minor characteristics that meet the diagnostic criteria. Alternatively, one major and three minor criteria can be present. Since there are many different symptoms that are considered major and minor, no two individuals with NBCCS will be exactly alike in their manifestations.

Examples of major criteria include:

- More than five basal cell carcinomas, or one before the age of 30 years
- Jaw cysts
- Two or more palmar or plantar pits
- Deposits of calcium or other salts on parts of the brain that can be seen on x-rays
- A first-degree relative (sibling, parent, or child) known to have NBCCS

Examples of minor criteria include:

- Macrocephaly
- A cleft lip or palate
- Eye abnormalities of various types
- Polydactyly
- Ovarian or cardiac fibromas
- Childhood medulloblastoma
- Rib or spinal anomalies of various types

There is no exact age by which someone can be assured they do not have NBCCS. This is because each possible

KEY TERMS

Autosomal dominant—A pattern of inheritance in which only one nonworking gene is needed to display the trait or disease.

Basal cell carcinoma—A cancer originating from the skin.

Carcinoma—Cancer that forms from tissue that covers various surfaces, glands, and organs of the body, such as the skin.

Cleft lip—An opening in the upper lip that can extend to the base of one or both nostrils.

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth, creating a connection between the nasal passages and the mouth.

Fibroma—An unusual growth of the tissue that provides stability and support in the body.

Genes—The units of inheritance, which contain the instructions to make one or more proteins; genes are located on chromosomes.

Macrocephaly—An unusually large head.

Medulloblastoma—A type of brain cancer.

Mutation—A change in a gene that causes it to either not function, or malfunction. This will result in manifestation of a disease, or alter a trait.

Palmar—Referring to the palms of the hand.

Plantar—Referring to the sole of the foot.

Polydactyly—The presence of extra fingers or toes.

Prevalence—The number of cases of a disease in a population at a specific period of time.

symptom can develop at a different time. For example, 90% of affected individuals develop jaw cysts by their second decade, but 10% of affected individuals never develop a single basal cell carcinoma. However, enough symptoms are usually present by the time the patient reaches their 20s or 30s that a diagnosis may be possible.

Alternatively, using a blood sample to test the *PTCH* gene for the presence of a mutation can also make a diagnosis of NBCCS. However, only 65%–80% of individuals with NBCCS will actually have a detectable mutation using the technology available as of 2015.

Treatment and management

Removal of the multiple skin tumors and jaw cysts is recommended. Failure to do so can lead to both the

development of basal cell carcinomas, along with social difficulties due to the disfiguring nature of these tumors. Removal of jaw cysts should be undertaken by an oral surgeon and the basal cell carcinomas by a plastic surgeon. Radiation therapy should be avoided as these can cause further development of the basal cell carcinomas.

Ovarian fibromas, if present, can be surgically removed. The same is true for cardiac fibromas, although they do not usually cause symptoms.

Since manifestations of NBCCS can vary, any affected individual should be monitored carefully by the appropriate specialist. These include a dermatologist (skin doctor), dentist or orthodontist, ophthalmologist (eye doctor), pediatrician, and geneticist (specialist in genetics). Special precautions should be taken to avoid radiation, in the form of both radiation treatment and sun exposure, as this increases the risk to form basal cell carcinomas. Typical methods to reduce sun exposure, such as sun block and hats, should be used.

Phototherapies (treatment of disease by means of light rays) and topical treatments (skin creams based on vitamin A) are currently under investigation as possible means of treatment.

Prognosis

The life expectancy of individuals with NBCCS is considered to be essentially average. However, the key to this is diagnosis and proper treatment.

Developmental delay can be associated with the enlarged head size, but intelligence is often normal. Therefore, head circumference should be monitored throughout childhood and any rapid changes evaluated by magnetic resonance imaging (MRI) right away.

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Next-generation sequencing

Definition

Next-generation sequencing (NGS) encompasses various technologies for rapidly determining DNA sequences. It is also called massively parallel sequencing or deep resequencing. NGS simultaneously sequences large numbers of relatively small DNA fragments. The sequences are then arranged in the correct order (aligned), using computers and bioinformatic techniques, to reveal the sequences of genes, whole exomes (the portion of DNA that codes for proteins), or whole genomes (all of the DNA in a cell, tissue, or organism). NGS has greatly increased the speed and reduced the cost of DNA sequencing, leading to many new genetic applications.

Description

DNA sequencing determines the exact order of nucleotide bases—the building blocks of DNA (designated A, T, G, and C)—to reveal an individual's genetic code. Whole-genome sequencing (WGS) determines the entire sequence of the more than three billion nucleotides in human cells. Whole-exome sequencing (WES) determines only the 1%–3% of DNA that encodes the instructions for making proteins. Targeted sequencing determines the DNA sequence of specific genes or regions of a chromosome.

NGS has revolutionized the use of DNA sequencing for identifying genetic disorders and variations in DNA sequences that increase susceptibility to specific diseases. It can readily determine relationships between individuals and reveal their ancestry. It is used to determine the DNA sequences of other organisms, including the trillions of bacteria and other microorganisms that live in and on the human body—the microbiome. NGS of ancient DNA has revolutionized the study of human history and evolution.

Origins

The original method for sequencing DNA—Sanger sequencing or first-generation sequencing, developed by

Frederick Sanger in 1975—enabled large-scale DNA sequencing for the first time. Sanger sequencing has since been automated and is still used to sequence short pieces of DNA, but, although it is extremely accurate, it is time-consuming, labor-intensive, and expensive. Sanger sequencing separates the DNA “double helix” into its two complementary strands and cuts it in such a way that the DNA fragments terminate at every possible nucleotide. Then the terminal nucleotide bases are labeled with a fluorescent compound. The DNA fragments are separated and ordered by size using a technique called electrophoresis. The fluorescent-labeled terminal base of each fragment (A, T, G, or C) is then identified to “read” the DNA sequence.

When the Human Genome Project (HGP) set out to determine the entire DNA sequence of humans in 1990, it required thousands of scientists at 20 large centers around the world performing Sanger sequencing on various regions of the genome. This spurred the development of new technologies that sequenced small DNA fragments and compiled these sequences into the correct order using powerful new computer software. These new technologies led to the completion of the HGP in 2003, several years ahead of schedule, and spearheaded the development of NGS. NGS first became available in 2005 and has developed and improved steadily since then. With NGS, an individual’s entire genome can be sequenced in just a few days. This has revolutionized genetic science and ushered in the beginnings of “personalized medicine” that can diagnose and treat disease according to an individual’s unique DNA.

NGS sequences thousands or millions of DNA fragments simultaneously (massively parallel), but the fragments are usually much shorter than those used for Sanger sequencing. This results in an immense amount of data. Thus, NGS requires huge data storage and analysis capabilities, which has ushered in the new science of bioinformatics to align (collate) the sequences and apply statistical and computational analysis to the genomic data. With NGS, the sequencing is so fast that the data processing and analysis have become the time-limiting factors.

Procedures

The advent of NGS has engendered fierce competition among biotechnology companies to develop commercial platforms for different types of sequencing using a variety of technologies. Each method has advantages and disadvantages. Genomic DNA is obtained from blood, saliva, or tissue. In a typical procedure, the two strands of the DNA double helix are separated and cleaved into fragments. The fragments can be amplified to make many copies using a procedure called

KEY TERMS

Bioinformatics—The use of computer science for collecting, classifying, and analyzing genetic information.

Epigenetic—A modification outside of the actual mutation of the DNA sequence, such as the addition of a methyl group.

Exome—The protein-encoding DNA sequences (exons) of the genome.

Genome—The entire DNA sequence of a cell or organism.

Human Genome Project—An international effort begun in 1990 and completed in 2003 to locate and identify the 100,000 genes on the 46 human chromosomes.

Microbiome—All of the microorganisms normally present in a given environment, such as the human body.

Nucleotide—A small molecule composed of three parts: a nitrogen base (a purine or pyrimidine), a sugar (ribose or deoxyribose), and phosphate; they serve as the building blocks of nucleic acids (DNA and RNA).

Personalized medicine—Diagnosis and treatment based on the DNA sequence of an individual or a cancer.

Polymerase chain reaction (PCR)—A laboratory process used to make a large number of copies of specific genetic information from small amounts of DNA.

RNA-sequencing—Next-generation sequencing (NGS) of RNAs in a cell or tissue.

Single-nucleotide polymorphism (SNP)—Single-nucleotide variant (SNV); a variation or point mutation in a single-nucleotide building block of DNA.

Whole-exome sequencing (WES)—Sequencing of all the protein-encoding DNA (exons) in a genome.

Whole-genome sequencing (WGS)—Sequencing of all the DNA in a genome.

polymerase chain reaction (PCR). The complementary strands of the fragments are rebuilt using nucleotide bases with fluorescent tags. A special laser camera records the incorporation of the complementary fluorescent-labeled bases into the growing DNA chains. A complete genomic sequence can be run in about three days, with an error rate of 1 base per 1,000.

Although the 1000 Genomes Project and similar endeavors are using NGS to sequence and compare whole human genomes, in general, WGS is still too expensive for large-scale sequencing to compare populations. WES is less expensive than WGS and more comprehensive than genome-wide association studies (GWAS), which use markers called single-nucleotide polymorphisms (SNPs) to identify common genetic variants that are risk factors for disease. WES covers only 2%–3% of the genome but includes the sequences that are most likely to be relevant. An individual's genome usually contains 3–4 million nucleotide changes or SNPs that differ from reference human genomes, but most of these are not significant changes. About 85% of disease-causing inherited mutations occur within exons—the protein-encoding portions of DNA—and these can be detected by WES. Thus, WES is a cost-effective means for analyzing genetic disorders that run in families, as well as for association studies in populations.

As of 2015, WES and NGS systems were variants on the same procedure. Genomic DNA is cut into fragments of about 500 bases to create what is called a “shotgun library.” Adapters are attached to the ends of the DNA fragments to serve as “primers” for PCR amplification. The amplified DNA library is hybridized to short complementary DNA sequences called oligonucleotides in the same way that the two complementary strands of the double helix hybridize by base pairing. The oligonucleotides are specific for exons and are called “baits.” Molecules of biotin are attached to the oligonucleotides, and the biotin binds to the protein streptavidin that is attached to magnetic beads. Thus, the DNA-bait hybrids bind to the beads and represent the exons in the genome (an exon-enriched library). The separated exons are again amplified by PCR on slides or plates to produce enough DNA for sequencing. Fluorescent nucleotides, DNA polymerase (the enzyme that adds nucleotides to the growing DNA chain), and short pieces of DNA called sequencing primers are added to the fragments, which are generally 25–350 nucleotides in length. As the fluorescently tagged bases are incorporated into each strand, laser activation records the fluorescence. Computers can determine many sequences simultaneously, and each fragment is sequenced 20–30 times.

Another type of NGS exome sequencer uses pH. Each time complementary bases from two DNA strands join together (hybridize), they release hydrogen ions, which cause miniscule increases in acidity that can be measured. As of 2015, this method could sequence an entire exome in less than one day for about \$400. Sequencing specific genes is even faster and cheaper.

WES reveals 20,000–25,000 SNPs, compared to the several million SNPs in a whole-genome sequence. Data

QUESTIONS TO ASK YOUR DOCTOR

- Can next-generation sequencing (NGS) be used to diagnose my disorder?
- Will whole-genome sequencing or whole-exome sequencing be performed?
- Can next-generation targeted sequencing be used?
- How much does NGS cost?
- Will my insurance pay for NGS?

processing compares these SNPs with control data to enrich for those that may be relevant. This filters out all but 500–700 SNPs. These remaining SNPs are examined more carefully, for example, to see whether they are in genes of particular interest or are changes that do not fit the inheritance pattern of the disorder being studied. Software can also predict mutations that may have significant effects on protein products. An important advantage of WES is that it may detect very rare mutations that cause genetic disorders or mutations in a gene that was not expected to be involved in a disorder.

Targeted sequencing can detect variants in genes of interest much faster and cheaper than WGS or WES. Targeted NGS methods include PCR-based target enrichment for clinical diagnostic testing of specific genes and hybridization-based enrichment methods that can cover larger genomic regions.

Limitations

The volume of data produced by NGS can be very extensive. A single run may produce millions or billions of short reads of about 50–150 nucleotides. This data must be quality controlled, stored, assembled, aligned, and annotated.

- Base calling is the process of identifying the nucleotide bases from the fluorescent signals produced by the sequencer. Different NGS platforms tend to produce different types of sequencing errors, and base callers must estimate the error frequencies.
- Incorrect alignment of sequences is a common problem. Often, sequences will be mapped to multiple locations on a reference genome. Several different strategies have been developed to deal with these “multi-reads.”
- Reconstructing a genome without a reference sequence requires longer sequenced fragments, and repeated

sequences can make such *de novo* assemblies very difficult.

- Hundreds of gigabytes of raw sequence data must be stored for potential future analysis and interpretation as analytic algorithms improve and genetic knowledge increases. Even shipping the data from the sequencing facility to the data analysis center can be a challenge.

There are other common problems with NGS:

- NGS requires several milligrams of DNA. This can be obtained easily from a few milliliters of blood, but obtaining enough DNA from tissue can be difficult.
- Coverage or depth is the average number of times that each nucleotide in a sequence is identified. Low-coverage sequencing identifies a given nucleotide only once or twice in only one or two reads. Thus, low coverage can easily result in misreading errors that may misidentify or miss a mutation.
- If the sequence is slightly misaligned with the reference genome, small base substitutions, insertions, and deletions can be missed. Alignment problems can also mistakenly indicate a mutation.
- Both WGS and WES identify thousands or millions of variations (SNPs), and it can be very difficult to determine which of these are relevant.
- Some control or reference genomic databases may contain unrecognized pathogenic mutations. In such cases, an important mutation may be discarded early in the analysis.

Cancerous tumors have unique genomes with many mutations, and sequencing of these genomes is an important application of NGS. However, routine methods for storing tumor tissues can lead to DNA degradation and chemical modification of nucleotides that cause sequence alterations. Variability of the genomes within the same tumor tissue or among different tumors from the same individual is also a challenge that must be overcome for personalized cancer diagnosis and treatment.

WES has some specific limitations:

- WES covers most—but not all—of the exome.
- WES misses DNA variations or mutations that are outside of the exome but that may affect the activity of a gene and the resulting protein production. These types of variations or mutations require more extensive sequencing or even WGS.
- WES sequences many short DNA fragments. Because short fragments are often repeated throughout the genome, they can be difficult to align properly. About 15%–30% of short fragments cannot be definitively assigned to a single location in the genome.
- Some disorders, such as Huntington disease, are caused by specific sequences of DNA that are repeated an

abnormal number of times. These are called “repeat expansions” and are not generally recognized by WES.

Applications

As of 2015, an individual’s entire genome could be sequenced for \$1,000 or less—cheaper than many routine medical tests. Thousands of human genomes are being sequenced to identify common and rare variations and disease-causing mutations. Projects such as the 1000 Genomes Project will identify variants that are present in only 1% of a population. NGS is also identifying many very rare and poorly understood genetic disorders. Finally, NGS is being used to sequence thousands of plant and animal genomes, as well as the genomes of billions of microorganisms that make up the human microbiome and many millions more that are present in the environment and have never been identified. NGS also can be used to identify epigenetic markers—chemical modifications to DNA that affect the activity of genes without changing the DNA sequence.

Cancer diagnosis and treatment stand to benefit from NGS, perhaps more than any other field of medicine. Cancers are characterized by mutations that differ from the individual’s normal genome. Furthermore, cancers that have spread (metastasized) can contain genomes that differ from the original cancer. Since many cancer treatments depend on the presence of specific mutations, the ability to rapidly sequence cancer genomes and compare them with the individual’s normal genome is expected to greatly improve cancer treatment and prognosis as the technology becomes more available and the costs continue to fall.

In addition to sequencing DNA (deoxyribonucleic acid), NGS can be used to sequence RNA (ribonucleic acid). RNA is a single strand that is complementary to a DNA strand, with “U” in place of “T,” and is copied (transcribed) from a DNA strand. There are many different types of RNA in cells, including messenger RNA (mRNAs) that produces proteins from protein-encoding genes. RNA-sequencing (RNA-seq) is “transcriptome” sequencing by NGS—the sequencing of all of the RNA present in cells, tissues, or organisms. Among other function, RNA-seq can identify and quantify which genes are active in specific cells or tissues at a given time. RNA-seq can also identify and quantify RNA that does not code for proteins but that have regulatory roles in the cell. RNA-seq has proved particularly useful for identifying gene fusions and aberrant nonprotein-coding RNA that are important in various cancers.

Third-generation sequencing

New sequencing platforms—called third generation—are being developed. These technologies sequence DNA directly, avoiding much of the sample preparation

required for Sanger and NGS sequencing. One emerging technology—single-molecule sequencing—directly sequences individual DNA or RNA molecules in biological samples without amplification.

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ORGANIZATIONS

- American College of Medical Genetics and Genomics, 7220 Wisconsin Ave., Suite 300, Bethesda, MA 29814, (301) 718-9603, (301) 718-9604, acmg@acmg.net, <https://www.acmg.net>
- Icahn Institute and Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Pl., Box 1498, New York, NY 10029-6574, (212) 241-6500, (212)-590-3300, <http://icahn.mssm.edu/departments-and-institutes/genomics>
- National Human Genome Research Institute, National Institutes of Health, Bldg. 31, Rm. 4B09, 31 Center Dr., MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, (301) 402-2218, <http://www.nhgri.nih.gov>.

Margaret Alic, PhD

NGLY1 deficiency

Definition

The *NGLY1* gene supplies the instructions for producing an enzyme called N-glycanase 1. This enzyme removes sugar molecules from damaged proteins to target the proteins for destruction by the cell. N-glycanase 1 enzyme is for the recycling of cellular waste products. Mutations (changes) in the *NGLY1* gene can cause an

inherited genetic disorder known as congenital disorder of deglycosylation (CDDG) or *NGLY1* deficiency. CDDG has a variety of signs and symptoms, including developmental delays, an inability to produce tears, and liver disease.

Since this disorder has only recently been identified—with only one or two descriptions of symptoms and possible treatments—the information below is an example of how many new genetic syndromes are now being treated and redefined as specific genetic disorders.

Description

N-glycanase 1, encoded by the *NGLY1* gene, is the enzyme that is responsible for removing sugar chains called glycans from misfolded (nonfunctional) N-linked glycoproteins. N-linked glycoproteins are proteins that have sugars attached to a nitrogen (N) atom on asparagine amino acid residues in the protein. N-glycanase 1 is present in the cytoplasm of most cells. It is part of an important cellular pathway known as the endoplasmic reticulum-associated degradation (ERAD) pathway, which is responsible for identifying and breaking down misfolded glycoproteins. Once N-glycanase 1 removes the glycan chain, the protein can be degraded by a protein complex known as the proteasome. In the absence of functional N-glycanase 1, cells can become clogged with misfolded and damaged proteins. Because N-glycanase 1 is important for cells throughout the body, a deficiency of the enzyme can have wide-ranging effects. N-glycanase 1 deficiency, or CDDG, is a member of a family of rare genetic disorders called congenital disorders of glycosylation (CDG), in which sugars are not properly attached to proteins. At least some cases of CDG had been associated with the *NGLY1* gene before the identification of CDDG.

In 2012, *NGLY1* deficiency became the first congenital (present at birth) deglycosylation disorder to be described. The story of its discovery has been recounted in articles by Matthew Might, the father of an affected child (Bertrand), and others. It is illustrative of the ways in which new genetic techniques and new media are combining forces to identify rare genetic disorders and connect affected families, with the goals of developing treatments and possibly cures.

Bertrand Might appeared normal at birth except for severe jaundice (yellowing of the skin and eyes indicating liver dysfunction), which is not unusual in newborns. He developed normally for the first two months of life, and then his development began to slow. By six months of age, he had lost almost all motor control. Might had no detectable brain damage, and his blood tests were normal except for extremely high levels of alpha-fetoprotein

KEY TERMS

Alpha-fetoprotein (AFP)—A fetal blood protein found in amniotic fluid.

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are required to express a trait or disorder.

Congenital disorder of deglycosylation (CDDG)—*NGLY1* deficiency or N-glycanase 1 deficiency, in which sugar chains cannot be removed from misfolded proteins so that they can undergo degradation; caused by mutations in the *NGLY1* gene.

Congenital disorder of glycosylation (CDG)—A family of genetic disorders that includes *NGLY1* deficiency (congenital disorder of deglycosylation), as well as disorders in which sugars are not properly attached to proteins (glycosylation).

Endoplasmic reticulum—An interconnected system of membranes that is involved in protein synthesis and the transport of materials within cells.

Endoplasmic reticulum-associated degradation (ERAD)—An important cellular pathway that includes N-glycanase 1 and is responsible for breaking down (degrading) misfolded glycoproteins.

Glycoproteins—Proteins with added sugar molecules.

N-glycanase 1—An enzyme encoded by the *NGLY1* gene that removes (cleaves) sugars called glycans from misfolded proteins.

Whole-exome sequencing (WES)—Sequencing of the 1%–3% of the DNA in the genome that encodes for proteins; used to identify genetic disorders.

(AFP). Ataxia telangiectasia (A-T), a degenerative, fatal, autosomal recessive genetic disorder, was the only known syndrome characterized by both high AFP and movement disorders. However, his symptoms differed from A-T, and a genetic test for A-T came back negative. He continued to have signs of liver dysfunction and, at eight months of age, his development halted. The discovery of chains of sugar molecules in Might's urine pointed to a family of rare genetic disorders known as inborn errors of cellular metabolism. These included CDG, in which the absence of an enzyme prevents sugars from being properly attached to proteins. Although the clinicians at Duke University were unable to diagnose the specific disorder, they discovered that his abnormal movements were actually different forms of epileptic seizures. In addition, Might's parents suddenly realized that

in his two years of life, although he cried, he had never produced tears. Eventually, the child was also diagnosed with a heart defect known as long QT syndrome.

The Duke physicians became convinced that Might suffered from a previously undescribed genetic syndrome, and they decided to sequence the DNA of the entire exomes of the child and his parents to see if they could find a mutation. The exome consists of the 2%–3% of human DNA that carries the instructions for making proteins. About 85% of disease-causing mutations are located in the exome. Whole-exome sequencing (WES) revealed that Might's parents each carried a different mutation in one of their two *NGLY1* genes, and he had inherited both of these mutated genes, leaving him with no functional N-glycanase 1. At first, it was believed that Might was the only human with CDDG or N-glycanase 1 deficiency. However, through his parents' efforts, especially Matthew Might's blog, at least 15 more children with CDDG were soon identified. The Might family's well-publicized story established WES as a new paradigm for identifying previously unrecognized genetic disorders.

Genetic profile

The *NGLY1* gene is located on the short arm (p) of chromosome 3 at 3p24.2. Mutations in *NGLY1* are inherited in an autosomal recessive pattern, meaning that an individual must inherit two mutated genes, one from each parent, in order to develop the disorder. Parents may be carriers of one mutated *NGLY1* gene and have no symptoms of the disorder. However, each of their children has a 25% risk of inheriting both mutant genes and a 50% risk of inheriting one mutated gene and being a carrier of the disorder.

As of 2015, the majority of known patients with *NGLY1* deficiency had a specific nonsense mutation—a mutation that does not code for an amino acid in the protein, so that the protein ends with the amino acid that preceded the mutation. This particular mutation appears to cause severe disease, although it is expected that more *NGLY1* mutations will be identified that cause a wider range of symptoms. From his father, Bertrand Might inherited the *NGLY1* nonsense mutation called R401X, meaning that instead of the amino acid arginine at amino acid position 401 in the protein, the N-glycanase 1 protein ends prematurely at this position. From his mother, he inherited an *NGLY1* gene that contained a frameshift mutation that changed the DNA sequence of the gene and the resulting amino acid sequence of the protein. As a result, Might had barely detectable levels of N-glycanase 1. Because his parents each had one normal *NGLY1* gene and one mutated *NGLY1* gene, they had lower-than-normal levels of N-glycanase 1. Five other

QUESTIONS TO ASK YOUR DOCTOR

- Why do you think my child might have *NGLY1* deficiency?
- Is genetic testing available for *NGLY1* deficiency?
- Should other family members be tested for *NGLY1* gene mutations?
- What are the chances that we could have another child with this disorder?
- What treatments are available for my child?

patients with CDDG from three families, who were all of European descent, were identified as having the same R401X nonsense mutation in both of their *NGLY1* genes (homozygous mutations). Several other *NGLY1* mutations that cause CDDG have also been identified.

Demographics

CDDG is presumed to be extremely rare, since Might was the first identified case worldwide. Nevertheless, within a few months of his diagnosis, several more cases had been identified. Many of the children subsequently diagnosed with *NGLY1* deficiency had previously been diagnosed with Rett syndrome or a mitochondrial disorder, because the signs and symptoms are similar. CDG is also extremely rare, with fewer than 500 known cases in the United States.

Signs and symptoms

The signs and symptoms of *NGLY1* deficiency vary greatly and can be markedly different between males and females. Signs and symptoms include the following:

- global developmental delay
- movement disorders, including involuntary movements
- reduced or absent tear production (hypolacrima or alacrima, respectively), leading to ulceration and scarring of the cornea
- liver dysfunction, including elevated liver enzymes that may tend toward normal values over time
- a relatively small head (microcephaly) that may be present at birth or become apparent over time
- diminished reflexes or complete absence of reflex responses
- seizures in about half of patients, usually intractable and including sudden jerks (myoclonic seizures); drops, such as sudden dropping of the head (atonic seizures); and spells of staring (absence seizures)

- hypotonia (poor muscle tone)
- peripheral neuropathy—pain, numbness, muscle weakness, and atrophy of the peripheral nerves
- small hands and feet
- strabismus—eyes that wander in different directions

Diagnosis

Various clinical tests may suggest *NGLY1* deficiency, including the following:

- liver biopsy showing inflammation and substances stored in liver cells (vacuolization) that are presumed to be accumulated misfolded glycoproteins
- elevated liver transaminase levels
- sometimes elevated AFP levels
- abnormal oligosaccharides (sugars) in the urine, including keratan sulfate, heparan sulfate, and chondroitin sulfate
- abnormal brain features on magnetic resonance imaging (MRI), including enlarged ventricles (the chambers in the brain containing cerebrospinal fluid), delayed myelination (the covering of nerve fibers with white sheaths), loss of myelin covering nerve cells, and sometimes loss of nerve cell axons
- abnormal electroencephalography (EEG)
- normal results on tests for CDG

As of 2015, genetic testing for *NGLY1* mutations was available through the Emory Genetics Laboratory and the Baylor College of Medicine.

Treatment and management

As of 2015, treatment of *NGLY1* deficiency was directed at managing symptoms. For example, Might's seizures were treated with an antiseizure medication, which was only partially effective. He then went on a ketogenic diet, which is a very high-fat diet that forces the body to switch from glucose to ketones as an energy source. For reasons that are not well understood, a ketogenic diet is often effective for intractable epilepsy. Might's seizures diminished on the diet, but he developed tonic (stiffened muscle) seizures. Subsequently, he was injected twice daily with high doses of adrenocorticotrophic hormone (ACTH), which can sometimes halt intractable epileptic seizures. Although ACTH was effective in halting the seizures, the side effects were severe, and he developed a serious respiratory infection from the suppression of his immune system. After it was discovered that Might had severe vitamin deficiencies because his liver was unable to store vitamins, large doses of vitamins enabled him to form some tears for the first time. It has been suggested that certain antioxidants may

be useful for reducing stress on endoplasmic reticula in cells that are clogged with undegraded abnormal proteins.

Prognosis

The long-term prognosis for children with *NGLY1* deficiency is unknown. Symptoms may improve for a time but usually return. In the future, it may be possible to treat CDDG with synthetic N-glycanase 1.

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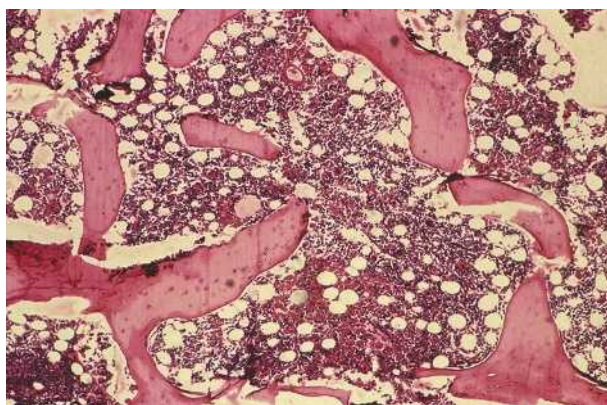
ORGANIZATIONS

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Light micrograph of bone marrow from a patient with Niemann-Pick disease, an inherited metabolic disorder in which a fatty substance called sphingomyelin accumulates in the spleen, lungs, liver, and bone marrow, sometimes the brain as well. (CNRI/Science Source)

main types of Niemann-Pick disease: NP type A (NPA), NP type B (NPB), and NP types C1 (NPC1) and C2 (NPC2). These types are based on the genetic mutations involved and the symptoms.

Description

Niemann-Pick disease is inherited through an autosomal recessive trait. The different types of NP are characterized by an abnormal accumulation of sphingomyelin. A sphingomyelin is any group of sphingolipids (consists of a lipid and a sphingosine) containing phosphorus. Accumulation occurs primarily in the tissue of the nervous system, including the brain.

Some characteristics of Niemann-Pick disease may be common for all types. Common symptoms include jaundice, hepatosplenomegaly (enlargement of the liver and spleen), physical and mental impairment, and feeding difficulties. Symptoms for most types of Niemann-Pick disease are seen in infancy or childhood.

Alternate names associated with the NP disorder are lipid histiocytosis, sphingomyelin lipidosis, and acid sphingomyelinase deficiency (ASD).

Genetic profile

NP is caused by an autosomal recessive genetic trait; therefore, the condition will not appear unless a person receives the same defective gene for fat metabolism from each parent. This means that if a person is heterozygous (i.e., has two different genes) for the trait, they will be a carrier, and if they are homozygous (i.e., have two of the same mutated genes), they will show the trait. There is a 25% chance for each pregnancy that the disorder will occur in the child(ren) if both parents are heterozygous

Niemann-Pick disease

Definition

Niemann-Pick disease (NP) is a disorder of fat metabolism that causes excessive quantities of lipids (fats) to accumulate in various organs, causing abnormalities of the skin, eyes, musculoskeletal system, nervous system, liver, and lymphoid organs. The disorder is named for German pediatricians Albert Niemann and Ludwig Pick. There are four

for the trait, and a 100% chance if both parents are homozygous for the trait.

NPA and NPB are caused by mutations in the *SMPD1* gene. This gene contains the instructions for making an enzyme called acid sphingomyelinase, which is important in the process of converting a lipid (fat) called sphingomyelin into a different lipid, called ceramide, so that it can be removed from cells. With too little of the enzyme sphingomyelinase, the lipid sphingomyelin accumulates to toxic levels within the cells, which causes cells to die. The death of these cells leads to organ failure, especially in the brain, lungs, liver, and spleen. NPA, which affects the brain, is the most severe type and is usually detected early in infancy. NPB is usually detected in mid-childhood. It does not affect the brain but causes abnormalities in the lungs spleen, and liver.

NPC1 is caused by mutations in the *NPC1* gene, and NPC2 is caused by mutations in the *NPC2* gene. Both genes are important in the production of a protein that helps cells move fats through the cell membrane and out of the cell. Scientists have identified more than 380 different mutations in the *NPC1* gene that can lead to NPC1. When these mutations occur, fat accumulates within the cell, leading to cellular death and causing movement problems, neurological impairment, lung and liver disease, and speech and feeding problems characteristic of NPC1 and NPC2.

Demographics

Niemann-Pick disease affects males and females equally and has been identified in all races. In the general population, it is thought to occur in about one in 250,000 individuals. It is much more common in people of eastern European Jewish descent (Ashkenazi), occurring in about one in 40,000 individuals. As many as one in 75 people in this ethnic group may be carriers of the mutated *SMPD1* gene. NPA is the most common form of the disease and is responsible for about 80% of NP disease cases. NPC1 is much more common than NPC2. NPC2 (formerly called NPD) occurs more often in descendants of French-Canadians (Acadians) from Nova Scotia.

Signs and symptoms

Type A

This is the infantile or acute form of Niemann-Pick disease. Abnormal accumulation of sphingomyelin is seen in the developing fetus. Sphingomyelin accumulation can represent 2% to 5% of the total body weight in individuals with type A. Symptoms may progress rapidly and include the following:

- Hepatosplenomegaly. Enlargement of the liver and spleen is due to the low levels of the enzyme

KEY TERMS

Allele—One of a pair of genes.

Hepatosplenomegaly—Enlargement of the liver and spleen.

Heterozygous—Having two different alleles for a genetic trait.

Homozygous—Having two identical alleles for a genetic trait.

Macula—Abnormal pigmentation in the tissue of the eye.

Sphingomyelin—A group of sphingolipids containing phosphorus.

Sphingomyelinase—An enzyme needed to break down sphingomyelin into ceramide.

sphingomyelinase, which is needed to break down sphingomyelin in the body. The decreased levels of this enzyme cause the sphingomyelin content of the liver and spleen to be abnormally high. Hepatosplenomegaly occurs between the ages of six and 12 months. Occurrence of liver enlargement is seen more commonly than that of the spleen.

- Musculoskeletal abnormalities. Degenerative muscle weakness and floppiness may occur due to a decline in motor and intellectual functioning. The cause is increased accumulation of sphingomyelin in the nervous system. Seizures and muscular spasms may also occur.
- Macula. Pigmentation in the tissue of the eyes may occur. Formation of cherry-red spots may be seen in approximately 50% of patients diagnosed with NPA. This is not visible and can only be detected by using special instrumentation.
- Additional abnormalities. These include jaundice, fever, and gastrointestinal (GI) problems such as vomiting, diarrhea, and abdominal distention.

Type B

This is the chronic form of Niemann-Pick disease. Symptoms progress slowly and begin during infancy through mid-childhood. Like type A, type B occurs due to a deficiency of the enzyme sphingomyelinase. Neurological involvement is minimal and usually absent. Symptoms are as follows:

- Hepatosplenomegaly. Abnormal enlargement of the liver and spleen occur due to the accumulation of sphingomyelin.

- **Macula.** The formation of cherry-red spots on the eyes may be seen in some affected individuals.
- **Additional abnormalities.** These include a slow growth rate and increased incidence of respiratory infections.

Type C1 and C2

These types of Niemann-Pick disease occur due to the inability of the body to break down cholesterol. This leads to a secondary deficiency of acid sphingomyelinase. The signs and symptoms of NPC1 and NPC2 are similar. They can develop at any time between infancy and adulthood but are usually seen in children between the ages of three and ten. The progression of symptoms in NPC1 and NPC2 are slow, and the losses of mental and motor function usually occur in early adulthood. Symptoms are as follows:

- **Hepatosplenomegaly.** The liver and spleen may be moderately enlarged due to the inability to break down cholesterol.
- **Musculoskeletal.** Psychomotor dysfunction, seizures, tremors, and spasticity of the muscles result due to excessive accumulation of cholesterol in the brain. An individual with NPC1 or NPC2 may also exhibit extreme muscle weakness due to emotional excitement and ataxia, which is the inability to coordinate voluntary muscle movements.
- **Eyes.** Both types of NPC are characterized by vertical gaze palsy. This results in the difficulty or loss of up-and-down movement. Some individuals may experience ophthalmoplegia (loss of muscle ability to move eyes). This is an impaired function of the muscles of the eyes and may cause the eyes to become stuck or fixed in an upward position.
- **Additional abnormalities.** These include dysarthria and jaundice. Dysarthria is the inability to form and speak words clearly. Jaundice is a yellow discoloration of the skin, the eyes, and possibly the mucous membranes.

Previously, there were three more identified types of Niemann-Pick disease: types D, E, and F. Researchers discovered that type D is actually a subset of NPC1 with the same genetic mutations. Niemann-Pick disease types E and F are rare and not well defined and are no longer used as diagnostic terms.

Diagnosis

Diagnosis of all types of NP is assisted by taking a detailed family history and a thorough examination of the individual. NPA and NPB are diagnosed through DNA testing or by a blood test. Blood tests for individuals with types A and B will show low levels of the enzyme sphingomyelinase in white blood cells and elevated sphingomyelin and free cholesterol. NPC1 and NPC2 can be diagnosed

QUESTIONS TO ASK YOUR DOCTOR

- How do the various types of Niemann-Pick disease differ from each other?
- How are each of these types of the disorder diagnosed?
- In what ways, if at all, is the treatment of Niemann-Pick dependent on the type of the disorder my child has?
- Are there groups interested in Niemann-Pick disease that can provide additional information and counseling about this condition?

by prenatal testing of fibroblastic cells to determine their ability to process and store cholesterol. This is done by testing the amniotic fluid (liquid that bathes and cushions the fetus). Formation of foam cells occurs in all types of Niemann-Pick disease and can be determined through a biopsy of bone marrow tissue.

Symptoms of Niemann-Pick disease may be similar to those of Refsum syndrome (a disorder of fat metabolism associated with abnormal accumulation of phytanic acid in the blood and other body tissues), Tay-Sachs disease (a disorder found in Eastern European Jewish descendants that results in deterioration of the central nervous system), Sandhoff disease (a lipid-storage disorder due to a deficiency of the enzyme hexosaminidase), Gaucher's disease (a lipid-storage disease), and sialidosis (a metabolic disorder due to a deficiency of the enzyme alpha-neuraminidase).

Treatment and management

There is no specific treatment available for any type of Niemann-Pick disease; however, as of 2021, phase 3 clinical trials of a drug are underway to treat NPC1. The drug is a formulation of hydroxypropyl beta cyclodextrin (Trappsol Cyclo). It is manufactured by Cyclo Therapeutics and has received orphan drug status. The drug is given intravenously. Participation in a clinical trial is voluntary and at no cost to the participant. All clinical trials receiving U.S. government funding, and some supported by private industry, are posted at <https://www.clinicaltrials.gov>. Foreign trials are listed at <https://www.orpha.net>

Until therapeutics become available to treat the various types of NP disease, individuals are treated on a symptomatic basis. People who are diagnosed with NPA and NPB have not benefited from enzyme-replacement therapies or organ transplants. Cholesterol-lowering

drugs and low-cholesterol diets are often used for individuals with NPC1 and NPC2.

Prognosis

The prognosis for all types of Niemann-Pick disease varies. In type A, death usually occurs in early childhood. In individuals with types C1 and C2, death usually occurs in adolescence or early adulthood. Individuals with type B have a prolonged survival rate due to the decrease of neurological involvement. Early diagnosis is important. Due to advances in medicine, an early diagnosis may increase life expectancy.

Affected individuals and their families may want to seek genetic counseling. Pregnant women can receive prenatal testing for some of the gene mutations that cause NP disease. Pregnant women who are likely carriers and have partners who are likely carriers should receive genetic counseling regarding the 25% chance of their child having NP disease.

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ORGANIZATIONS

National Niemann-Pick Disease Foundation, Inc. P.O. Box 49, 401 Madison Avenue, Suite B, Fort Atkinson, WI 53538, (877) 287-3672, (920) 563-0931, nnpdf@nnpdf.org, <https://www.nnpdf.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <https://rarediseases.org>

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Niikawa-Kuroki syndrome see **Kabuki syndrome**

Nijmegen breakage syndrome

Definition

Nijmegen breakage syndrome (NBS) is a condition in which chromosomes are susceptible to breakage. Symptoms include short stature, small head size, and increased risk for learning disabilities/intellectual disability, infections, and cancer.

Description

Nijmegen breakage syndrome gets its name from the fact that the first patient was described in Nijmegen in the Netherlands; a registry of patients is maintained there. Patients with the syndrome are susceptible to having their chromosomes break. These breaks result in rearrangements of chromosomes called translocations, in which two chromosomes exchange pieces, and inversions, in which a section of a chromosome breaks off and rejoins the chromosome upside down. Chromosome rearrangements in NBS most commonly involve chromosomes 7 and 14. Genes involved in the immune system are located on these chromosomes; as a result of disruptions of these genes, most patients with NBS have an increased rate of infections, particularly those involving the respiratory system and the urinary tract. The chromosome breaks also increase susceptibility to cancer. People with NBS are more prone to chromosome breaks when exposed to radiation as well. Other defining features of NBS are short stature and small head size.

Genetic profile

NBS is an autosomal recessive disease, which means that one abnormal gene from each parent must be inherited to develop symptoms. A person with only one defective gene copy is called a carrier and will not show signs of NBS but has a 50% chance of passing along the gene to offspring with each pregnancy. Couples in which both parents are carriers of NBS have a 25% chance in each pregnancy of conceiving an affected child. The gene for NBS is on chromosome 8 and is called the *NBS1* gene, coding for a protein called nibrin, which is found in all cells throughout the body. Normal nibrin is believed to be important in the repair of DNA that has been damaged by breaks in both strands.

Most patients have a specific change in both copies of the nibrin gene in which a string of five DNA bases, ACAA, is missing from a specific area of the gene, leading to a shortened, or truncated, version of nibrin. A few other mutations have been reported in single patients.

All of these mutations also result in a shortened, nonfunctional version of nibrin.

Demographics

NBS is extremely rare. Approximately 150 patients have been reported in medical literature. Most patients have been of Slavic or other European descent, with a few patients reported from New Zealand, Mexico, and the United States.

Signs and symptoms

Virtually all patients with NBS have microcephaly, or a small head size (in the lower 3%), with about 75% having this feature present at birth. Young children with NBS show impaired growth. Babies with NBS are either born small or begin to experience growth delay during their first two years. The growth rate is normal after that, but the children always remain small for their ages. According to data available, approximately 40% have normal intelligence, 50% have borderline to mild intellectual disability (IQ of 55 to 70), and 10% have moderate intellectual disability (IQ of 40 to 54). There is a characteristic facial appearance, which includes a receding forehead, long nose, receding chin, extra folds of skin underneath the eyes, freckles on the nose and cheeks, large ears, and thin hair. Patients frequently have café-au-lait spots (areas of skin that are the color of coffee with milk), and other pigment changes in the skin and eyes.

The incidence of certain birth defects is increased in NBS, with about half of patients having malformed fingers or extra skin between the fingers (called syndactyly). A few patients have been reported to have anal malformations, lack of development of the ovaries and consequent infertility, hip abnormalities, and bone, kidney, and brain abnormalities. Notably lacking is the ataxia, which is progressive loss of coordination, seen in a disorder called ataxia-telangiectasia (A-T), which is otherwise very similar to NBS but is caused by a mutation in a different gene.

People with NBS are at increased risk for infections, most commonly affecting the respiratory tract and urinary tract. Infections of the gastrointestinal tract have also been reported. They are also at increased risk for cancer, mostly B cell lymphoma. Leukemia and other cancers have also been reported.

Diagnosis

A diagnosis of NBS is suspected in children with small head size, slow growth at birth, characteristic facial features including a receding chin and prominent nose,

KEY TERMS

Balanced chromosome translocation—A rearrangement of the chromosomes in which two chromosomes have broken and exchanged pieces without the loss of genetic material.

Chromosome inversion—Rearrangement of a chromosome in which a section of a chromosome breaks off and rejoins the chromosome upside down.

Microcephaly—Abnormal smallness of the head; it is often associated with intellectual disability.

recurrent infections, cancer (particularly B cell lymphoma), and borderline to moderate intellectual disability. Prior to the discovery of the nibrin gene, diagnosis could only be confirmed by studying the levels of immune system proteins called immunoglobulins, looking for particular chromosomal changes involving chromosomes 7 and 14, and assessing radiation sensitivity in cells from patients.

The gene for NBS was discovered in 1998, so it is now possible to look for a mutation in a patient's nibrin gene. If a mutation other than the common one is found, it is important to do further investigation to determine whether or not it causes disease, as non-disease-causing changes have been reported in the nibrin gene.

Adults who are at risk for having children with NBS, such as siblings of patients, can have carrier testing to determine if they have one altered nibrin gene and are carriers for NBS. During pregnancy, the DNA of a fetus can be tested using cells obtained using the procedures called chorionic villus sampling (CVS), in which cells from the placenta are studied, or amniocentesis, in which skin cells from the amniotic fluid surrounding the baby are tested.

Treatment and management

There is no specific treatment for NBS, although folic acid (a vitamin B derivative) is recommended for prevention of chromosome breaks, since repair of these breaks is compromised in NBS. Similarly, vitamin E is recommended for prevention of further cell damage. For treatment of cancer, high doses of radiation must be avoided, since the damage inflicted on the cells could be fatal. Research studies in 2015 provided proof of concept studies in mice for the use of antisense oligonucleotides as a potential cancer prophylaxis for patients with NBS.

QUESTIONS TO ASK YOUR DOCTOR

- To what does the term “breakage” refer in the name of this disorder?
- Is there a way to prevent the occurrence of Nijmegen breakage syndrome in our future children?
- How common is Nijmegen breakage syndrome in the United States and worldwide?
- What medical problems are typically associated with this condition?

Prognosis

Patients with NBS have a decreased lifespan because of the tendency toward infection and cancer. Most patients do not survive past 30–40 years of age.

Resources

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- “Nijmegen breakage syndrome.” Medscape. <https://emedicine.medscape.com/article/1116869-overview> (accessed June 15, 2021).

ORGANIZATIONS

- Immune Deficiency Foundation, 110 West Rd., Suite 300, Towson, MD 21204, (800) 296-4433, (410) 321-9165, <http://primaryimmune.org>.
- Leukemia & Lymphoma Society, 1311 Mamaroneck Ave., Suite 310, White Plains, NY 10605, (914) 949-5213, (914) 949-6691, <http://www.lls.org>.

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Noack syndrome see **Pfeiffer syndrome**

Noninvasive prenatal screening

Definition

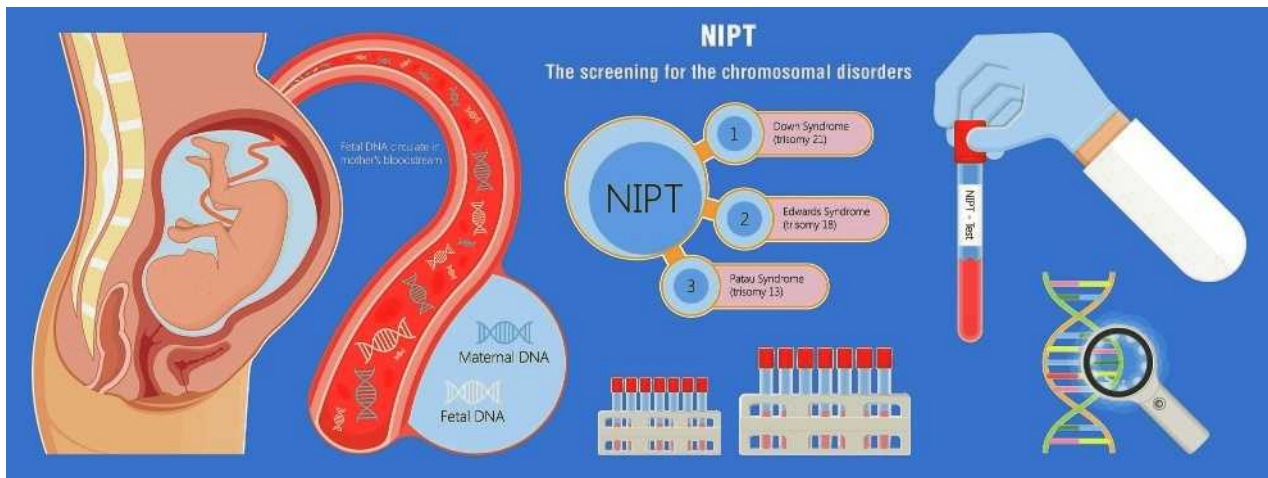
Noninvasive prenatal screening (NIPS) is an assay or blood test given to a pregnant woman to estimate the risk that the unborn child has a chromosome disorder. It is also known as noninvasive prenatal testing (NIPT), the cell-free fetal DNA test, or the cell-free DNA prenatal screen for fetal aneuploidy, its formal name. *Aneuploidy* is the medical term for an abnormal number of chromosomes in a cell, whether extra or missing chromosomes.

Purpose

The most common reason for performing NIPS is to screen the fetus during the first trimester of pregnancy for an increased risk of three trisomies (chromosome disorders in which there are three copies of specific chromosomes): trisomy 13 (Patau syndrome); trisomy 18 (Edwards syndrome); and trisomy 21 (Down syndrome). While Down syndrome is the most common trisomy, its symptoms vary considerably in severity. Some children with the syndrome are able to finish high school and find employment with accommodation. On the other hand, about 90% of children born with Patau syndrome or Edwards syndrome die within a year after birth.

A version of NIPS called genome-wide NIPS can be used to screen all 23 sets of human chromosomes; thus, it can screen for disorders of the sex chromosomes, which also means that it can be used to identify the child's sex before birth. Genome-wide NIPS can also be used to screen for microdeletion syndromes, which are a group of disorders characterized by the loss of small segments of DNA from specific chromosomes. With the exception of DiGeorge syndrome, caused by a microdeletion on chromosome 22 at 22q11.2 that leads to the loss of 30 to 40 genes, most microdeletion syndromes are quite rare.

In addition, it is not clear as of 2021 whether present genome-wide versions of NIPS are as effective in identifying microdeletions as more widely recognized types of diagnostic testing. Researchers at Harvard University reported in March 2021 that genome-wide NIPS does not detect clinically significant chromosomal abnormalities at the same rate as chromosomal microarray (CMA) testing. CMA testing is a procedure in which samples of DNA from the patient and a control subject are labeled with two different fluorescent substances, then mixed and allowed to bind (hybridize) to short fragments of synthetic DNA, known as probes, on the surface of the microarray (a glass or plastic chip). The chip can then be analyzed to see whether the patient's DNA binds to



Noninvasive prenatal testing. (Shutterstock/rumruay)

sequences on the chip representing normal DNA or whether it binds to sequences containing a microdeletion.

Precautions

There are several precautions to keep in mind regarding NIPS. First of all, although the procedure is sometimes called a noninvasive prenatal test or NIPT, it is *not* a diagnostic test; it can only assess whether the risk of a chromosomal aberration is high or low. This characteristic means that NIPS can yield both false positives (indicating that the fetus has an abnormality when in fact it does not) and false negatives (indicating that genetic abnormalities are not present when they actually are). For this reason, genetic counselors and gynecologists recommend that a positive result from NIPS be followed up by an invasive diagnostic test like amniocentesis or chorionic villus sampling to confirm the positive finding.

A second precaution in regard to NIPS is that the accuracy of the test is affected by its timing (number of weeks of gestation) and by the patient's body mass index (BMI). Because NIPS analyzes cell-free fetal DNA (cffDNA) that is circulating in the patient's bloodstream, there must be a sufficient quantity of this type of DNA to yield reliable results. Cell-free fetal DNA is present in the mother's blood when the bloodstream contains both material from the placenta and cell-free DNA from the mother herself. The proportion of cell-free DNA that comes from the placenta is called the fetal fraction, and it should be above 4% for best results. The fetal fraction does not usually reach this level until the tenth week of pregnancy, and it is also inversely proportionate to the mother's weight. If the fetal fraction is too low, it may mean that the sample was taken too early; that the mother is obese; or that the fetus is abnormal.

A third precaution is the need for counseling if the results of the screening test are positive and/or if the determination of the baby's sex is problematic for the parents. Since NIPS was introduced by private health care providers in 2011, it has been introduced in some countries by public health care services, partly because of its noninvasiveness and partly because of its relatively low expense. Its increased use means, however, that growing numbers of people from countries with widely varying ethical attitudes toward pregnancy termination are confronted with difficult decisions. In some countries, most notably Germany, policy debates about the provision of public health insurance for NIPS are heated because of concerns about reviving the eugenic practices of the Nazi era (1933–1945), during which children with genetic disorders were euthanized. In other countries, the possibility of using NIPS for prenatal sex selection is worrisome because of a strong popular preference for male children. As a result, health care providers in most countries urge patients to undergo follow-up diagnostic testing along with consultation with their gynecologist and a genetic counselor before making a decision about the pregnancy on the basis of NIPS screening alone.

Description

NIPS is done by a simple blood draw from the patient's arm. After the sample is taken, it is sent to a laboratory for measurement of the fetal fraction and evaluation of the cell-free fetal DNA contained in the sample. It takes about a week for the results of the screening test to be reported to the patient's doctor.

Preparation

No physical preparation is needed for the blood draw. However, even though NIPS is a standard

KEY TERMS

Amniocentesis—A diagnostic procedure in which a small sample of amniotic fluid is withdrawn from the uterus of a pregnant woman through a needle inserted in the abdomen. The fluid is then analyzed to detect genetic abnormalities in the fetus or to determine fetal sex.

Aneuploidy—An abnormal number of chromosomes in a cell, whether extra or missing chromosomes.

Assay—A laboratory test designed to identify and measure the amount of a specific substance.

Base pair (bp)—Any of the complementary nucleotide bases (adenine-thymine and cytosine-guanine in DNA; adenine-uracil and cytosine-guanine in RNA) held together by weak hydrogen bonds. Base pairs form links between the two strands of DNA.

Body mass index (BMI)—A measure of body fat derived from a person's height and weight. It is calculated by taking the person's weight in kilograms and dividing by the square of the person's height in meters.

Chorionic villus sampling (CVS)—An invasive diagnostic test for genetic disorders in which a small sample of cells is taken from the placenta of a pregnant woman, either through the cervix or through the abdominal wall for testing.

Chromosomal aberrations—A general term for abnormalities in either the number or the structure of chromosomes.

Chromosomal microarray (CMA) testing—A prenatal genetic test used to diagnose microdeletion syndromes and some aneuploidies. It consists of DNA samples from the patient and a reference source that have been labeled with fluorescent dyes and allowed to hybridize or bind to the synthetic DNA on the glass or plastic chip. The chip is then scanned by a computer to determine whether the patient's DNA binds to the normal DNA sequence or whether it binds to the sequence representing a DNA mutation.

Ethics—The branch of philosophy dealing with questions of good and evil, and with moral duties and obligations in human society.

Eugenics—A set of beliefs and practices intended to improve the genetic quality of a country's human population, either by limiting the reproduction of people considered unfit or by encouraging the reproduction of healthier, more intelligent, and more attractive people.

False negative—A test result that indicates that a disease or condition is not present when it really is; sometimes called a type II error.

False positive—A test result that indicates that a person has a disease or condition when they do not; it is sometimes called a type I error.

Fetal fraction—The proportion of cell-free DNA in a pregnant woman's blood that comes from the placenta. The fetal fraction should be above 4% for the most accurate results.

Genome—The total amount of genetic information within an organism's chromosomes, including its genes and DNA sequences.

Microdeletion—A chromosome deletion that is too small to be detected by standard karyotyping methods. Microdeletions are typically one to three mega bases in length (one to three million base pairs), whereas standard deletions are five mega bases or longer.

Nuchal—Referring to the nape of the neck.

Phlebotomist—A nurse or other health care worker with special training in drawing venous blood for testing or analysis.

Placenta—An organ that develops in humans and other mammals during pregnancy that lines the wall of the uterus and is attached to the fetus by the umbilical cord. It is sometimes called the afterbirth because it is expelled from the uterus after the baby is delivered.

Trisomy—A type of aneuploidy in which there are three copies of a specific chromosome in cells instead of the normal two. Genetic disorders caused by trisomies include Down syndrome (trisomy 21) and Edwards syndrome (trisomy 18).

procedure offered to pregnant women in the United States as of 2021, the patient should discuss the screener with her gynecologist before the test to be sure she understands why it is recommended and whether it is the right test for her. Some laboratories offer patients

a choice about screening for sex chromosome abnormalities and/or microdeletion syndromes in addition to the standard aneuploidies, and the patient should consider whether she prefers to opt in or opt out for this information.

QUESTIONS TO ASK YOUR DOCTOR

- What is your opinion of NIPS as a genetic screening test?
- Do you recommend it to your pregnant patients?
- What advice or counseling do you give patients before the test?
- Do you think that future versions of NIPS will be able to screen for a wider range of genetic disorders?

Aftercare

Aftercare for NIPS is the same as for any other blood test; the nurse or phlebotomist applies a clean dressing over the location of the venipuncture. The patient is asked to apply gentle pressure for a few seconds to help the blood clot and to keep the dressing on the arm for a few hours.

Risks

One reason why NIPS is increasingly recommended to patients is that it carries no risk to the pregnancy, in contrast to invasive diagnostic tests. There are few risks to the blood test itself. Some patients may experience swelling or minor bruising at the site of the venipuncture, but applying ice to the area or taking an over-the-counter pain reliever is all that is usually needed. The risk of infection is very low.

Results

The result of a NIPS test are given as positive or increased/high risk; negative or low risk; and indeterminate or “no call.” A positive result means that the fetus has a higher chance of having the chromosomal abnormality in question; it does not mean that the fetus definitely has the abnormality. Similarly, a negative result does not mean that the fetus does not have the chromosomal abnormalities being tested for, only that the risk is lower.

An indeterminate or “no call” finding may mean that the test was performed too early in the pregnancy, before there was enough cffDNA in the mother’s blood to be detected in the test. It can also mean that the mother’s weight has affected the test results, as obese women have a lower proportion of cffDNA in their blood. Last, an indeterminate finding is more likely if the mother is carrying twins or triplets.

Gynecologists generally recommend an invasive diagnostic test like amniocentesis or chorionic villus sampling, rather than repeating NIPS, if the test results are indeterminate.

Alternatives

Alternatives to NIPS for first-trimester genetic screening include:

- **Maternal blood serum screening.** The mother’s blood can be measured for pregnancy-associated plasma protein A (PAPP-A) and for human chorionic gonadotropin (hCG), a hormone that is important in the early stages of pregnancy. Low levels of PAPP-A and high levels of hCG indicate an increased risk that the fetus has Down syndrome.
- **Nuchal transparency measurement.** Nuchal transparency refers to a clear space at the back of the baby’s neck that can be detected by ultrasound. An enlargement of this space (greater than the 99th percentile for the fetus’s gestational age) indicates an increased risk of Down syndrome.

Another option is to wait until the second trimester of pregnancy and perform the following screening tests:

- **Maternal blood serum screening.** In the second trimester, this test will include measurements of alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol (a female sex hormone whose levels are increased during pregnancy), which is called a triple screen. If inhibin A (a protein complex that can be used to screen for Down syndrome) is also measured, the test is called a quad screen.
- **Integrated screening.** In integrated screening, the results of first-trimester screening tests are combined with the findings of second-trimester tests.

If any of these screening tests yields a positive result, indicating an increased risk of a chromosomal disorder, gynecologists recommend offering the patient diagnostic testing by CVS or amniocentesis.

Research

There are 56 clinical trials of NIPS registered with the NIH as of mid-2021, in countries including France, Denmark, the United Kingdom, Sweden, Belgium, Italy, and Turkey as well as the United States and Canada. Some of these trials are evaluating the accuracy of NIPS in detecting single-gene (monogenic) disorders or micro-deletion syndromes, while other trials are concerned with evaluating patients’ access to NIPS, their responses to the test, or designing modified versions of NIPS to be used in screening multiple pregnancies.

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- American Society of Human Genetics (ASHG), 6120 Executive Boulevard, Suite 500, Rockville, MD 20852, (301) 634-7300, society@ashg.org, <https://www.ashg.org/>
- American Society for Reproductive Medicine (ASRM), J. Benjamin Younger Office of Public Affairs, 726 7th Street, SE, Washington, D.C. 20003, (202) 863-4985, asrm@asrm.org, <https://www.asrm.org/>
- Chromosome Disorder Outreach, Inc., P.O. Box 724, Boca Raton, FL 33429-0724, (561) 395-4252, info@chromodisorder.org, <https://chromodisorder.org>
- National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, <https://www.genome.gov/about-nhgri/Contact>, <https://www.genome.gov/>
- National Society of Genetic Counselors (NSGC), 330 North Wabash Avenue, Suite 2000, Chicago, IL 60611, (312) 321-6834, nsgc@nsgc.org, <https://www.nsgc.org>
- Society for Maternal-Fetal Medicine (SMFM), 409 12th Street, SW, Washington, D.C. 20024, [no telephone number given], smfm@smfm.org, <https://www.smfm.org/>

Rebecca J. Frey, PhD

Nonpolyposis colon cancer see **Muir-Torre syndrome**

Noonan syndrome

Definition

Noonan syndrome is a relatively common genetic condition with a wide range of symptoms. People with Noonan syndrome can have many different features, but the most common are unique facial features, a heart defect at birth and/or heart problems later in life, short stature, a broad or webbed neck, chest deformities, and intellectual disability.

Description

Noonan syndrome was first described by the pediatrician and heart specialist Jacqueline Noonan in 1963. It is part of a group of conditions that are caused by pathogenic variants (mutations) in genes in the RAS-MAPK pathway, which allows cells to communicate and affects processes like cell growth and death. This group of conditions, including Noonan syndrome, are sometimes called RASopathies. There can be overlap in symptoms between Noonan syndrome and different RASopathies, which can sometimes make the diagnosis difficult. Since Noonan syndrome can be caused by variants in many different genes, it can cause a wide range of symptoms, and different individuals often have different combinations of characteristics. A diagnosis of Noonan disease is usually first made through examination of clinical features, detailed physical examination, and family and medical history. The next step is usually genetic testing. About 20 out of 100 people with this condition (20%) do not have a known gene variant, since not all variants have been discovered.

Genetic profile

Noonan syndrome can be caused by variants (mutations) in over 20 genes. Nine genes involved in the RAS-MAPK pathway are known to be associated with 70% to 85% of patients with Noonan Syndrome. These genes are PTPN11 (responsible gene for 50% of patients), SOS1, KRAS, NRAS, BRAF, RAF1, MAP2K1, CBL, and SHOC2.

In most cases, Noonan syndrome is inherited in an autosomal dominant manner. This means that an affected individual has one copy of the gene variant and has a 50% chance of passing it on to their male or female children. About half of people with Noonan syndrome have a family history of it. For the other half, the gene variant likely occurred as a new event in their conception, which means that they were the first person in their family to be diagnosed with the condition. The person with this new

mutation would have a 50% chance of passing it on to their children.

In some rare cases, Noonan syndrome can be inherited in an autosomal recessive manner. For example, there have been at least 12 families with variants in the LZTR1 gene that appear autosomal recessive. In those families, the parents of affected children have a variant in one copy of the LZTR1 gene but do not have any symptoms. Their children with Noonan syndrome all had variants in both copies of the LZTR1 gene, which they inherited from both parents. The parents are considered silent carriers, since they do not have any symptoms, which is fairly common in autosomal recessive conditions. With this type of inheritance, only parents who are both carriers of variants in the same gene can have an affected child. Two carriers have a 25% chance of having an affected male or female child. Parents who are blood-related are more likely to have a child with a recessive condition, since they are more likely to have similar gene variants.

Demographics

Noonan syndrome occurs in between one in 1,000 and one in 2,500 live births. It does not seem to be more likely to affect a certain ethnicity, although many studies have been done in only a few countries such as the Netherlands, Canada, and the United States.

Signs and symptoms

Symptoms of Noonan syndrome are common at birth. People with Noonan syndrome are often born with heart defects. Pulmonary stenosis, which causes a blockage of flow of blood, resulting from a narrowing in part of the heart, is the most common heart defect. Muscle weakness is sometimes present, as is increased flexibility of the joints. Occasionally, feeding problems may occur



Ultrasound showing a cardiac deformity as the result of Noonan syndrome. (Dr. Darsin/Science Source)

KEY TERMS

Amniocentesis—A procedure performed at 16 to 18 weeks of pregnancy, in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Café-au-lait spots—Birthmarks that may appear anywhere on the skin; named after the French coffee drink because of the light-brown color of the marks.

Cryptorchidism—A condition in which one or both testes fail to descend normally.

Cystic hygroma—An accumulation of fluid behind the fetal neck, often caused by improper drainage of the lymphatic system in utero.

Karyotype—A standard arrangement of photographic or computer-generated images of chromosome pairs from a cell in ascending numerical order, from largest to smallest.

Neurofibromatosis—A progressive genetic condition often including multiple café-au-lait spots, multiple raised nodules on the skin known as neurofibromas, developmental delays, slightly larger head sizes, and freckling of the armpits, groin area, and iris.

Nystagmus—Involuntary, rhythmic movement of the eye.

Pectus carinatum—An abnormality of the chest in which the sternum (breastbone) is pushed outward. It is sometimes called "pigeon breast."

Pectus excavatum—An abnormality of the chest in which the sternum (breastbone) sinks inward; sometimes called "funnel chest."

Phenotype—The physical expression of an individual's genes.

Pterygium colli—Webbing or broadening of the neck, usually found at birth and usually on both sides of the neck.

Pulmonary stenosis—Narrowing of the pulmonary valve of the heart, between the right ventricle and the pulmonary artery, limiting the amount of blood going to the lungs.

Strabismus—An improper muscle balance of the ocular muscles resulting in crossed or divergent eyes.

Suture—"Seam" that joins two surfaces together.

Turner syndrome—Chromosome abnormality characterized by short stature and ovarian failure, caused by an absent X chromosome. Occurs only in females.

in infants with Noonan syndrome, because of a poor sucking reflex. Short stature by adulthood is common, though birth length is typically normal. Developmental delays may become apparent, because individuals are slower to attain milestones, such as sitting and walking. Behavioral problems may be more common but often are not significant enough for medical attention.

Many facial features are found in Noonan syndrome, often involving the eyes. Eyes may be wide-set or may appear half-closed because of droopy eyelids, and the corners may turn downward. Some other findings, such as nystagmus and strabismus, may occur. Interestingly, most people with Noonan syndrome have pale blue- or green-colored eyes. Often, the ears are low-set (lower than eye-level), and the top portion of cartilage on the ear is folded down more than usual. Hearing loss may occur, most often due to frequent ear infections. A very high and broad forehead is common. An individual's face may take on an inverted triangular shape. As mentioned earlier, facial features may change over time. An infant with the syndrome may appear more striking than an

adult who has it, as the features may gradually become less obvious. Sometimes, studying childhood photographs of an individual's presumably "unaffected" parents may reveal clues. Parents may have more obvious features of the condition in their childhood photographs.

Chest wall abnormalities, such as a shield chest, pectus carinatum, and pectus excavatum, occur in the majority of people with NS1. These are thought to occur because of early closure of the sutures underneath these areas. Additionally, widely spaced nipples are not uncommon. Scoliosis (curving of the spine) may occur, along with other spine abnormalities.

Lymphatic abnormalities may be common, often due to abnormal drainage or blockage in the lymph glands. This may cause lymphedema, or swelling, in the limbs. Lymphedema may occur behind the neck (often prenatally), and this is thought to be the cause of the broad/webbed neck in the condition. Prenatal lymphedema is thought to obstruct the proper formation of the ears, eyes, and nipples as well, causing the mentioned abnormalities in all three.

Individuals with Noonan syndrome may have problems with coagulation, shown by abnormal bleeding or mild-to-severe bruising. Von Willebrand disease and abnormalities in levels of factors V, VIII, XI, XII, and protein C (all proteins involved in clotting of blood) are common, alone or in combination. These problems may lessen as the person ages, even though the mentioned coagulation proteins may still be present in abnormal amounts. Rarely, some forms of leukemia and other cancers occur.

Kidney problems are often mild but can occur in patients with Noonan syndrome. The most common finding is a widening of the pelvic (cup-shaped) cavity of the kidney. In males, smaller penis size and cryptorchidism are sometimes seen. Cryptorchidism may lead to improper sperm formation in these men, although sexual function is typically normal. It is not as common to see an affected man have a child with Noonan syndrome, and this is probably due to cryptorchidism. Puberty may be delayed in some women with NS1, but fertility is not usually compromised.

Lastly, follicular keratosis is common on the face and joints. It is a set of dark birthmarks that often show up during the first few months of life, typically along the eyebrows, eyes, cheeks, and scalp. Generally, it progresses until puberty and then stops. Sometimes, it may leave scars, which may prevent hair growth in those areas. Café-au-lait spots can occur, not unlike those seen in neurofibromatosis.

Diagnosis

Diagnosing Noonan syndrome comes from a clinical diagnosis, based on findings and symptoms. Genetic testing can help diagnose this syndrome. One challenge faced in the diagnosis of Noonan syndrome is that there are several conditions that mimic it. If a female has symptoms, a chromosomal study is crucial to determine whether she has Turner syndrome, as she would have a missing X chromosome. Other chromosomal conditions that are similar include trisomy 8p (three copies of the small arm of chromosome 8) and trisomy 22 mosaicism (mixed cell lines, with some having three copies of chromosome 22). A karyotype would help to rule these out.

Cardio-facio-cutaneous syndrome (CFC) can be confused with Noonan syndrome, since it results in similar facial features, short stature, lymphedema, and developmental delays, as well as similar heart defects and skin findings. These conditions likely have similar features because they both result from gene variants in the same RAS-MAPK pathway. There are other similar conditions that result from variants in genes in the same pathway (for

QUESTIONS TO ASK YOUR DOCTOR

- Are there visual signs by which Noonan syndrome can be diagnosed, and are these signs a sufficient basis for diagnosing the condition?
- What are the most serious medical problems associated with this genetic disorder?
- What information or advice can a genetic counselor provide about the possibility of our having a child with Noonan syndrome?
- Please describe the challenges we would face in the future as the parents of a child with Noonan syndrome.

example, Watson and multiple lentigines/LEOPARD syndrome, which are also associated with pulmonary stenosis, wide-set eyes, chest deformities, and mental delays). Genetic testing can help differentiate conditions resulting from different gene variants on this pathway.

Most individuals are diagnosed with Noonan syndrome in childhood. A diagnosis can sometimes be made during pregnancy, since lymphedema, cystic hygroma, heart defects, and sometimes facial features can sometimes be seen on a prenatal ultrasound. Prenatal testing of the fetus can be done to help make a diagnosis.

Artificial intelligence

Promising research suggests that computers may help diagnose Noonan syndrome. In one study, a computer analyzed pictures of people with and without Noonan syndrome and were able to make an accurate diagnosis 91% of the time. This type of technology may be particularly helpful for Noonan syndrome, which can be difficult to diagnose.

Treatment and management

Treatment is symptom-specific, as not everyone will have the same needs. For short stature, some individuals have responded to growth hormone therapy. The exact cause of the short stature is not well defined, and therapies are currently being studied. Muscle weakness and early developmental delays often necessitate an early intervention program, which combines physical, speech, and occupational therapies. Heart defects need to be closely followed, and treatment can sometimes include beta blockers or surgeries, such as opening of the pulmonary valve. For individuals with clotting problems, aspirin and medications containing it should be avoided, as

they prevent clotting. Treatments using various blood factors may be necessary to help with proper clotting. Drainage may be necessary for problematic lymphedema, but it is rare. Cryptorchidism may be surgically corrected, and testosterone replacement should be considered in males with abnormal sexual development. Back braces may be needed for scoliosis and other skeletal problems. Unfortunately, medications such as creams for the follicular keratosis are usually not helpful. Developmental delays should be assessed early, and special education classes may help. In summary, these various treatment modalities require careful coordination, and many issues last for a patient's entire life. A team approach may be beneficial.

New treatment for heart problems and lymphatic disorders

Promising research suggests that a drug called Trametinib appears to improve the outcome for some infants with Noonan syndrome and heart problems. This drug has been tested on infants who have a variant in the RIT1 gene. Normally, only 34% of these infants survive to one year. This drug also appears to help some people with Noonan syndrome who also have lymphatic disorders.

Prognosis

Prognosis for Noonan syndrome is largely dependent on the extent of the various medical problems, particularly heart defects. Individuals with a severe form of the condition may have a shorter lifespan than those with a milder presentation. In addition, presence of mental deficiency in 25% of individuals affects the long-term prognosis.

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ORGANIZATIONS

Noonan Syndrome Foundation, (866) 875-8928, (866) 875-1258, info@teamnoonan.org, <http://www.teamnoonan.org>

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Norman-Landing disease see **GM1-gangliosidosis**

Norrie disease

Definition

Norrie disease (ND) is blindness that is evident at birth or within the first few months of life and may involve deafness, intellectual disability, and behavioral problems.

Description

ND was first described in the 1920s and 1930s as an inherited form of blindness affecting only males. Recognizable changes in certain parts of the eye were identified that lead to a wasting-away or shrinking of the eye over time.

At birth, a grayish yellow tumor-like mass is observed to cover or replace the retina of the eye, whereas the remainder of the eye is usually of normal shape, size and form. Over time, changes in this mass and progressive deterioration of the lens, iris, and cornea cause the eye to appear milky in color and become very small and shrunken. ND is always present in both eyes and although some abnormalities in the eye develop later, blindness is often present at birth. Some degree of intellectual disability, behavior problems, and deafness may also occur.

ND is inherited in an X-linked recessive manner, affecting almost only males. The gene for ND was found in the 1990s and genetic testing is available.

ND has also been referred to as the following:

- Norrie-Warburg syndrome
- Atrophia bulborum hereditaria

KEY TERMS

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light, resulting in blurry vision. Surgery may be performed to remove the cataract.

Cochlea—A bony structure shaped like a snail shell located in the inner ear. It is responsible for changing sound waves from the environment into electrical messages that the brain can understand, so people can hear.

Cornea—The transparent structure of the eye over the lens that is continuous with the sclera in forming the outermost protective layer of the eye.

Iris—The colored part of the eye, containing pigment and muscle cells that contract and dilate the pupil.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

- Congenital progressive oculo-acoustico-cerebral degeneration
- Episkopi blindness
- Pseudoglioma congenita

Genetic profile

ND is an X-linked recessive condition that affects primarily males. Genetic studies of many families led to the identification of the gene *NDP* (Norrie disease protein), which is located at Xp11 that is on the shorter or upper arm of the X chromosome. *NDP* encodes the protein Norrin, whose function is not well understood. Preliminary evidence suggests that norrin plays a role in directing how cells develop to become specialized (differentiation).

Many different kinds of mutations have been described for the *NDP* gene that were thought to lead to ND. The majority of these mutations are called point mutations, which alter just a single unit of the genetic code. Most of the identified point mutations are unique to the type of ND occurring in a family, but the type of point mutation does not seem to determine severity of disease. Other errors that can alter the *NDP* gene are called deletions, which permanently remove a portion of the genetic code from the gene. Individuals with deletions in the *NDP* gene are thought to have more severe forms of ND that usually include profound intellectual disability, seizures, small head size, and growth delays.

The X chromosome is one of the human sex chromosomes. A human being has 23 pairs of chromosomes in each cell of their body. One of each chromosome is inherited from the mother and the other is inherited from the father, making a total of 46 chromosomes. The 23rd pair is the sex chromosome pair. Females have two X chromosomes and males have an X and Y chromosome pair. Females therefore, have two copies of all the genes on the X chromosome but males have only one copy. Mothers pass on either one of their X chromosomes to all of their children, and fathers pass on their X chromosome to their daughters and their Y to their sons.

Males affected with ND have a mutation in the only copy of the *NDP* gene on their X chromosome and cannot make any normal norrin protein. Mothers of such affected males are usually carriers of ND; they have one *NDP* gene with a mutation on one X chromosome and one normal *NDP* gene on the other X chromosome that is sufficient for norrin protein function, so that they do not show signs of ND. Women that are carriers for ND have a 50% chance of passing the disease gene onto each of their children. If that child is male he will be affected with ND; if that child is female she will be a carrier of ND but not affected. Affected males that have children would pass on their disease gene to all of their daughters who would be carriers of ND. Their sons inherit their Y chromosome and would not inherit the gene for ND from their fathers.

Genetic testing for mutations in the *NDP* gene is clinically available to help confirm a diagnosis of ND. As of 2021, this testing is able to identify gene mutations in about 70% of affected males. If such a mutation were found in an affected individual, accurate carrier testing would be available for females in that family. Additionally, diagnosis of a pregnancy could be offered to women who are at risk for having sons with ND.

Demographics

ND has been observed to affect males of many ethnic backgrounds, and no ethnic group appears to predominate. The incidence is unknown, however.

Signs and symptoms

The first sign of ND is usually the reflection of a white area from within the eye, which gives the appearance of a white pupil. This is caused by a mass or growth behind the lens of the eye that covers the retina. This mass tends to grow and cause total blindness. It may also develop blood vessels that may burst and further damage the eye. At birth the iris, lens, cornea, and globe of the eye are generally otherwise normal. The problems in the retina develop over the first few months and until about

QUESTIONS TO ASK YOUR DOCTOR

- Are there medical problems other than vision loss associated with Norrie disease?
- Are there prenatal tests or other procedures by which Norrie disease can be diagnosed in our child?
- What types of medications, surgical procedures, or other procedures are recommended for the care of a child with Norrie disease?
- What associations or agencies assist parents and children with Norrie disease?

10 years of age progressive changes in other parts of the eye can also occur. Cataracts form, and the iris can stick or become attached to the cornea and/or the lens of the eye. The iris will also often decrease in size as ND impairs the development and growth of the eye. Pressure in the fluid within the eye may increase, which can be painful. The retina often becomes detached and may thicken. Toward the end stages of the disease, the eye globe is seen to shrink considerably in size and appear sunken within the eye socket. In cases of ND both eyes are usually affected, and the changes are usually the same in each eye.

Approximately 50% of affected males have some degree of developmental delay or intellectual disability. Some may show behavioral problems or psychosis-like features. Hearing loss may develop in 30%–40% of males with ND starting in early childhood. If speech is developed before the onset of deafness, it is usually preserved. Mental impairment and hearing loss do not necessarily occur together. The role that the norrin protein plays in causing mental impairment and hearing loss is unknown.

The symptoms associated with ND are diverse within a family as well as between families. On rare occasions, carrier females may show some of the retinal problems, such as retinal detachment, and may have some degree of vision loss.

Diagnosis

The diagnosis of ND is usually made by clinical examination of the eye by an ophthalmologist. Gene testing can be pursued as well, keeping in mind that as many as 30% of affected males cannot be identified using current methods.

The symptoms of ND have considerable overlap with a few other eye diseases, and ND must be distinguished from other eye conditions:

- Persistent hyperplastic primary vitreous (PHPV)
- Familial exudative vitreoretinopathy (FEVR)
- Retinoblastoma (RB)
- Retinopathy of prematurity (ROP)
- Incontinentia pigmenti type 2 (IP2)

PHPV and FEVR have been shown to be associated with mutations in the *NDP* gene and may represent a more mild condition in the broad spectrum of ND.

Treatment and management

Since the symptoms of ND are often present at birth, little can be done to change them or prevent the disease from progressing. If the retina is still attached to the back of the eye, surgery or laser therapy may be helpful. An ophthalmologist should follow all children with ND to monitor the changes in the disease, including the pressure within the eye. Occasionally surgery may be necessary, and rarely the eye is removed because of pain.

The child's hearing should also be monitored regularly so that deafness can be detected early. For individuals with hearing loss, hearing aids are usually quite successful. Cochlear implants may be considered when hearing aids are not helpful in restoring hearing.

Developmental delays or intellectual disability, as well as lifelong behavioral problems, can be a continuous challenge. Educational intervention and therapies may be helpful and can maximize a person's educational potential.

Prognosis

The lifespan of an individual with ND may be within the normal range. Risks associated with deafness, blindness, and intellectual disability, including injury or illness, might shorten the lifespan. General health, however, is normal.

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- American Council of the Blind, 1155 15th St. NW, Suite 720, Washington, DC 20005, (202) 467-5081, (800) 424-8666, <http://www.acb.org>
- American Society for Deaf Children, PO Box 3355, Gettysburg, PA 17325, (717) 334-7922, (800) 942-ASDC, <http://deafchildren.org>
- National Association of the Deaf, 814 Thayer, Suite 250, Silver Spring, MD 20910-4500, (301) 587-1788, nadinfo@nad.org, <http://www.nad.org>
- National Federation for the Blind, 1800 Johnson St., Baltimore, MD 21230, (410) 659-9314, epc@roundley.com, <http://www.nfb.org>
- Norrie Disease Association, Massachusetts General Hospital, E No. 6217, 149 13th St., Charlestown, MA 02129, (617) 726-5718, sims@helix.mgh.harvard.edu, <http://www.norriedisease.org>

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Nucleic acid therapies

Definition

Nucleic acid therapies treat disease through the use of nucleic acids such as DNA and RNA or closely related chemicals. They work by inhibiting the function of a particular gene or through adding, replacing, or editing of a gene.

Description

DNA, RNA, and the creation of proteins

In order to better understand nucleic acid therapies it is necessary to understand DNA and RNA along with how they work together to make proteins.

Deoxyribonucleic acid (DNA) is a molecule that contains the instructions for building and maintaining an organism. Most DNA is found in the cell nucleus. The instructions are stored in the DNA as a sequence of bases: adenine (A), cytosine (C), guanine (G), and thymine (T). A three-base sequence in the DNA contains the instructions for making a particular amino acid. For example, CGC codes for the amino acid alanine. Proteins are made up of one amino acid or several amino acids strung together. Proteins are the building blocks of life. They

guide the development and functioning of the body. The sequence of DNA that contains the instructions for a particular protein is a gene.

The DNA molecule is double stranded, and the two strands join together to form a spiral that looks a little like a twisting staircase. Each step of the staircase is made from the pairing of two bases: (A) pairs with (T) and (C) pairs with (G). These are called base pairs.

In order for a protein to be produced, the DNA sequence that contains a gene needs to be transcribed into a single-stranded molecule called messenger RNA (mRNA). Generally one gene on the DNA is transcribed to one mRNA molecule, making one protein. The RNA sequence will match the DNA sequence, except that when (T) is found on the DNA sequence it will be replaced by uracil (U) in the RNA sequence.

The translation of mRNA into proteins occurs in the ribosome, a complex molecule made of RNA and proteins that acts like a protein synthesis factory. At the start of protein synthesis, the ribosome binds to the start of the mRNA. The ribosome recognizes the start of the mRNA, since all mRNA molecules start with the sequence AUG.

A transfer RNA molecule (tRNA), carrying the amino acid methionine, will bind to the complementary AUG sequence and start the chain of amino acids with methionine. The mRNA sequence will continue to be translated by the ribosome with tRNA molecules bringing the correct amino acids and adding them to the growing chain. The creation of the chain of amino acids (protein) continues until the ribosome reaches a stop sequence (UAA, UAG, and UGA). The ribosome recognizes that this is the end of the protein sequence since there are no tRNA molecules that are complementary to this sequence. The new protein is released, and the mRNA ribosome complex comes apart.

Types of nucleic acid therapies

Although the storage of genetic information and the creation of proteins are important functions of DNA and RNA, these molecules have other functions. Thus they are good therapeutic targets. Nucleic acid therapies work by inhibiting the function of a particular gene or through adding, replacing, or editing of a gene. These types of therapies are potentially effective because they have long-lasting effects and even sometimes provide a cure.

Potential challenges with these therapies include the following issues:

- how to deliver the therapy
- how to mass production of the therapy at a low cost
- how to minimize toxicity
- how to sustain the effect over a period of time

DNA therapies

ANTISENSE OLIGONUCLEOTIDES (ASOS) AND DNA APTAMERS. ASOs are single, short strands of DNA of about 8–50 bases in length. They bind to a target mRNA and either destroy it or stop it from functioning.

The use of ASOs are researched for neurodegenerative diseases, such as Alzheimer's, Parkinson's, Huntington's, and ALS. Fomivirsen and Mipomersen are the only two ASOs that have been approved by the FDA.

Fomivirsen was developed in 1998 to treat cytomegalovirus (CMV) retinitis, a serious viral eye infection. Fomivirsen is an ASO that works by binding to a section of the mRNA of the virus involved in reproducing itself. This drug effectively stops the viral infection and has a long lasting effect. It was taken off the market because very few people were getting this condition.

Mipomersen is used to treat people with familial hypercholesterolemia (FH). Their bodies cannot properly transport cholesterol out of the body, so they have high LDL levels. Left untreated, FH results in increased

cholesterol in the arteries (atherosclerosis), which in turn results in early heart attacks in young adults and sometimes in children.

Mipomersen is an ASO that binds to the mRNA of the abnormal APOB protein found in FH and prevents its synthesis. APOB is the main component of low density lipoprotein (LDL), which is responsible for carrying cholesterol to the various tissues of the body. Mipomersen helps treat FH by causing cholesterol bound to the LDL to be destroyed and cleared from the body by the liver.

The DNA aptamer is a single-stranded DNA molecule about 56–120 bases in length. Aptamers can bind to targets such as proteins, carbohydrates, molecules, and toxins, and affect their function. This can be used to treat infectious diseases and diseases that result in the production of too much or abnormal protein. Aptamers form variety of shapes that allow it to bind well to their targets.

GENE THERAPY. Gene therapy involves treating a disease by adding, removing, or changing the genetic material in the cells of a patient.

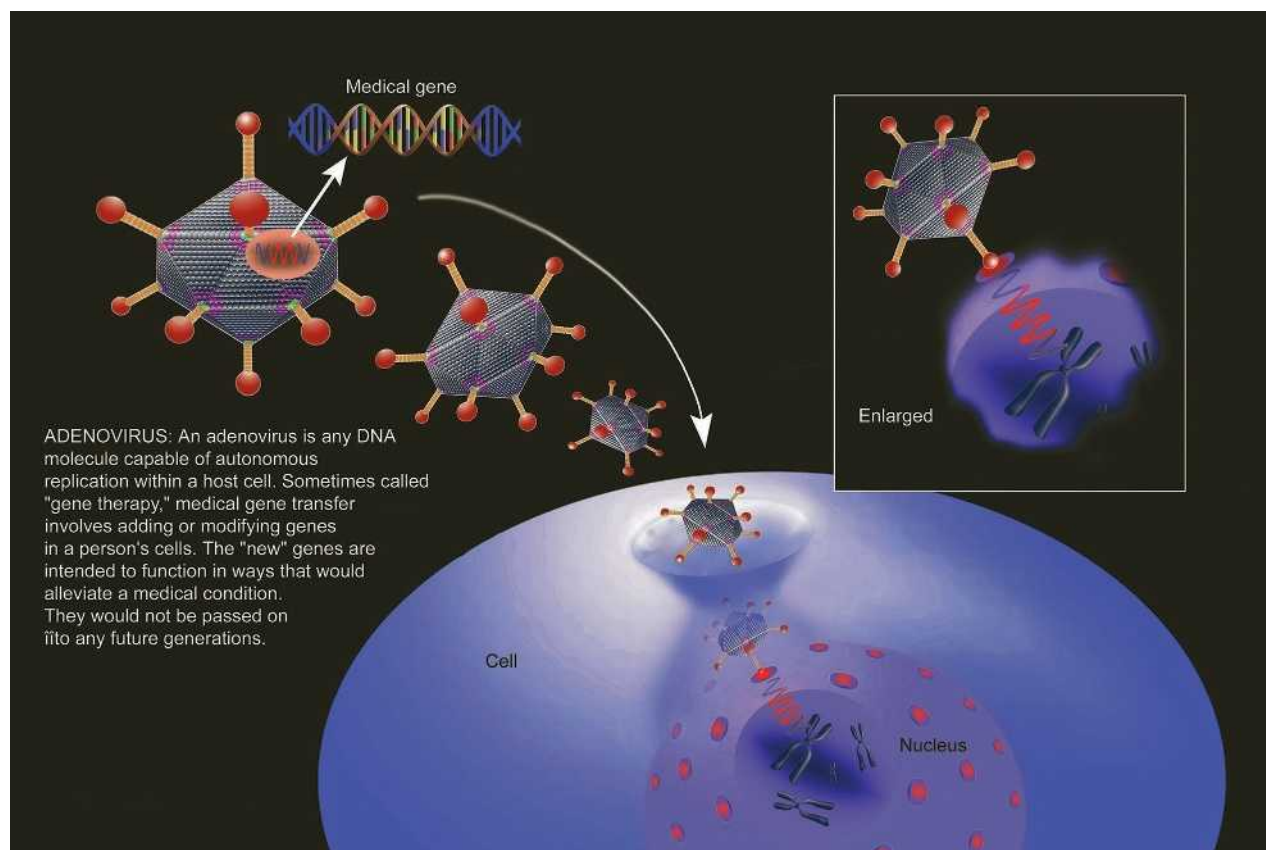


Diagram of an adenovirus (upper left) being used to administer genetic material into a cell (bottom right). Adenoviruses are DNA (deoxyribonucleic acid) viruses that infect human cells by injecting DNA into the nucleus. Usually this results in disease, but the virus can be genetically engineered so that it transplants human DNA into the cell nucleus for medically beneficial purposes. Transplanting DNA in this way can replace a faulty gene with a normal version. (Patrick Landmann/Science Source)

KEY TERMS

DNA (deoxyribonucleic acid)—The genetic material that contains the instructions for creating proteins.

DNA base—One unit in a DNA sequence. The four DNA bases are adenine (A), cytosine (C), guanine (G), and thymine (T). The sequence of these bases is the genetic code that contains the instructions for creating proteins.

DNA sequence—Contains the instructions for creating proteins. A three base sequence in the DNA contains the instructions for making a particular amino acid.

Gene—A unit of information on DNA that contains the instructions for making a protein.

Genome—The complete set of genetic instructions of an organism.

Messenger RNA (mRNA)—A sequence of bases that contain the instructions for a protein. The mRNA sequence is translated into a string of amino acids that forms a protein.

Pathogenic variant—Any change in the sequence of a genome that causes disease.

Protein—The building blocks for life that guide the development and function of the body.

Ribonucleic acid (RNA)—The genetic material that is involved in creating proteins.

Ribosome—A complex molecule made of RNA and proteins that acts like a protein synthesis factory.

Tissue—Substance that is made up of cells that have a common function. The four types of tissue are: connective, epithelial (skin), muscle, and nervous tissue.

Transfer RNA (tRNA)—A small RNA molecule that binds to a complementary mRNA sequence and then attaches the corresponding amino acid to the protein chain.

Variant—Change in the sequence of a genome.

Gene therapy was initially designed to treat inherited diseases, such as cystic fibrosis. It has been investigated as a treatment for cancers, autoimmune-diseases such as arthritis, and some infectious diseases. Gene therapy can be somatic or germline. Somatic gene therapy involves adding, removing, or changing genetic material in tissue or cells. Doing so results in the production of a naturally occurring protein that is lacking or not functioning

correctly in an individual patient. Germline gene therapy adds, removes, or changes the genetic material in reproductive cells, or early embryos in order to correct genetic defects that may be passed on to future generations.

In the United States, both nucleic acid-based (*in vivo*) treatments and cell-based (*ex vivo*) treatments are investigated. Nucleic acid-based gene therapy uses vectors (such as viruses) to deliver modified genes to target cells. Cell-based gene therapy techniques remove cells from the patient in order to genetically alter them then reintroduce them to the patient's body. As of 2021, gene therapies for the following diseases were being developed in the United States: cystic fibrosis (using adenoviral vector); HIV infection (cell-based); malignant melanoma (cell-based); Duchenne muscular dystrophy (cell-based); hemophilia B (cell-based); kidney cancer (cell-based); Gaucher disease (retroviral vector); breast cancer (retroviral vector); and lung cancer (retroviral vector). When a cell or individual is treated using gene therapy and successful incorporation of engineered genes has occurred, the cell or individual is said to be transgenic.

RNA therapies

In the early 1980s, researchers discovered that RNA plays a major role in all areas of protein synthesis. These findings laid the groundwork for RNA therapies.

RNA INTERFERENCE AND SHORT INTERFERING RNAS (SIRNAS). In 1986, RNA interference was discovered (RNAi). RNAi is naturally used by an organism to provide protection from invading viruses by preventing the translation of certain genes into proteins. Researchers call this gene silencing.

RNA interference therapy is done with short interfering RNAs (siRNAs), which are small fragments of RNA about 21 bases long. During RNAi, a siRNA binds to a complementary sequence of mRNA in a cell, which results in the destruction or inactivation of the mRNA and prevents the translation of mRNA into protein.

RNAi is used by researchers to study gene function. RNAi is also studied to treat infectious diseases and genetic conditions that result in the production of abnormal proteins, such as many cancers and neurodegenerative diseases. It can be used against cancer by blocking the production of proteins in cancer cells so that they die or stop multiplying. siRNAs are more stable than ASOs, which is an advantage. Potential problems with siRNA include their being challenging to deliver to the cell and their mistakenly suppressing other (unintended) genes.

Three siRNA therapies have been approved in the United States. Patisiran, approved in 2018, is used to treat hereditary transthyretin amyloidosis (hATTR), a progressive condition that results from increased transthyretin protein

and damage to various organs, including the nerves. Build up of transthyretin in the nerves causes loss of function of the lower limbs, feet, and hands. hATTR can also affect the heart, kidneys, eyes, and gastrointestinal tract. Patisiran reduces the production of transthyretin, which in turn reduces the symptoms and slows progression of the disease.

MICRORNAS (MIRNAS). MicroRNAs (miRNAs) are short RNA molecules that do not have instructions for the creation of a protein. miRNAs help to balance proteins in the body by reducing the production of a protein when there is too much already in the body. Dysregulation of miRNAs is a common cause of symptoms in many diseases. One benefit of using miRNAs is that they can target multiple genes at once. This ability can be useful for the treatment of diseases such as cancer, which results from the dysregulation of multiple proteins.

miRNAs therapies are being developed for Huntington's disease, which is caused by a pathogenic variation (mutation) in the huntingtin (HTT) gene, which results in the production of an abnormal HTT protein. This causes progressive deterioration, uncontrolled movements, mental health problems, and cognitive decline. The abnormal HTT protein appears to decrease the function of naturally occurring miRNAs, which causes the overproduction of the proteins these miRNAs normally regulate. The overproduction of proteins causes the symptoms of Huntington's disease. The RNAi therapies that are being developed for Huntington's disease deliver miRNAs that destroy the mRNA for HTT. This results in a decrease in production of the HTT protein. These therapies have as of 2021 only been tested in animals, but they appear to decrease the level of HTT while improving motor function and increasing lifespan.

RNA APTAMERS (RNA DECOYS). RNA aptamers are small RNAs that can bind to proteins and prevent their functioning. They can also be used to transport siRNAs into the cell. An advantage of RNA aptamers is that they can target compounds both outside and inside the cell. Unlike other RNA therapies, they do not need to enter the cell in order to work.

Pegaptanib was the first RNA aptamer approved in the United States. Pegaptanib treats age-related macular degeneration (AMD), which causes severe and progressive vision problems. Pegaptanib binds to a protein called VEGF, which inhibits the production of new blood vessels that can become out of control in AMD.

RIBOZYMES. Ribozymes are a type of RNA that can be used to suppress gene function. They work by binding to an mRNA and preventing the production of a protein. Both naturally occurring and synthesized ribozymes can be used in therapy. Two promising areas for ribozyme therapies are cancer and virology. Ribozymes can also be used in drug development to identify genes that have a particular function and would be good targets for new therapies.

QUESTIONS TO ASK YOUR DOCTOR

- Would any nucleic acid therapies help treat my disease?
- What are the risks of nucleic acid therapies?
- Are there any clinical trials for nucleic acid therapies that I might join?

CIRCULAR RNAS. Circular RNAs have the ends of their strand stuck together, unlike typical RNA, which forms a linear strand. Circular RNAs do not usually contain the instructions for the production of proteins. Circular RNAs seem to be a risk factor for a number of diseases, such as atherosclerosis, Parkinson's disease, Alzheimer's disease, and cancers. Researchers study the role of circular RNAs and ways in which they might be used as therapies.

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O

Obesity

Definition

Obesity is the state of being overweight to the degree that one's health and potential life expectancy are affected. Clinically, obesity is measured by using a scale called body mass index (BMI), which is calculated by dividing weight in kilograms by the square of height in meters. According to the Centers for Disease Control and Prevention (CDC), Division of Nutrition, Physical Activity, and Obesity, a BMI of 30.0 or higher is considered clinically obese.

Description

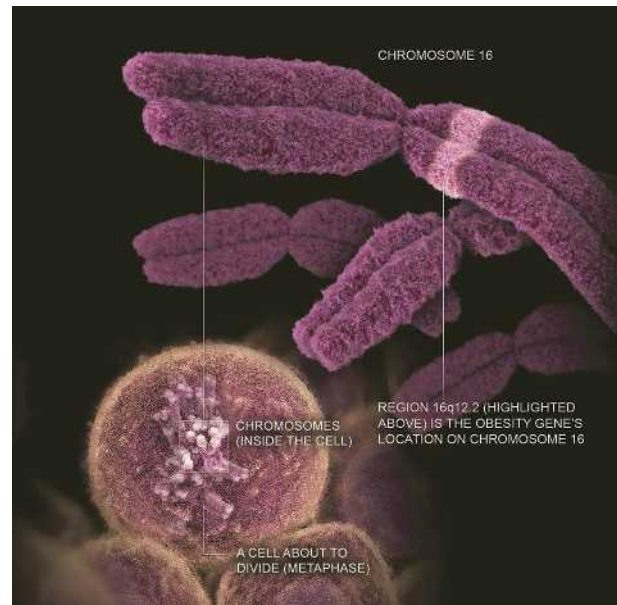
Obesity is caused when a person consumes more calories than is needed to fuel his or her body. According to the CDC, about 40% of all American adults and 20% of American adolescents are overweight. This is a serious public health concern, since overweight and obesity are associated with serious illnesses that are among the leading causes of death worldwide, such as heart disease, diabetes, stroke, and cancer.

Genetic profile

Many genetic syndromes include obesity as a feature. In these syndromes, genetic mutations have been identified that cause obesity. Syndromes associated with obesity include Alstrom syndrome, Bardet-Biedl syndrome, Cohen syndrome, fragile X syndrome, Leptin receptor deficiency, and Prader-Willi syndrome. In many of these syndromes, an identified genetic mutation causes an abnormal protein to be formed. The abnormal protein alters perception and senses so that the individual constantly feels hungry and is unable to feel full or satiated after eating, which leads to an obsession with food and to overeating and obesity. Overeating is a hallmark feature of Prader-Willi syndrome in particular. Mutations in the following genes have been shown to cause obesity

within syndromes: *ALMS1*, *BBS1*, *BBS10*, *FMRI*, *LEP*, *LEPR*, *OCA2*, and *VSB13B*.

Using BMI as a measure for obesity, researchers have determined that it is a heterogeneous trait impacted by multiple genetic and environmental factors. Estimates of the heritability of BMI vary from 31% to 90%. Monogenetic obesity is caused by mutations of a single gene, and such mutations generally result in severe, early-onset obesity. Genetic mutations in the melanocortin system, which control energy balance, such as leptin (*LEP*), leptin receptor (*LEP*), proopiomelanocortin



Visualization of the location of the "obesity gene" (FTO) in region 16q12.2 (highlighted) on chromosome 16. The FTO gene is widely expressed or "turned on" in the hypothalamus (the part of the brain that controls appetite) and in the pancreatic islets where insulin is produced. People who have one copy of FTO weigh, on average, 4.5 lbs more than people who do not have it; people who have two copies weigh about 9 lbs more on average. (The Visual MD/ Science Source)

(*POM*), melanocortin-4 receptor (*MC4R*), preproconvertase 1 (*PCSK1*), single-minded 1 (*SIM1*), brain-derived neurotrophic factor (*BDNF*), and tyrosine kinase receptor tropomyosin-related kinase B (*TrkB*), are associated with monogenic obesity.

Genome-wide association studies (GWAS) have identified more than 900 genetic variants associated with risk for, and development of, polygenic obesity. *FTO* on chromosome 16 is one of the most studied genes associated with fat mass and obesity. Variants of this gene are associated with either high or low risk of obesity. Among the many other genes associated with BMI and obesity are: *BMIQ1* (7q31), *BMIQ2* (13q14), *BMIQ3* (6q23-q25), *BMIQ4* aka:*UCP2* (11q24), *BMIQ5* (16p13), *BMIQ6* (20pter-p11.2), *BMIQ7* (4p15-p14), *BMIQ8* (10p), *BMIQ9* (*MC3R*) (20q), *BMIQ10* (*FFAR4*) on ch10q, *BMIQ11* aka:*SLC6A14* (Xq24), *BMIQ12* aka:*PCSK1* (5q15-q21), *BMIQ13* (2q14.1), *BMIQ14* (16q12.2), *BMIQ15* (17q23.2-q25.1), *BMIQ16* (16p11.2), *BMIQ17* (9p13.3), and *BMIQ18*(6q14.2). These genes contribute to obesity through a variety of different mechanisms. Mutations in the *BMIQ10* gene change proteins that metabolize fatty acids, which leads to abnormal insulin response. Mutations in the *BMIQ9* gene alter energy homeostasis and energy use so that, even when less food is consumed, weight still remains high. Mutations in the *BMIQ12* gene alter hormones that are thought to contribute to reduced metabolic rate and disrupted absorption in the small intestine. Mutations in *BMIQ11* are thought to be associated with X-linked obesity. When examining this gene, a significant difference was found between obese and non-obese individuals. Mutations in the *BMIQ4* gene lead to a weakening of the mitochondrial membrane, causing them to leak ATP and to be inefficient delivery vessels for energy in the body. Many of these mutations are also associated with higher rates of diabetes.

GWAS also found that several genes involved in governing energy homeostasis (the balance of energy intake and expenditure) including *LEP*, *POMC*, *BDNF*, *PCSK1*, *SIM1*, and *TrkB* are associated with obesity as well as with development of the central nervous system and neurodegenerative diseases. Other genes associated with obesity including *NEGR1*, *NRXN3*, *CADM2*, *GRID1*, *ELAVL4*, and *SCG3* are related to synaptic function and neurotransmitter signaling, the processes used by neurons to communicate with other cells.

As research into the genetics of obesity continues, more genes related to the complex functions of metabolism and body size are discovered, and the intricate interplays among obesity, genetics, and environment are explored. For example, research reveals that environmental factors such as lifestyle changes (exercise and diet)



A doctor examining an obese patient. (Sunabesyou/Shutterstock)

can modulate the obesity risk associated with some genetic variants.

In 2021, researchers reported identification of 62 genes that are associated with higher levels of body fat and a lower risk of cardiovascular and metabolic diseases. The genes are involved with a variety of functions, including regulation and development of fat cells, distribution of body fat, energy regulation, and inflammation. These genes may help to explain why up to 45% of people who are obese have healthy blood pressure, glucose, and lipid levels and as a result are not at increased risk for many conditions caused or exacerbated by obesity.

Another study published in 2021 finds that the genetic risk factors associated with childhood obesity differ from those in adulthood. The researchers developed polygenic risk scores (scores that indicate the risk of developing a disease or disorder when compared to people who have a different genetic constitution) for people of various ages. They found that childhood scores accurately predicted BMI at age 10 and that adult risk scores predicted adult BMI. The researchers also suggest that the genetic risks for childhood obesity vary by race and ethnicity. These findings may be used to develop obesity-prevention programs.

Many discoveries about genetic factors that contribute to non-syndromic obesity have come from the Human Microbiome Project. The term “microbiome” refers to all of the genetic material contained in the micro-organisms in and on the human body. Much of this research has focused on the micro-organisms of the human digestive tract, or gut. Researchers have discovered a symbiotic relationship between the bacteria in the gut and the health of the human host. Most of the bacteria found in the human body are beneficial and necessary for health. Researchers have found that there is a significant difference between the metabolic activities of the micro-

KEY TERMS

Calorie—A unit of energy that represents the amount of heat a specific amount of food will create in the human body.

Energy homeostasis—The ability of all living things to maintain energy balance.

Heterogeneous trait—A trait that is caused by both genetic and nongenetic factors.

Hypertension—High blood pressure.

Prader-Willi syndrome—A rare genetic disorder caused by missing genes on chromosome 15. Individuals with this syndrome have intellectual and physical symptoms and a constant feeling of hunger that may cause them to overeat.

organisms in the digestive tract of lean individuals and those of obese individuals, suggesting that the genetics of the microbiome is a contributing factor in obesity.

Demographics

In 2019, the most recent year for which data were available, more than 42% of all American adults were obese, up 26% from 2008. Among youth, obesity rates were similar for males and females. Among adults, females had a higher obesity rate than males, and middle-aged males and females had a higher rates of obesity than younger males and females. African Americans had higher obesity rates (49.6%) than Latinx (44.8%) or white Americans (42.2%), and the lowest obesity rates in adults were seen in adults of Asian descent (17.4%).

Signs and symptoms

The definition of obesity is a BMI of 30.0 or greater.

Diagnosis

Obesity is diagnosed by physical examination. Genetic screenings may be helpful in determining whether obesity is caused by genetic mutations or environmental factors or, most likely, a combination of both. This information may be useful in developing treatment plans and strategies.

Treatment and management

Treatment for obesity that is not part of a genetic syndrome generally involves diet management and exercise. Registered dietitians and physical therapists may

be helpful in ensuring that the individual is able to approach weight loss in a healthy way. A supportive peer group and counseling to address the psychological issues surrounding eating have also been shown to be helpful additions to a treatment plan.

Medication may be prescribed to help reduce appetite. The medical guidelines for the use of medications to aid weight loss include a BMI of 30 or greater, or a BMI of 27 or greater in the presence of medical complications such as diabetes, hypertension, or sleep apnea. Common weight-loss medications include orlistat (Xenical), lorcaserin (Belviq), phentermine and topiramate (Qsymia), bupropion and naltrexone (Contrave), and liraglutide (Saxenda). Medication might not be suitable for individuals with certain medical conditions such as cardiac disease, people taking some other medications, or pregnant women.

In cases of clinically severe obesity, which may be life-threatening (people with a BMI of 40 or higher, or those with a BMI of 35 to 39.9 and other medical conditions), surgical treatment such as gastric bypass surgery, LapBand, or gastric sleeve may be prescribed.

Gastric bypass involves restricting the size of the stomach by stapling the stomach to itself and creating a smaller upper portion to receive food, and a larger lower portion that is not used. The next step connects the smaller upper pouch of the stomach directly to the small intestine so that the food travels from the pouch directly to the small intestine, and less food is absorbed. Weight loss occurs because far fewer calories may be consumed. The risks associated with gastric bypass include less than one percent mortality in the 30 days following surgery; however, the vast majority of patients who have gastric bypass have fewer comorbidities, a longer life expectancy, and lower risk of death.

Another surgical treatment is laparoscopic adjustable gastric banding (LAGB), also called LapBand. Much like gastric bypass, the stomach is separated into two sections; however, rather than using staples, the stomach is divided using an inflatable band. Like a belt, the band is pulled tight, thus creating a small channel between the two pouches. The band keeps the opening from expanding and may be left in place permanently.

A more invasive and major surgery, biliopancreatic diversion with duodenal switch, involves removing a large part of the stomach. The surgeon leaves the valve that releases food to the small intestine and the first part of the small intestine (duodenum). Next, the middle section of the intestine is closed, and the last part is attached to the duodenum. The separated section of the intestine is reattached to the end of the intestine to allow

QUESTIONS TO ASK YOUR DOCTOR

- How can I manage my child's constant need to eat?
- How can I help my child lose weight?
- What is my BMI?
- Which treatment would you recommend?
- Should I consider surgery or medications?
- What other conditions do I have?
- What other diseases am I at risk of developing?

bile and digestive juices to flow into this part of the intestine.

Another surgical treatment for obesity is gastric sleeve. In this procedure, part of the stomach is removed, creating a smaller pouch. Less complicated than gastric bypass or biliopancreatic diversion with duodenal switch, this procedure does not involve reconnecting to the duodenum.

In 2014, the FDA approved a treatment for obesity called vagal nerve blockade. It involves implanting a device under the skin of the abdomen. The device sends electrical pulses to the abdominal vagus nerve, which tells the brain when the stomach feels empty or full. The FDA approved vagal nerve blockage for use by adults with a BMI of 35 to 39.9 who have been unable to lose weight with a weight-loss program and who have at least one obesity-related condition, such as type 2 diabetes.

In 2015, the FDA approved a dual-balloon system for obesity treatment of patients with a BMI of 30 to 40 and one or more obesity-related condition. In this treatment, two attached balloons are inserted into the patient's stomach and then filled with saltwater. The balloons take up space in the patient's stomach for up to six months, after which time they should be removed.

Following weight loss, it is important to have a plan to help prevent regaining the weight. The most effective way to avoid regaining weight is through exercise and physical movement. Doctors recommend attempting 40 to 60 minutes of exercise per day. It may be helpful to maintain a support group and continue counseling after a goal weight has been reached.

Treatment for obesity for individuals with genetic syndromes involves a more psychological, behavioral approach. It is important to consider the developmental level of the individual when planning interventions, since many individuals with genetic syndromes also have

developmental delays or intellectual disabilities. Limiting access to food (except during meals) is important, as is following a nutritious meal plan. A registered dietician with experience working with individuals with special genetic conditions is a great addition to the health care team.

Prognosis

Individuals with obesity are at risk of developing serious and sometimes life-threatening medical conditions such as diabetes, heart disease, hypertension, sleep apnea, and stroke, and they are at increased risk of developing several types of cancer, including cancers of the colon, esophagus, gallbladder, kidney, pancreas, liver, and prostate, as well as uterine and postmenopausal breast cancer. The CDC estimates that there are over 300,000 premature deaths in the United States each year due to obesity. Left untreated, the prognosis may be poor; however, with proper nutrition and weight loss, many of the risks can be reduced or eliminated.

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The Obesity Society, 1110 Bonifant Street, Suite 500, Silver Spring, MD 20910, (301) 563-6526 or (800) 974-3084, (301) 563-6595, <http://www.obesity.org>

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Revised by Barbara Wexler, MPH

Obesity-hypotonia syndrome see **Cohen syndrome**

Oculodentodigital syndrome

Definition

Oculodentodigital syndrome (ODDS) is a relatively rare genetic condition with specific medical findings involving the eyes, skeletal system, brain, dentition, and face.

Description

Most fully described by the German ophthalmologist Dr. Gerard Meyer-Schwickerath and others in 1957, today ODDS is also known as oculodentodigital dysplasia, oculodentosseous dysplasia, and Meyer-Schwickerath syndrome.

People with ODDS experience symptoms differently. Overall, the symptoms usually affect the eyes, teeth, hands, feet, face, bones, hair, and brain.

Common signs of ODDS include a slightly indented nasal bone, thin nose with small nasal openings, thin and upturned nostrils, small eyes with iris abnormalities, small corneas, webbing of the fingers or toes, and weakened enamel on the teeth.

Genetic profile

ODDS is an inherited disorder caused by mutations in *GJA1*, also known as the connexin-43 gene. This gene is located on chromosome 6.

ODDS is most commonly inherited in an autosomal dominant pattern. In this type, family history of the

syndrome is common and the condition may be present in several generations. A person with ODDS has a 50% of having an affected child. The exact signs and symptoms may vary from person to person, even within the same family.

Instances of autosomal dominant inheritance with no family history also exist, in which a person develops ODDS from a new mutation that occurred by chance during his or her conception. There are reports of these chance mutations being possibly associated with an older average age for the father.

Rarely, ODDS has been reported to follow an autosomal recessive pattern of inheritance. In this type, there may be no family history and the condition may only show up in one generation. Two parents would have a 25% chance of having another affected son or daughter once their child is diagnosed with ODDS.

In 1997, a unique family history of ODDS was reported. In this family, relatives in successive generations had more severe neurological signs of ODDS than their older relatives, and these signs showed up at an earlier age in each successive generation. A similar family history was reported in 2002, again involving neurological symptoms of ODDS. These patterns suggest the genetic phenomenon called anticipation, which has been described in other genetic conditions. The hallmark of anticipation is people with progressively worse symptoms in successive generations of the same family.

Demographics

ODDS occurs worldwide, affecting males and females equally. The exact incidence is not known, but it is not a common condition.

Signs and symptoms

Ocular and facial findings

Small, sunken eyes that are closer together or wider apart are common features in ODDS. Additionally, the corneas of a person with ODDS may be smaller than normal. Other eye findings include glaucoma, cataracts, iris abnormalities, poor vision, and an extra fold of skin near the nose at the upper eyelid.

Facial characteristics of people with ODDS can be unique to them and their affected family members. A striking facial feature is the narrow, longer nose seen in the condition. People with ODDS may also have narrow and upturned nostrils, a prominent jaw, and smaller head size.

Dental and mouth findings

A common dental finding of ODDS is weaker tooth enamel, making teeth prone to decay and cavities. People with ODDS may also be born with teeth that are smaller than average, missing teeth, or have a premature loss of teeth. Cleft lip and cleft palate have also been seen in ODDS.

Skeletal and digital findings

People with ODDS can have enlargement of specific bones. These include bones in the hands, feet, ribs, and skull. This can cause the forearm to turn outward in some people. Some with the condition are prone to their hips dislocating.

The hands and feet of people with ODDS can be significantly affected. Some may have severe webbing between their fourth and pinky fingers, so much so that they look like one large, joined finger. The pinky finger may be shortened, curved, or permanently flexed as well. Webbing has also been seen between the third and fourth toes of people with ODDS.

Neurological findings

Less emphasis has been given to the neurological and other associated symptoms of ODDS, though they can be very problematic for the person with the syndrome. Some people with ODDS have very tight and stiff muscles with increased reflexes. This can result in difficulty with controlled muscle movements such as those needed for walking and speaking. Intellectual disabilities are sometimes seen, and others may have muscle weakness of their limbs that can be similar to paralysis.

Changes in the brain are found in people with ODDS. Examples of these are loss in the natural white matter and hardening within some brain structures.

Other findings

A common finding in ODDS is conductive hearing loss, which is usually related to sound waves not being able to travel through the normal ear pathways.

Thickening of the skin on the palms and soles of people with ODDS is common. It may be yellow-orange in color, but is not usually associated with blisters.

Another occasional finding in ODDS is very fine, dry hair. It may also be sparse and slower to grow than usual.

Diagnosis

Genetic testing from a blood sample is available for those suspected to have a clinical diagnosis. This testing

studies the *GJA1* gene carefully to look for disease-causing mutations. An abnormal genetic test result is one that finds a mutation in a person's copy of *GJA1*. Finding this mutation confirms the diagnosis of ODDS. Once a mutation has been found, other at-risk family members can also be tested. Genetic testing can also be offered during the second trimester of a pregnancy via an amniocentesis procedure, if a couple desires such information during that time.

Genetic testing should be offered in conjunction with careful genetic counseling for the affected individual, the family members, or the expectant couple.

A diagnosis is more often made after the careful identification and study of a person's symptoms and family history. A diagnosis may be suspected by a team of specialists, including an ophthalmologist, dermatologist, dentist, orthopedist, medical geneticist, neurologist, and otolaryngologist.

Treatment and management

Ocular and facial findings

The formation or appearance of the eyes cannot be treated and typically does not cause medical complications. Glaucoma, however, can lead to vision loss or blindness if left untreated. It may be treated with prescription eye drops, surgery, or laser treatments. The goal of glaucoma treatments is to reduce the pressure within the eye, thereby reducing the risk of damage to the eye structures and subsequent vision loss.

Some cataracts may be treated with surgery to remove the natural lens of the eye using various procedure options. The ophthalmologist will then replace it with a new, clear artificial lens. Some cataracts, especially those present at birth, may not be treatable and also may not cause serious vision problems for the person.

Facial characteristics seen in ODDS are not treatable and usually cause no medical complications.

Dental and mouth findings

People with ODDS have teeth that are prone to decay and cavities. Dentists can treat these to prevent further decay; teeth left untreated may need to be removed if the decay is too severe. Common treatment for cavities can include fillings, crowns, or root canal procedures in more complicated cases.

Those with a cleft lip may have it corrected with a surgery in the first few months of life. A cleft palate can be repaired through stages of surgery, often first happening in the first year of life. These surgeries usually require a multidisciplinary team consisting of a plastic surgeon,

KEY TERMS

Amniocentesis—A procedure involving removal of a small amniotic fluid sample during pregnancy to obtain fetal chromosome results.

Cataract—A change in the eye's lens that causes it to become cloudy in appearance, rather than clear.

Cleft lip—Abnormal opening in the upper lip.

Cleft palate—Abnormal opening in the upper roof of the mouth.

Cornea—Transparent outer layer of the eyeball.

Glaucoma—An eye disease that usually involves high pressure in the eye, which can lead to vision problems or blindness if left untreated.

Iris—Colored part of the eye that contains the pupil in the center.

Magnetic resonance imaging (MRI) scan—Procedure that shows internal organs and tissues of the body using magnetic fields and signals.

Mutation—Small change in the sequence of a gene.

pediatric dentist, pediatric anesthesiologist, nurses, dietitian/feeding specialist, and social worker.

Skeletal and digital findings

Many of the internal bone changes in people with ODDS cannot be treated. Those with significant webbing between their fingers and toes may find surgery helpful to gain mobility, the use of their digits, or cosmetic improvement. In cases where the bones are not webbed, surgery to separate the fingers or toes may be possible with the help of an orthopedic surgeon and plastic surgeon.

Children with hips that dislocate may require treatment with a harness or splint that keeps the hips in place. If this is not successful, a plaster cast may be necessary. Sometimes surgery by an orthopedic surgeon is needed to replace a hip in more severe cases.

Neurological findings

A magnetic resonance imaging (MRI) scan or other imaging study of the brain can document the changes sometimes seen in ODDS. Treatments may help those with increased muscle tone and problems with stiffness. Medications, physical therapy involving motion exercises, active stretching exercises, and occupational therapy can help. A combination of these is important in order for the person with ODDS to gain mobility and independence.

Mental delays and intellectual disabilities may be assessed by a child development team or early childhood program. Extra assistance is sometimes available through early intervention programs and special education in schools. Social workers are useful to connect families to helpful resources.

Other findings

Hearing loss is best assessed and treated by an otolaryngologist and audiologist. Once determined as conductive hearing loss, treatments can include the use of antibiotics if an infection is present, ear drops, or hearing aids.

Skin changes are best assessed and treated by a dermatologist. Treatments may include the use of topical ointments or creams. Oral medications or carefully removing the outermost layer of skin to reduce thickness is helpful in some people. Treatments to change the hair texture or thickness are not usually necessary because it causes no medical complications.

A psychologist, genetic counselor, or therapist can be helpful for some people with ODDS. Living with visible skin and digit changes can be difficult, and some may find it easier to talk to an objective person or to other families in a support group.

Prognosis

ODDS can involve a combination of severe medical complications in some cases. Since no two people experience the exact same type of symptoms, it is impossible to predict which characteristics a child newly diagnosed with the condition will exhibit. No specific lifespan ranges are known, but might be lower in those who have more serious medical concerns. Newer medical treatments continue to offer hope for those with ODDS and their families.

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National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06180, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Deepti Babu, MS, CGC

Okihiro syndrome see **Duane retraction syndrome**

Olfactogenitalis of De Morsier see **Kallmann syndrome**

Oligohydramnios sequence

Definition

Oligohydramnios sequence occurs as a result of having very little or no fluid (called amniotic fluid) surrounding a developing fetus during a pregnancy. “Oligohydramnios” means that there is less amniotic fluid present around the fetus than normal. A “sequence” is a chain of events that occurs as a result of a single abnormality or problem. Oligohydramnios sequence is therefore used to describe the features that a fetus develops as a result of very low or absent amount of amniotic fluid. In 1946, Dr. Edith Potter first described the physical features seen in oligohydramnios sequence. Because of her description, oligohydramnios sequence has also been known as Potter syndrome or Potter sequence.

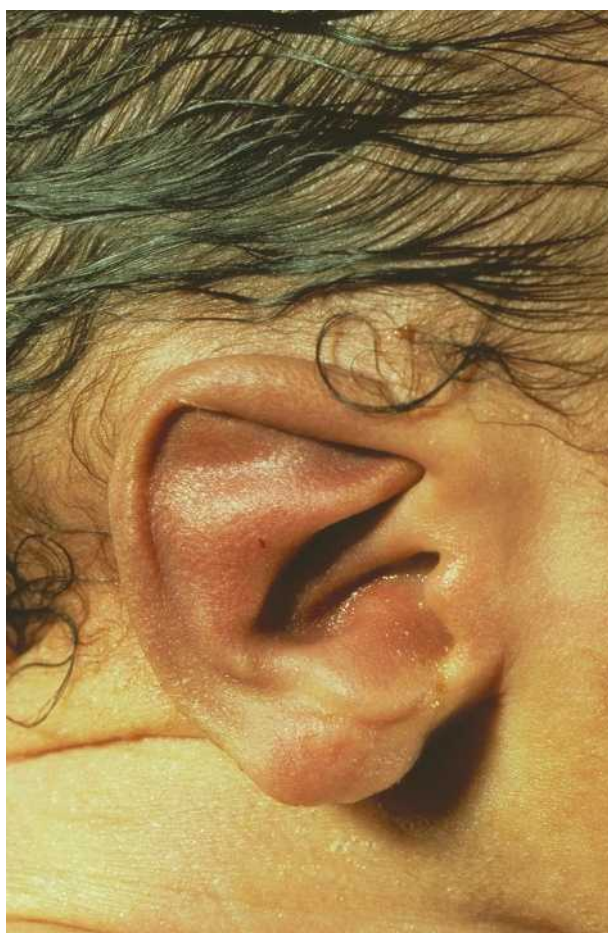
Description

During a pregnancy, the amount of amniotic fluid typically increases through the seventh month and then slightly decreases during the eighth and ninth months. During the first 16 weeks of the pregnancy, the mother’s body produces the amniotic fluid. At approximately 16 weeks, the fetal kidneys begin to function, producing the majority of the amniotic fluid from that point until the end of the pregnancy. The amount of amniotic fluid, as it increases, causes the space around the fetus

(amniotic cavity) to expand, allowing enough room for the fetus to grow and develop normally.

Oligohydramnios typically is diagnosed during the second and/or third trimester of a pregnancy. When the oligohydramnios is severe enough and is present for an extended period of time, oligohydramnios sequence tends to develop. There are several problems that can cause oligohydramnios to occur. Severe oligohydramnios can develop when there are abnormalities with the fetal renal system or when there is a constant leakage of amniotic fluid. Sometimes, the cause of the severe oligohydramnios is unknown.

Approximately 50% of the time, fetal renal system abnormalities cause severe oligohydramnios, resulting in the fetus developing oligohydramnios sequence. This is because if there is a problem with the fetal renal system, there is the possibility that not enough amniotic fluid is being produced. Renal system abnormalities that have been associated with the development of oligohydramnios sequence include the absence of both kidneys (renal



Low-set ears are a common feature of infants with oligohydramnios sequence. (Custom Medical Stock)

agenesis), bilateral cystic kidneys, absence of one kidney with the other kidney being cystic, and obstructions that block the urine from exiting the renal system. In a fetus affected with oligohydramnios sequence, sometimes the renal system abnormality is the only abnormality the fetus has. However, approximately 54% of fetuses with oligohydramnios sequence due to a renal system abnormality will have other birth defects or differences with their growth and development. Sometimes the presence of other abnormalities indicates that the fetus may be affected with a syndrome or condition in which a renal system problem can be a feature. Renal system abnormalities in a fetus can also be associated with certain maternal illnesses, such as insulin-dependent diabetes mellitus, or the use of certain medications during a pregnancy.

Severe oligohydramnios can also develop even when the fetal renal system appears normal. In this situation, often the oligohydramnios occurs as the result of chronic leakage of amniotic fluid. Chronic leakage of amniotic fluid can result from an infection or prolonged premature rupture of the membranes that surround the fetus (PROM). In chronic leakage of amniotic fluid, the fetus still produces enough amniotic fluid; however, there is an opening in the membrane surrounding the fetus, causing the amniotic fluid to leak out from the amniotic cavity.

Genetic profile

The chance for oligohydramnios sequence to occur again in a future pregnancy or in a family member's pregnancy is dependent on the underlying problem or syndrome that caused the oligohydramnios sequence to develop. There have been many fetuses affected with oligohydramnios sequence where the underlying cause of the severe oligohydramnios has been a genetic abnormality. However, not all causes of severe oligohydramnios that result in the development of oligohydramnios sequence have a genetic basis. The genetic abnormalities that have caused oligohydramnios developing during a pregnancy include a single gene change, a missing gene, or a chromosome anomaly.

Although some fetuses with oligohydramnios sequence have been found to have a chromosome anomaly, the likelihood that a chromosome anomaly is the underlying cause of the renal system anomaly or other problem resulting in the severe oligohydramnios is low. A chromosome anomaly can be a difference in the total number of chromosomes a fetus has (such as having an extra or missing chromosome), a missing piece of a chromosome, an extra piece of a chromosome, or a rearrangement of the chromosomal material. Some of the chromosome anomalies can occur for the first time at the conception of the fetus (sporadic), while other chromosome anomalies can be inherited from a parent. Both

sporadic and inherited chromosome anomalies have been seen in fetuses with oligohydramnios sequence. The chance for a chromosome anomaly to occur again in a family is dependent on the specific chromosome anomaly. When the chromosome anomaly is considered to be sporadic, the chance for chromosome anomaly to occur again in a pregnancy is 1% added to the mother's age-related risk to have a baby with a chromosome anomaly. If the chromosome anomaly (typically a rearrangement of chromosomal material) was inherited from a parent, the recurrence risk would be based on the specific chromosome arrangement involved. However, even if a chromosome anomaly were to recur in a future pregnancy, it does not necessarily mean that the fetus would develop oligohydramnios that could cause the development of oligohydramnios sequence.

Many of the genetic conditions that can cause oligohydramnios sequence are inherited in an autosomal recessive manner. An autosomal recessive condition is caused by a difference in a gene. Like chromosomes, the genes also come in pairs. An autosomal recessive condition occurs when both genes in a pair don't function properly. Typically, genes don't function properly because there is a change within the gene causing it not to work or because the gene is missing. An individual has an autosomal recessive condition when they inherit one non-working gene from their mother and the same non-working gene from their father. These parents are called "carriers" for that condition. Carriers of a condition typically do not exhibit any symptoms of that condition. With autosomal recessive inheritance, when two carriers for the same condition have a baby, there is a 25% chance for that baby to inherit the condition. There are several autosomal recessive conditions that can cause fetal renal abnormalities potentially resulting in the fetus developing oligohydramnios sequence.

Oligohydramnios sequence has also been seen in some fetuses with an autosomal dominant condition. An autosomal dominant condition occurs when only one gene in a pair does not function properly or is missing. This non-working gene can either be inherited from a parent or occur for the first time at conception. There are many autosomal dominant conditions where affected family members have different features and severity of the same condition. If a fetus is felt to have had oligohydramnios sequence that has been associated with an autosomal dominant condition, it would have to be determined if the condition was inherited from a parent or occurred for the first time. If the condition was inherited from a parent, that parent would have a 50% chance of passing the condition on with each future pregnancy.

Sometimes the fetus with oligohydramnios sequence has a condition or syndrome that is known to occur

KEY TERMS

Anomaly—Different from the normal or expected. Unusual or irregular structure.

Bilateral—Relating to or affecting both sides of the body or both of a pair of organs.

Fetus—The term used to describe a developing human infant from approximately the third month of pregnancy until delivery. The term “embryo” is used prior to the third month.

Hypoplasia—Incomplete or underdevelopment of a tissue or organ.

Renal system—The organs involved with the production and output of urine.

Syndrome—A group of signs and symptoms that collectively characterize a disease or disorder.

Teratogen—Any drug, chemical, maternal disease, or exposure that can cause physical or functional defects in an exposed embryo or fetus.

Unilateral—Refers to one side of the body or only one organ in a pair.

sporadically. Sporadic conditions are conditions that tend to occur once in a family and the pattern of inheritance is unknown. Since there are some families where a sporadic condition has occurred more than one time, a recurrence risk of approximately 1% or less is often given to families where only one pregnancy has been affected with a sporadic condition.

Sometimes examinations of family members of an affected pregnancy can help determine the exact diagnosis and pattern of inheritance. It is estimated that approximately 9% of first-degree relatives (parent, brother, or sister) of a fetus who developed oligohydramnios sequence as a result of a renal abnormality will also have renal abnormalities that do not cause any problems or symptoms. It is important to remember that if a pregnancy inherits a condition that is associated with oligohydramnios sequence, it does not necessarily mean that the pregnancy will develop oligohydramnios sequence. Therefore, for each subsequent pregnancy, the risk is related to inheriting the condition or syndrome, not necessarily to developing oligohydramnios sequence.

Demographics

There is no one group of individuals or one particular sex that has a higher risk to develop oligohydramnios sequence. Although, some of the inherited conditions that have been associated with oligohydramnios sequence

may be more common in certain regions of the world or in certain ethnic groups.

Signs and symptoms

With severe oligohydramnios, because of the lack of amniotic fluid, the amniotic cavity remains small, thereby constricting the fetus. As the fetus grows, the amniotic cavity tightens around the fetus, inhibiting normal growth and development. This typically results in the formation of certain facial features, overall small size, wrinkled skin, and immobile arms and legs.

The facial features seen in oligohydramnios sequence include a flattened face; wide-set eyes; a flattened, beaked nose; ears set lower on the head than expected (low-set ears); and a small, receding chin (micrognathia).

Because the movement of the arms and legs are restricted, a variety of limb deformities can occur, including bilateral clubfoot (both feet turned to the side), dislocated hips, broad flat hands, and joint contractures (inability for the joints to fully extend). Contractures tend to be seen more often in fetuses where the oligohydramnios occurred during the second trimester. Broad, flat hands tend to be seen more often in fetuses where the oligohydramnios began during the third trimester.

Fetuses with oligohydramnios sequence also tend to have pulmonary hypoplasia (underdevelopment of the lungs). The pulmonary hypoplasia is felt to occur as a result of the compression of the fetal chest (thorax), although it has been suggested that pulmonary hypoplasia may develop before 16 weeks of pregnancy in some cases. Therefore, regardless of the cause of the severe oligohydramnios, the physical features that develop and are seen in oligohydramnios sequence tend to be the same.

Diagnosis

An ultrasound examination during the second and/or third trimester of a pregnancy is a good tool to help detect the presence of oligohydramnios. Since oligohydramnios can occur later in a pregnancy, an ultrasound examination performed during the second trimester may not detect the presence of oligohydramnios. In pregnancies affected with oligohydramnios, an ultrasound examination can be difficult to perform because there is less amniotic fluid around the fetus. Therefore, an ultrasound examination may not be able to detect the underlying cause of the oligohydramnios.

In some situations, an amniocentesis (injection of fluid into the amniotic cavity) is performed. This can sometimes help determine if the cause of the oligohydramnios was leakage of the amniotic fluid.

Amnioinfusions may also be used to help visualize the fetus on ultrasound in attempts to detect any fetal abnormalities.

Additionally, maternal serum screening may detect the presence of oligohydramnios in a pregnancy. Maternal serum screening is a blood test offered to pregnant women to help determine the chance that their baby may have Down syndrome, Trisomy 18, and spina bifida. This test is typically performed between the 15th and 20th week of a pregnancy. The test works by measuring amount of certain substances in the maternal circulation.

Alpha-fetoprotein (AFP) is a protein produced mainly by the fetal liver and is one of the substances measured in the mother's blood. The level of AFP in the mother's blood has been used to help find pregnancies at higher risk to have spina bifida. An elevated AFP in the mother's blood, which is greater than 2.5 multiples of the median (MoM), has also been associated with several conditions, including the presence of oligohydramnios in a pregnancy. Since oligohydramnios is just one of several explanations for an elevated AFP level, an ultrasound examination is recommended when there is an elevated AFP level. However, not all pregnancies affected with oligohydramnios will have an elevated AFP level; some pregnancies with oligohydramnios will have the AFP level within the normal range.

Because fetuses with oligohydramnios sequence can have other anomalies, a detailed examination of the fetus should be performed. Knowing all the abnormalities a fetus has is important in making an accurate diagnosis. Knowing the cause of the oligohydramnios and if it is related to a syndrome or genetic condition is essential in predicting the chance for the condition to occur again in a future pregnancy. Sometimes the fetal abnormalities can be detected on a prenatal ultrasound examination or on an external examination of the fetus after delivery. However, several studies have shown that an external examination of the fetus can miss some fetal abnormalities and have stressed the importance of performing an autopsy to make an accurate diagnosis.

Treatment and management

There is currently no treatment or prevention for oligohydramnios sequence. Amnioinfusions, which can assist in determining the cause of the oligohydramnios in a pregnancy, are not recommended as a treatment for oligohydramnios sequence.

Prognosis

Pregnancies affected with oligohydramnios sequence can miscarry, be stillborn, or die shortly after birth. This

condition is almost always fatal because the lungs do not develop completely (pulmonary hypoplasia).

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National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

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Ollier disease see **Chondrosarcoma**

Omphalocele

Definition

An omphalocele occurs when the abdominal wall does not close properly during fetal development. The extent to which abdominal contents protrude through the base of the umbilical cord will vary. A membrane usually covers the defect.

Description

An omphalocele is an abnormal closure of the abdominal wall. Between the sixth and tenth weeks of pregnancy, the intestines normally protrude into the umbilical cord as the baby is developing. During the tenth week, the intestines should return and rotate in such a way that the abdomen is closed around the umbilical

KEY TERMS

Acetylcholinesterase (ACHE)—An enzyme found in nerve tissue.

Alpha-fetoprotein (AFP)—A chemical substance produced by the fetus and found in the fetal circulation. AFP is also found in abnormally high concentrations in most patients with primary liver cancer.

Amniocentesis—A procedure performed at 16-18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Amniotic fluid—The fluid that surrounds a developing baby during pregnancy.

Analyte—A chemical substance such as an enzyme, hormone, or protein.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Beckwith-Wiedemann syndrome—A collection of health problems present at birth including an omphalocele, large tongue, and large body size.

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Gastroschisis—A small defect in the abdominal wall normally located to the right of the umbilicus, and not covered by a membrane, where intestines and other organs may protrude.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Macroglossia—A large tongue.

Macrosomia—Overall large size due to overgrowth.

Maternal serum screening—A blood test offered to pregnant women usually under the age of 35, which measures analytes in the mother's blood that are present only during pregnancy, to screen for Down syndrome, trisomy 18, and neural tube defects.

Multifactorial—Describes a disease that is the product of the interaction of multiple genetic and environmental factors.

Omphalocele—A birth defect where the bowel, and sometimes the liver, protrudes through an opening in the baby's abdomen near the umbilical cord.

Polyhydramnios—A condition in which there is too much fluid around the fetus in the amniotic sac.

Thoracic cavity—The chest.

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.

Ventilator—Mechanical breathing machine.

Ventral wall defect—An opening in the abdomen (ventral wall). Examples include omphalocele and gastroschisis.

cord. An omphalocele occurs when the intestines do not return, and this closure does not occur properly.

Genetic profile

In one-third of infants, an omphalocele occurs by itself, and is said to be an isolated abnormality. The cause of an isolated omphalocele is suspected to be multifactorial. Multifactorial means that many factors, both genetic and environmental, contribute to the cause. The specific genes involved, as well as the specific environmental factors are largely unknown. The chance for a couple to have

another baby with an omphalocele after they have had one with an isolated omphalocele is approximately 1 in 100 or 1%.

The remaining two-thirds of babies with an omphalocele have other birth defects, including problems with the heart (heart disease), spine (spina bifida), digestive system, urinary system, and the limbs.

Approximately 30% of babies with an omphalocele have a chromosome abnormality as the underlying cause of the omphalocele. Babies with chromosome abnormalities usually have multiple birth defects, so many babies

will have other medical problems in addition to the omphalocele. Chromosomes are structures in the center of the cell that contain our genes; our genes code for our traits, such as blood type or eye color. The normal number of chromosomes is 46; having extra or missing chromosome material is associated with health problems. Babies with an omphalocele may have an extra chromosome number 13, 18, 21, or others. An omphalocele is sometimes said to occur more often in a mother who is older. This is because the chance for a chromosome abnormality to occur increases with maternal age.

Some infants with an omphalocele have a syndrome (collection of health problems). An example is Beckwith-Wiedemann syndrome, where a baby is born larger than normal (macrosomia), has an omphalocele, and has a large tongue (macroglossia). Finally, in some families, an omphalocele has been reported to be inherited as an autosomal dominant or autosomal recessive trait. Autosomal means that males and females are equally affected. Dominant means that only one gene is necessary to produce the condition, while recessive means that two genes are necessary to have the condition. With autosomal dominant inheritance, there is a 50% chance with each pregnancy to have an affected child, while with autosomal recessive inheritance, the recurrence risk is 25%.

Demographics

Omphalocele is estimated to occur in 1 in 4,000 to 1 in 6,000 liveborns. Males are slightly more often affected than females (1.5:1).

Signs and symptoms

Anytime an infant is born with an omphalocele, a thorough physical examination is performed to determine whether the omphalocele is isolated or associated with other health problems. To determine this, various studies may be performed such as a chromosome study, which is done from a small blood sample. Since the chest cavity may be small in an infant born with an omphalocele, the baby may have underdeveloped lungs requiring breathing assistance with a ventilator (mechanical breathing machine). In 10% to 20% of infants, the sac has torn (ruptured), requiring immediate surgical repair, due to the risk of infection.

Diagnosis

During pregnancy, two different signs may cause a physician to suspect an omphalocele: increased fluid around the baby (polyhydramnios) on a fetal ultrasound and/or an abnormal maternal serum screening test showing an elevated amount of alpha-fetoprotein (AFP).

QUESTIONS TO ASK YOUR DOCTOR

- What does the term “omphalocele” mean?
- Why is omphalocele considered to be a genetic disorder?
- What factors determine the prognosis of a child born with omphalocele?
- How is omphalocele diagnosed either pre- or postnatally?

Maternal serum screening, measuring analytes present in the mother’s bloodstream only during pregnancy, is offered to pregnant women usually over the age of 35. This screening may detect various disorders such as Down syndrome, trisomy 18, and abnormalities of the spine (such as spina bifida). Other problems can give an abnormal test result, and an omphalocele is an example.

An ultrasound is often performed as the first step when a woman’s maternal serum screening is abnormal, if one has not already been performed. Omphalocele is usually identifiable on fetal ultrasound. If a woman’s fetal ultrasound showed an omphalocele or polyhydramnios, or if she had an abnormal maternal serum screening test, an amniocentesis may be offered.

Amniocentesis is a procedure done under ultrasound guidance where a long thin needle is inserted into the mother’s abdomen, then into the uterus, to withdraw a couple tablespoons of amniotic fluid (fluid surrounding the developing baby) to study. Measurement of the AFP in the amniotic fluid can then be done to test for problems such as omphalocele. In addition, a chromosome analysis for the baby can be performed on the cells contained in the amniotic fluid. When the AFP in the amniotic fluid is elevated, an additional test is used to look for the presence or absence of an enzyme found in nerve tissue, called acetylcholinesterase, or ACHE. ACHE is present in the amniotic fluid only when a baby has an opening such as spina bifida or an omphalocele. Not all babies with an omphalocele will cause the maternal serum screening test to be abnormal or to cause extra fluid accumulation, but many will. At birth, an omphalocele is diagnosed by visual/physical examination.

Treatment and management

Treatment and management of an omphalocele depends upon the size of the abnormality, whether the sac is intact or ruptured, and whether other health problems are present. A small omphalocele is usually

repaired by surgery shortly after birth, where an operation is performed to return the organs to the abdomen and close the opening in the abdominal wall. If the omphalocele is large, where most of the intestines, liver, and/or spleen are present outside of the body, the repair is done in stages because the abdomen is small and may not be able to hold all of the organs at once. Initially, sterile protective gauze is placed over the abdominal organs whether the omphalocele is large or small. The exposed organs are then gradually moved back into the abdomen over several days or weeks. The abdominal wall is surgically closed once all of the organs have been returned to the abdomen. Infants are often on a breathing machine (ventilator) until the abdominal cavity increases in size since returning the organs to the abdomen may crowd the lungs in the chest area.

Prognosis

The prognosis of an infant born with an omphalocele depends upon the size of the defect, whether there was a loss of blood flow to part of the intestines or other organs, and the extent of other abnormalities. The survival rate overall for an infant born with an isolated omphalocele has improved greatly over the past 40 years, from 60% to over 90%.

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ORGANIZATIONS

American Congress of Obstetricians and Gynecologists, PO Box 70620, Washington, DC 20024-9998, (202) 638-5577 or (800) 673-8444, resources@acog.org, <http://www.acog.org>
American Pediatric Surgical Association, 1061 E. Main St., Suite 300, East Dundee, IL 60118, (309) 733-7874, info@apsapedsurg.org, <http://www.apsapedsurg.org>

Catherine L. Tesla, MS, CGC

Oncogene

Definition

In a cell with normal control regulation (non-cancerous), genes produce proteins that provide regulated cell division. Cancer is the disease caused by cells that have lost their ability to control their regulation. The abnormal proteins allowing the non-regulated cancerous state are produced by genes known as oncogenes. The normal gene from which the oncogene evolved is called a proto-oncogene.

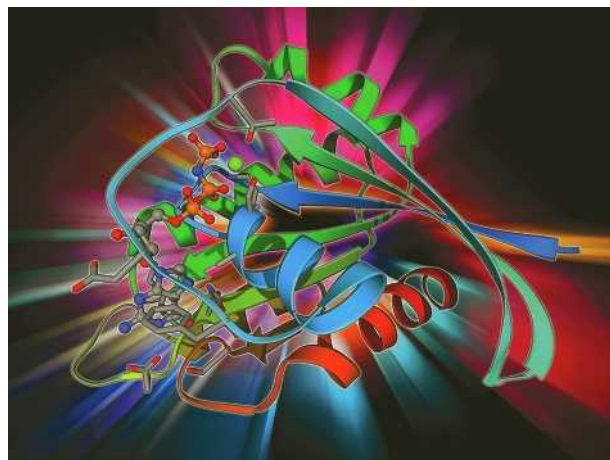
Description

History

The word "oncogene" comes from the Greek term "oncos," which means "tumor." Oncogenes were originally discovered in certain types of animal viruses that were capable of inducing tumors in the animals they infected. These viral oncogenes, called v-onc, were later found in human tumors, although most human cancers do not appear to be caused by viruses. Since their original discovery, hundreds of oncogenes have been found but only a small number of them are known to affect humans. Although different oncogenes have different functions, they are all somehow involved in the process of transformation (change) of normal cells to cancerous cells.

The transformation of normal cells into cancerous cells

The process by which normal cells are transformed into cancerous cells is a complex, multi-step process involving a breakdown in the normal cell cycle. Normally, a somatic cell goes through a growth cycle in which it



Molecular model of an oncogene protein. (Laguna Design/ Science Photo Library/Alamy)

produces new cells. The two main stages of this cycle are interphase (genetic material in the cell duplicates) and mitosis (the cell divides to produce two other identical cells). The process of cell division is necessary for the growth of tissues and organs of the body and for the replacement of damaged cells. Normal cells have a limited lifespan and only go through the cell cycle a limited number of times.

Different cell types are produced by the regulation of which genes in a given cell are allowed to be expressed. One way cancer is caused is by de-regulation of those genes related to control of the cell cycle and the development of oncogenes. If the oncogene is present in a skin cell, the patient will have skin cancer; in a breast cell, breast cancer will result, and so on.

Cells that lose control of their cell cycle and replicate out of control are called cancer cells. Cancer cells undergo many cell divisions often at a quicker rate than normal cells and do not have a limited lifespan. This allows them to eventually overwhelm the body with a large number of abnormal cells and eventually affect the functioning of the normal cells.

A cell becomes cancerous only after changes occur in a number of genes that are involved in the regulation of its cell cycle. A change in a regulatory gene can cause it to stop producing a normal regulatory protein or can produce an abnormal protein that does not regulate the cell in a normal manner. When changes occur in one regulatory gene this often causes changes in other regulatory genes. Cancers in different types of cells can be caused by changes in different types of regulatory genes.

Proto-oncogenes and tumor-suppressor genes are the two most common genes involved in regulating the cell cycle. Proto-oncogenes and tumor-suppressor genes have different functions in the cell cycle. Tumor-suppressor genes produce proteins that are involved in prevention of uncontrolled cell growth and division. Since two of each type of gene are inherited, two of each type of tumor-suppressor gene are also inherited. Both tumor suppressor genes of a pair need to be changed in order for the protein produced to stop functioning as a tumor suppressor. Mutated tumor-suppressor genes therefore act in an autosomal recessive manner.

Proto-oncogenes produce proteins that are largely involved in stimulating the growth and division of cells in a controlled manner. Each proto-oncogene produces a different protein that has a unique role in regulating the cell cycles of particular types of cells. We inherit two of each type of proto-oncogene. A change in only one proto-oncogene of a pair converts it into an oncogene. The oncogene produces an abnormal protein, which is somehow involved in stimulating uncontrolled cell

growth. An oncogene acts in an autosomal dominant manner since only one proto-oncogene of a pair needs to be changed in the formation of an oncogene.

Classes of proto-oncogene

There are five major classes of proto-oncogene/ oncogenes: (1) growth factors, (2) growth factor receptors, (3) signal transducers (4) transcription factors, and (5) programmed cell death regulators.

GROWTH FACTORS. Some proto-oncogenes produce proteins, called growth factors, which indirectly stimulate growth of the cell by activating receptors on the surface of the cell. Different growth factors activate different receptors, found on different cells of the body. Mutations in growth factor proto-oncogene result in oncogenes that promote uncontrolled growth in cells for which they have a receptor. For example, platelet-derived growth factor (PDGF) is a proto-oncogene that helps to promote wound healing by stimulating the growth of cells around a wound. PDGF can be mutated into an oncogene called v-sis (PDGFB), which is often present in connective-tissue tumors.

GROWTH FACTOR RECEPTORS. Growth factor receptors are found on the surface of cells and are activated by growth factors. Growth factors send signals to the center of the cell (nucleus) and stimulate cells that are at rest to enter the cell cycle. Different cells have different growth factors receptors. Mutations in a proto-oncogene that are growth factor receptors can result in oncogenes that produce receptors that do not require growth factors to stimulate cell growth. Overstimulation of cells to enter the cell cycle can result and promote uncontrolled cell growth. Most proto-oncogene growth factor receptors are called tyrosine kinases and are very involved in controlling cell shape and growth. One example of a tyrosine kinase is called GDFNR. The RET (rearranged during transfection) oncogene is a mutated form of GDFNR and is commonly found in cancerous thyroid cells.

SIGNAL TRANSDUCERS. Signal transducers are proteins that relay cell cycle stimulation signals, from growth factor receptors to proteins in the nucleus of the cell. The transfer of signals to the nucleus is a stepwise process that involves a large number of proto-oncogenes and is often called the signal transduction cascade. Mutations in proto-oncogene involved in this cascade can cause unregulated activity, which can result in abnormal cell proliferation. Signal transducer oncogenes are the largest class of oncogenes. The RAS family is a group of 50 related signal transducer oncogenes that are found in approximately 20% of tumors.

TRANSCRIPTION FACTORS. Transcription factors are proteins found in the nucleus of the cell that ultimately

KEY TERMS

Autosomal dominant manner—An abnormal gene on one of the 22 pairs of non-sex chromosomes that will display the defect when only one copy is inherited.

Benign—A non-cancerous tumor that does not spread and is not life-threatening.

Cell—The smallest living units of the body, which group together to form tissues and help the body perform specific functions.

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Leukemia—Cancer of the blood forming organs that results in an overproduction of white blood cells.

Lymphoma—A malignant tumor of the lymph nodes.

Mitosis—The process by which a somatic cell divides.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Nucleus—The central part of a cell that contains most of its genetic material, including chromosomes and DNA.

Parathyroid glands—A pair of glands adjacent to the thyroid gland that primarily regulate blood calcium levels.

Pheochromocytoma—A small vascular tumor of the inner region of the adrenal gland. The tumor causes uncontrolled and irregular secretion of certain hormones.

Proliferation—The growth or production of cells.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

Proto-oncogene—A gene involved in stimulating the normal growth and division of cells in a controlled manner.

Replicate—Produce identical copies of itself.

Somatic cells—All the cells of the body except for the egg and sperm cells.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosome material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

Tumor suppressor gene—Genes involved in controlling normal cell growth and preventing cancer.

receive the signals from the growth factor receptors. Transcription factors directly control the expression of genes that are involved in the growth and proliferation of cells. Transcription factors produced by oncogenes typically do not require growth factor receptor stimulation and thus can result in uncontrolled cell proliferation. Transcription factor proto-oncogenes are often changed into oncogenes by chromosomal translocations in leukemias, lymphomas, and solid tumors. C-myc is a common transcription factor oncogene that results from a chromosomal translocation and is often found in leukemias and lymphomas.

PROGRAMMED CELL DEATH REGULATORS. Normal cells have a predetermined lifespan and different genes regulate their growth and death. Cells that have been damaged or have an abnormal cell cycle may develop into cancer cells. Usually these cells are destroyed

through a process called programmed cell death (apoptosis). Cells that have developed into cancer cells, however, do not undergo apoptosis. Mutated proto-oncogenes may inhibit the death of abnormal cells, which can lead to the formation and spread of cancer. The bcl-2 oncogene, for example, inhibits cell death in cancerous cells of the immune system.

Mechanisms of transformation of proto-oncogene into oncogenes

It is not known in most cases what triggers a particular proto-oncogene to change into an oncogene. There appear to be environmental triggers such as exposure to toxic chemicals. There also appear to be genetic triggers since changes in other genes in a particular cell can trigger changes in proto-oncogenes.

The mechanisms through which proto-oncogenes are changed into oncogenes are, however, better understood. Proto-oncogenes are transformed into oncogenes through: (1) mutation, (2) chromosomal translocation, and (3) gene amplification.

A tiny change, called a mutation, in a proto-oncogene can convert it into an oncogene. The mutation results in an oncogene that produces a protein with an abnormal structure. These mutations often make the protein resistant to regulation and cause uncontrolled and continuous activity of the protein. The RAS family of oncogenes, found in approximately 20% of tumors, are examples of oncogenes caused by mutations.

Chromosomal translocations, which result from errors in mitosis, have also been implicated in the transformation of proto-oncogenes into oncogenes. Chromosomal translocations result in the transfer of a proto-oncogene from its normal location on a chromosome to a different location on another chromosome. Sometimes this translocation results in the transfer of a proto-oncogene next to a gene involved in the immune system. This results in an oncogene that is controlled by the immune system gene and as a result becomes deregulated. One example of this mechanism is the transfer of the c-myc proto-oncogene from its normal location on chromosome 8 to a location near an immune system gene on chromosome 14. This translocation results in the deregulation of c-myc and is involved in the development of Burkitt's lymphoma. The translocated c-myc proto-oncogene is found in the cancer cells of approximately 85% of people with Burkitt's lymphoma.

In other cases, the translocation results in the fusion of a proto-oncogene with another gene. The resulting oncogene produces an unregulated protein that is involved in stimulating uncontrolled cell proliferation. The first discovered fusion oncogene resulted from a Philadelphia chromosome translocation. This type of translocation is found in the leukemia cells of greater than 95% of patients with a chronic form of leukemia. The Philadelphia chromosome translocation results in the fusion of the c-abl proto-oncogene, normally found on chromosome 9, to the *BCR* gene found on chromosome 22. The fused gene produces an unregulated transcription factor protein that has a different structure than the normal protein. It is not known how this protein contributes to the formation of cancer cells.

Some oncogenes result when multiple copies of a proto-oncogene are created (gene amplification). Gene amplification often results in hundreds of copies of a gene, which results in increased production of proteins and increased cell growth. Multiple copies of proto-oncogenes are found in many tumors. Sometimes

amplified genes form separate chromosomes called double minute chromosomes and sometimes they are found within normal chromosomes.

Inherited oncogenes

In most cases, oncogenes result from changes in proto-oncogenes in select somatic cells and are not passed on to future generations. People with an inherited oncogene, however, do exist. They possess one changed proto-oncogene (oncogene) and one unchanged proto-oncogene in all of their somatic cells. The somatic cells have two of each chromosome and therefore two of each gene since one of each type of chromosome is inherited from the mother in the egg cell and one of each is inherited from the father in the sperm cell. The egg and sperm cells have undergone a number of divisions in their cell cycle and therefore only contain one of each type of chromosome and one of each type of gene. A person with an inherited oncogene has a changed proto-oncogene in approximately 50% of their egg or sperm cells and an unchanged proto-oncogene in the other 50% of their egg or sperm cells, and therefore has a 50% chance of passing this oncogene on to their children.

A person only has to inherit a change in one proto-oncogene of a pair to have an increased risk of cancer. This is called autosomal dominant inheritance. Not all people with an inherited oncogene develop cancer, since mutations in other genes that regulate the cell cycle need to occur in a cell for it to be transformed into a cancerous cell. The presence of an oncogene in a cell does, however, make it more likely that changes will occur in other regulatory genes. The degree of cancer risk depends on the type of oncogene inherited as well as other genetic factors and environmental exposures. The types of cancers that are likely to develop depend on the type of oncogene that has been inherited.

Multiple endocrine neoplasia type II (MENII) is one example of a condition caused by an inherited oncogene. People with MENII have usually inherited the *RET* oncogene. They have approximately a 70% chance of developing thyroid cancer, a 50% chance of developing a tumor of the adrenal glands (pheochromocytoma), and about a 5%–10% chance of developing symptomatic parathyroid disease.

Oncogenes as targets for cancer treatment

The discovery of oncogenes approximately 20 years ago has played an important role in developing an understanding of cancer. Oncogenes promise to play an even greater role in development of improved cancer therapies since oncogenes may be important targets for drugs that are used for the treatment of cancer. The goal of

these therapies is to selectively destroy cancer cells while leaving normal cells intact. Many anti-cancer therapies currently under development are designed to interfere with oncogenic signal transducer proteins, which relay the signals involved in triggering the abnormal growth of tumor cells. Other therapies hope to trigger specific oncogenes to cause programmed cell death in cancer cells. Whatever the mechanism by which they operate, it is hoped that these experimental therapies will offer a great improvement over current cancer treatments.

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Lisa Maria Andres, MS, CGC

Onychoosteodysplasia see **Nail-Patella syndrome**

Opitz-Frias syndrome see **Opitz syndrome**

Opitz-Kaveggia syndrome see **FG syndrome**

Opitz syndrome

Definition

Opitz syndrome is a heterogeneous genetic condition characterized by a range of midline birth defects such as hypertelorism, clefts in the lips and larynx, heart defects, hypospadias, and agenesis of the corpus callosum.

Description

Opitz syndrome or Opitz G/BBB syndrome, as it is sometimes called, includes G syndrome and BBB syndrome, which were originally thought to be two different syndromes, as described in 1969 by Dr. John Opitz. G

Frequencies of common conditions associated with Opitz syndrome

Hypospadias	93%	LTE cleft/fistula	38%
Hypertelorism	91%	Cleft lip and palate	32%
Swallowing problems	81%	Strabismus	28%
Ear abnormalities	72%	Heart defects	27%
Developmental delay	43%	Imperforate anus	21%
Kidney anomalies	42%	Undescended testes	20%

(Gale)

syndrome was named after one family affected with the syndrome whose last name began with the initial G, and BBB syndrome was named after the surname of three different families. Subsequent research suggested that these two conditions were one disorder, but researchers could not agree on how the disorder was inherited. It wasn't until 1995 that Dr. Nathaniel Robin and his colleagues demonstrated that Opitz syndrome had both X-linked and autosomal dominant forms.

Opitz syndrome is a complex condition that has many symptoms, most of which affect organs along the midline of the body such as clefts in the lip and larynx, heart defects, hypospadias, and agenesis of the corpus callosum. Opitz syndrome has variable expressivity, which means that different people with the disorder can have different symptoms. This condition also has decreased penetrance, which means that not all people who inherit the disorder will have symptoms.

Genetic profile

Opitz syndrome is a genetically heterogeneous condition. There appear to be at least two to three genes that can cause Opitz syndrome when changed (mutated) or deleted. Opitz syndrome can be caused by changes in genes found on the X chromosome (X-linked) and changes in or deletion of a gene found on chromosome 22 (autosomal dominant).

Chromosomes, genes, and proteins

Each cell of the body, except for the egg and sperm cells, contains 23 pairs of chromosomes—46 chromosomes in total. The egg and sperm cells contain only one of each type of chromosome and therefore contain 23 chromosomes in total. Males and females have 22 pairs of chromosomes, called the autosomes, numbered 1 to 22 in order of decreasing size. The other pair of chromosomes, called the sex chromosomes, determines the sex of the individual. Women possess two identical chromosomes called the X chromosomes, while men possess one X chromosome and one Y chromosome. Since every egg cell contains an X chromosome, women pass on the X

chromosome to their daughters and sons. Some sperm cells contain an X chromosome, and some sperm cells contain a Y chromosome. Men pass the X chromosome on to their daughters and the Y chromosome on to their sons. Each type of chromosome contains different genes that are found at specific locations along the chromosome. Men and women inherit two of each type of autosomal gene since they inherit two of each type of autosome. Women inherit two of each type of X-linked gene since they possess two X chromosomes. Men inherit only one of each X-linked gene since they possess only one X chromosome.

Each gene contains the instructions for the production of a particular protein. The proteins produced by genes have many functions and work together to create the traits of the human body such as hair and eye color and are involved in controlling the basic functions of the human body. Changes or deletions of genes can cause them to produce abnormal protein, less protein, or no protein. This can prevent the protein from functioning normally.

Autosomal dominant Opitz syndrome

The gene responsible for the autosomal dominant form of Opitz syndrome is known as the *SPECCIL* gene, which is located on chromosome 22q11. In some cases, the deletion or gene change is inherited from either the mother or father who has the gene change or deletion in one chromosome 22 in the somatic cells. The other chromosome 22 found in each of the somatic cells is normal. Some of the egg or sperm cells contain the gene change or deletion in chromosome 22, and some contain a normal chromosome 22. In other cases the deletion has occurred spontaneously during conception or is only found in some of the egg or sperm cells of either parent but not in the other cells of the body.

Parents who have had a child with an autosomal dominant form of Opitz syndrome may or may not be at increased risk for having other affected children. If one of the parents is diagnosed with Opitz syndrome, then each of the children has a 50% chance of inheriting the condition. If neither parent has symptoms of Opitz syndrome or possesses a deletion, then it becomes more difficult to assess their chances of having other affected children.

In many cases they would not be at increased risk since the gene alteration occurred spontaneously in the embryo during conception. It is possible, however, that one of the parents is a carrier, meaning he or she possesses a change in the autosomal dominant Opitz gene but does not have any obvious symptoms. This parent's

children would each have a 50% chance of inheriting the Opitz gene.

X-linked Opitz syndrome

Some people with the X-linked form of Opitz syndrome have a change (mutation) in a gene found on the X chromosome called the *MID1* (midline1) gene. It is believed that the *MID* genes produce proteins involved in the development of midline organs. Changes in the *MID* gene prevent the production of enough normal protein for normal organ development.

The X-linked form of Opitz syndrome is inherited differently by men and women. A woman with an X-linked form of Opitz syndrome has typically inherited a changed *MID* gene from her mother and a changed *MID* gene from her father. This occurs very infrequently. All of this woman's sons will have Opitz syndrome, and all of her daughters will be carriers for Opitz syndrome. Only women can be carriers for Opitz syndrome, since carriers possess one changed *MID* gene and one unchanged *MID* gene. Most carriers for the X-linked form of Opitz syndrome do not have symptoms, since one normal *MID* gene is usually sufficient to promote normal development. Some carriers do have symptoms, but they tend to be very mild. Daughters of carriers of Opitz syndrome have a 50% chance of being carriers, and sons have a 50% chance of being affected with Opitz syndrome. A man with an X-linked form of Opitz syndrome will have normal sons, but all of his daughters will be carriers.

Demographics

Opitz syndrome is a rare disorder that appears to affect all ethnic groups. The frequency of this disorder is unknown, since people with this disorder exhibit a wide range of symptoms, making it difficult to diagnose. Many people possess mild or non-detectable symptoms.

Signs and symptoms

People with Opitz syndrome exhibit a wide range of medical problems and in some cases may not exhibit any detectable symptoms. This may be due in part to the genetic heterogeneity of this condition. Even people with Opitz syndrome who are from the same family can have different problems. This may mean there are other genetic and non-genetic factors that influence the development of symptoms in individuals who have inherited a changed or deleted Opitz gene. Most individuals with Opitz syndrome only have a few symptoms of the disorder, such as wide-set eyes and a broad, prominent forehead. Opitz syndrome can, however, affect many of the organs and structures of the body and primarily

KEY TERMS

Agenesis of the corpus callosum—Failure of the corpus callosum to form and develop. The corpus callosum is the band of nerve fibers located between the two sides, or hemispheres, of the brain.

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman’s abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Anomaly—Different from the normal or expected. Unusual or irregular structure.

Autosome—Chromosomes that do not determine the sex of an individual.

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Cleft—An elongated opening or slit in an organ.

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Congenital—Refers to a disorder that is present at birth.

Cryptorchidism—A condition in which one or both testes fail to descend normally.

Deletion—The absence of genetic material that is normally found in a chromosome. Often, the genetic material is missing due to an error in replication of an egg or sperm cell.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

DNA testing—Analysis of DNA (the genetic component of cells) in order to determine changes in genes that may indicate a specific disorder.

Esophagus—The part of the digestive tract that connects the mouth and stomach; the food pipe.

FISH (fluorescence in situ hybridization)—Technique used to detect small deletions or rearrangements

affects the development of midline organs. The most common symptoms are hypertelorism (wide-spaced eyes); broad, prominent forehead; heart defects; hypospadias (urinary opening of the penis present on the underside of the penis instead of its normal location at the tip); undescended testicles; an abnormality of the anal opening; agenesis of the corpus callosum (absence of the tissue that connects the two sides of the brain); cleft lip; and clefts and abnormalities of the pharynx (throat) and larynx (voice-box), trachea (wind-pipe), and esophagus.

People with Opitz syndrome usually have a distinctive look to the face, such as a broad, prominent forehead; cleft lip; wide-set eyes that may be crossed; wide noses with upturned nostrils; small chins or jaws; malformed ears; crowded, absent, or misplaced teeth; and hair that may form a “widow’s peak.” In many cases, the head may appear large or small and out of proportion to the rest of the body.

Often, people with Opitz syndrome have difficulties swallowing because of abnormalities in the pharynx, larynx, trachea, or esophagus. This can sometimes result in

food entering the trachea instead of the esophagus, which can cause damage to the lungs and pneumonia. It can also sometimes be fatal in small infants. Abnormalities in the trachea can sometimes make breathing difficult and may result in a hoarse or weak voice and wheezing.

Both males and females may have abnormal genitals and abnormalities in the anal opening. Males can have hypospadias and undescended testicles, and girls may have minor malformation of their external genitalia. Heart defects are also often present, and abnormalities of the kidney can be present as well. Intelligence is usually normal, but mild intellectual disability can sometimes be present. Twins appear more common in families affected with Opitz syndrome.

Males and females with the dominant form of Opitz syndrome are equally likely to have symptoms, whereas carrier females with the X-linked form of Opitz syndrome are less likely to have symptoms than males with the condition. In general, males with the X-linked form of Opitz syndrome tend to be more severely affected than females and males with the autosomal dominant form of Opitz syndrome. People with X-linked Opitz syndrome and

in chromosomes by attempting to attach a fluorescent (glowing) piece of a chromosome to a sample of cells obtained from a patient.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Geneticist—A specialist (MD or PhD) who has training and certification in diagnosing, managing, and counseling individuals/families with genetic disorders. Genetic counselors hold a master's degree in medical genetics and provide many of the same services as geneticists.

Heterogeneous—A set of symptoms or a disorder caused by several different gene mutations.

Hypertelorism—A wider-than-normal space between the eyes.

Hypospadias—An abnormality of the penis in which the urethral opening is located on the underside of the penis rather than at its tip.

Hypotonia—Reduced or diminished muscle tone.

Microcephaly—An abnormally small head.

Midline defects—Defects involving organs along the center of the body such as the lips, penis, and corpus callosum.

Midline organs—Organs found along the center of the body such as the lips, penis, and corpus callosum.

Polydactyly—The presence of extra fingers or toes.

Prenatal testing—Testing for a disease such as a genetic condition in an unborn baby.

Sex chromosomes—The X and Y chromosomes that determine the sex of the individual.

Somatic cells—All the cells of the body except for the egg and sperm cells.

Strabismus—An improper muscle balance of the ocular muscles resulting in crossed or divergent eyes.

Syndactyly—Webbing or fusion between the fingers or toes.

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.

Undescended testicles—Testicles that failed to move from the abdomen to the scrotum during the development of the fetus.

X-linked gene—A gene found on the X chromosome.

dominant Opitz syndrome generally appear to exhibit the same range of symptoms. The only known exceptions are upturned nostrils and clefts at the back of throat, which appear to only occur in people with X-linked Opitz syndrome.

Diagnosis

Diagnostic evaluation

The diagnosis and cause of Opitz syndrome is often difficult to establish. In most cases, it is diagnosed through a clinical evaluation and not through a blood test. This means that a genetic specialist (geneticist) has examined the patient and found enough symptoms of Opitz syndrome to make a diagnosis. Since not all patients have obvious symptoms or even any symptoms at all, this can be a difficult task. It can also be difficult to establish whether an individual has an X-linked form or an autosomal dominant form, and whether it has been inherited or occurred spontaneously. In many cases, the geneticist has to rely on physical examinations or pictures of multiple family members and a description of the family's medical history to establish the cause of

Opitz syndrome. In some cases the cause cannot be established.

Sometimes a clinical diagnosis is confirmed through fluorescence in situ hybridization (FISH). FISH testing can detect whether a person has a deletion of the region of chromosome 22 that is associated with Opitz syndrome. Fluorescent (glowing) pieces of DNA containing the region that is deleted in Opitz syndrome are mixed with a sample of cells obtained from a blood sample. If there is a deletion in one of the chromosomes, the DNA will only stick to one chromosome and not the other and only one glowing section of a chromosome will be visible instead of two. Most patients with the autosomal dominant form of Opitz syndrome cannot be diagnosed through FISH testing since they possess a tiny change in the gene that cannot be detected with the procedure. As of early 2015, DNA testing for the X-linked form of Opitz disease was available through clinical laboratories.

Prenatal testing

It is difficult to diagnose Opitz syndrome in a baby prior to its birth. Sometimes doctors and technicians

QUESTIONS TO ASK YOUR DOCTOR

- What are the characteristic features of Opitz syndrome?
- On what tests or other measures is a differential diagnosis of Opitz syndrome based?
- What kinds of treatments are typically necessary for a child born with Opitz syndrome?
- Can you recommend an organization that provides information about this genetic condition and support for parents who have a child with Opitz syndrome?

(ultrasonographers) who specialize in performing ultrasound evaluations are able to see physical features of Opitz syndrome in the fetus. Some of the features they may look for in the ultrasound evaluation are heart defects, wide spacing between the eyes, clefts in the lip, hypospadias, and agenesis of the corpus callosum. It is very difficult, however, even for experts to diagnose or rule out Opitz syndrome through an ultrasound evaluation.

Opitz syndrome can be definitively diagnosed in a baby prior to its birth if an *MID* gene change is detected in the mother or if a deletion in chromosome 22 is detected in the mother or father. Cells from the baby are obtained through amniocentesis or chorionic villus sampling. These cells are analyzed for the particular *MID* gene change or chromosome 22 deletion found in one of the parents.

Treatment and management

There was no cure for Opitz syndrome and no treatment for the underlying condition. Management of the condition involves diagnosing and managing the symptoms. Clefts, heart defects, and genital abnormalities can often be repaired by surgery. Feeding difficulties can sometimes be managed using feeding tubes through the nose, stomach, or small intestine. Anti-reflux medications can be prescribed to lessen the risk for aspiration until laryngeal function is demonstrated. Early recognition and intervention with special education may help individuals with intellectual disability.

Prognosis

For most patients, the prognosis and quality of life of Opitz syndrome is good, with individuals typically living a normal lifespan. The prognosis, however, is very dependent on the type of organ abnormality and the

quality of medical care. Patients with severe heart defects and major abnormalities in the trachea and esophagus may have a poorer prognosis.

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ORGANIZATIONS

- AboutFace, 1057 Steeles Ave. W, PO Box 702, North York, ON, Canada M2R 2S9, (416) 597-2229 or (800) 665-3223, (416) 597-8494, info@aboutface.ca, <http://www.aboutface.ca>
- Cleft Palate Foundation, 1504 E. Franklin St., Suite 102, Chapel Hill, NC 27514-2820, (800) 242-5338 or (919) 933-9044, (919) 933-9604, info@cleftline.org, <http://www.cleftline.org>

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Oral-facial-digital syndrome

Definition

Oral-facial-digital (OFD) syndrome is a generic name for a variety of different genetic disorders that result in malformations of the mouth, teeth, jaw, facial bones, hands, and feet.

Description

Oral-facial-digital syndrome includes several different, but possibly related, genetic disorders. OFD syndromes are also referred to as digito-oro-facial syndromes. There are 13 different OFD syndromes,

identified as OFD syndrome type I, type II, and so on. OFD syndromes are so named because they all cause changes in the oral structures, including the tongue, teeth, and jaw; the facial structures, including the head, eyes, and nose; and the digits (fingers and toes). OFD syndromes are also frequently associated with developmental delay.

The different OFD syndromes are distinguished from each other based on the specific physical symptoms and the mode of inheritance. There are many alternate names for OFD syndromes. A partial list of these is:

- OFD syndrome type I: Gorlin syndrome I, Gorlin-Psaume syndrome, Papillon-Leage syndrome
- OFD syndrome type II: Mohr syndrome, Mohr-Claussen syndrome
- OFD syndrome type III: Sugarman syndrome
- OFD syndrome type IV: Baraitser-Burn syndrome
- OFD syndrome type V: Thurston syndrome



One of the traits found in individuals with OFD syndrome is webbing of the fingers and toes. (Chassenet/BSIP SA/Alamy)

KEY TERM

Digit—A finger or toe.

- OFD syndrome type VI: Varadi syndrome, Varadi-Papp syndrome
- OFD syndrome type VII: Whelan syndrome

Genetic profile

The mode of inheritance of OFD syndrome depends on the type of the syndrome. Type I is inherited as an X-linked dominant trait and is only found in females because it is fatal in males. X-linked means that the syndrome is carried on the female sex chromosome, while dominant means that only one parent has to pass on the gene mutation in order for the child to be affected with the syndrome.

OFD syndrome type VII is inherited either as an X-linked or autosomal dominant pattern of inheritance. Autosomal means that the syndrome is not carried on a sex chromosome.

OFD syndrome types II, III, IV, V, and VI are passed on through an autosomal recessive pattern of inheritance. Recessive means that both parents must carry the gene mutation in order for their child to have the disorder.

OFD syndrome types VIII and IX are characterized by either an autosomal or X-linked recessive pattern of inheritance.

The gene location for OFD syndrome type I has been assigned to Xp22.3-22.2, or on the 22nd band of the p arm of the X chromosome. The specific gene mutations responsible for the other types of OFD syndrome has not been identified.

Demographics

There does not appear to be any clear-cut ethnic pattern to the incidence of OFD syndrome. Most types of OFD syndrome affect males and females with equal probability, although type I, the most common type, affects only females (since it is lethal in males before birth). The estimated incidence of OFD syndrome is between 1 in 50,000 to 250,000 infants, with most of the cases being of the type I variety.

Signs and symptoms

The symptoms observed in people affected by OFD syndrome vary depending on the specific type of the syndrome. In general, the symptoms include the following:

QUESTIONS TO ASK YOUR DOCTOR

- How did this disorder get its name?
- What signs and symptoms are typically associated with oral-facial-digital syndrome?
- What information is available about the genetic basis of this condition?
- What information is needed in order to make a prognosis for any particular individual with this disorder?

Oral features:

- Cleft lip
- Cleft palate or highly arched palate
- Lobed or split tongue
- Tumors of the tongue
- Missing or extra teeth
- Gum disease
- Misaligned bite
- Smaller than normal jaw

Facial features:

- Small or wide set eyes
- Missing structures of the eye
- Broad base or tip of the nose
- One nostril smaller than the other
- Low-set or angled ears

Digital features:

- Extra fingers or toes
- Abnormally short fingers
- Webbing between fingers or toes
- Clubfoot
- Permanently flexed fingers

Mental development and central nervous system:

- Intellectual disabilities
- Brain abnormalities
- Seizures
- Spasmodic movements or tics
- Delayed motor and speech development

Other:

- Growth retardation
- Cardiovascular abnormalities

- Sunken chest
- Susceptibility to respiratory infection

Diagnosis

Diagnosis is usually made based on the observation of clinical symptoms. There is currently no medical test that can definitively confirm the diagnosis of OFD syndrome, with the exception of genetic screening for OFD syndrome type I.

Treatment and management

Treatment of OFD syndrome is directed toward the specific symptoms of each case. Surgical correction of the oral and facial malformations associated with OFD syndrome is often required.

Prognosis

Prognosis depends on the specific type of OFD syndrome and the symptoms present in the individual. OFD syndrome type I is lethal in males before birth. However, other types of OFD syndrome are found in both males and females. Due to the wide variety of symptoms seen in the 13 types of the syndrome, overall survival rates are not available.

Resources

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- "Oral-Facial-Digital Syndrome." NORD. <https://rarediseases.org/rare-diseases/oral-facial-digital-syndrome/> (accessed June 15, 2021).

ORGANIZATIONS

- Children's Craniofacial Association (CCA), 13140 Coit Rd., Suite 517, Dallas, TX 75240, (214) 570-9909 or (800)

535-3643, (214) 570-8811, contactCCA@ccakids.com,
<http://www.ccakids.com>
 FACES: The National Craniofacial Association, PO Box 11082,
 Chattanooga, TN 37401, (423) 266-1632 or (800)
 332-2373, <http://www.faces-cranio.org>
 National Organization for Rare Disorders (NORD), 55 Kenosia
 Ave., Danbury, CT 06180, (203) 744-0100, (203)
 798-2291, <http://rarediseases.org>

Paul A. Johnson

Organic acidemias

Definition

Organic acidemias are a collection of amino and fatty acid oxidation disorders that cause non-amino organic acids to accumulate and be excreted in the urine.

Description

Organic acidemias are divided into two categories: disorders of amino acid metabolism and disorders involving fatty acid oxidation. There are several dozen different organic acidemia disorders. They are caused by inherited deficiencies in specific enzymes involved in the breakdown of branched-chain amino acids, lysine and tryptophan, or fatty acids. Some of these disorders have more than one cause.

Amino acids are chemical compounds from which proteins are made. There are about 40 amino acids in the human body. Proteins in the body are formed through various combinations of roughly half of these amino acids. The other 20 play different roles in metabolism. Organic acidemias involving amino acid metabolism disorders include isovaleric acidemia, 3-methylcrotonylglycemia, combined carboxylase deficiency, hydroxymethylglutaric acidemia, propionic acidemia, methylmalonic acidemia, beta-ketothiolase deficiency, and glutaric acidemia type I.

Fatty acids, part of a larger group of organic acids, are caused by the breakdown of fats and oils in the body. Organic acidemias caused by fatty acid oxidation disorders include glutaric acidemia type II short-chain acyl-CoA dehydrogenase (SCAD) deficiency, medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, long-chain acyl-CoA dehydrogenase (LCAD) deficiency, very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, and long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency.

Most organic acidemias are considered rare, occurring in less than 1 in 5,000 persons. However, MCAD occurs in about 1 in 17,000 births. Most of these disorders produce life-threatening illnesses that can occur in

newborns, infants, children, and adults. In nearly all cases, though, the symptoms appear during the first few years of life, usually in children age two or younger. If left undiagnosed and untreated in young children, they can also delay physical development.

Genetic profile

Genes are the blueprint for the human body, directing the development of cells and tissue. Mutations in some genes can cause genetic disorders such as the organic acidemias. Every cell in the body has 23 pairs of chromosomes, 22 pairs of which contain two copies of individual genes. The 23rd pair of chromosomes is called the sex chromosome because it determines a person's gender. Men have an X and a Y chromosome while women have two X chromosomes.

Organic acidemias are generally believed to be autosomal recessive disorders that affect males and females. Autosomal means that the gene does not reside on the sex chromosome. People with only one abnormal gene are carriers but since the gene is recessive, they do not have the disorder. Their children will be carriers of the disorder 50% of the time but not show symptoms of the disease. Both parents must have one of the abnormal genes for a child to have symptoms of an organic acidemia. When both parents have the abnormal gene, there is a 25% chance each child will inherit both abnormal genes and have the disease. There is a 50% chance each child will inherit one abnormal gene and become a carrier of the disorder but not have the disease itself. There is a 25% chance each child will inherit neither abnormal gene and not have the disease nor be a carrier.

Demographics

Organic acidemias affect males and females roughly equally. The disorders primarily occur in Caucasian children of Northern European ancestry, such as English, Irish, German, French, and Swedish. In a 1994 study by Duke University Medical Center, 120 subjects with MCAD were studied. Of these, 118 were Caucasian, one was African American, and one was Native American; 65 were female and 55 were male; and 112 were from the United States while the other eight were from Great Britain, Canada, Australia, and Ireland.

Signs and symptoms

Symptoms of organic acidemias vary with type and sometimes even within a specific disorder. Isovaleric acidemia (IA) can present itself in two ways: acute severe or chronic intermittent. Roughly half of IA patients have the acute severe disorder and half the chronic intermittent

KEY TERMS

Acidosis—A condition of decreased alkalinity resulting from abnormally high acid levels (low pH) in the blood and tissues. Usually indicated by sickly sweet breath, headaches, nausea, vomiting, and visual impairments.

Alopecia—Loss of hair or baldness.

Biotin—A growth vitamin of the vitamin B complex found naturally in liver, egg yolks, and yeast.

Branched-chain—An open chain of atoms having one or more side chains.

Dystonia—Painful involuntary muscle cramps or spasms.

Homocysteine—An amino acid that is not used to produce proteins in the human body.

Hyperammonemia—An excess of ammonia in the blood.

Hypotonia—Reduced or diminished muscle tone.

Ketoacidosis—A condition that results when organic compounds (such as propionic acid, ketones, and fatty acids) build up in the blood and urine.

Ketolactic acidosis—The overproduction of ketones and lactic acid.

Ketonuria—The presence of excess ketone bodies (organic carbohydrate-related compounds) in the urine.

L-carnitine—A substance made in the body that carries wastes from the body's cells into the urine.

Lysine—A crystalline basic amino acid essential to nutrition.

Metabolic acidosis—High acidity (low pH) in the body due to abnormal metabolism, excessive acid intake, or retention in the kidneys.

Neutropenia—A condition in which the number of leukocytes (a type of white or colorless blood cell) is abnormally low, mainly in neutrophils (a type of blood cell).

Organic aciduria—The condition of having organic acid in the urine.

Pancytopenia—An abnormal reduction in the number of erythrocytes (red blood cells), leukocytes (a type of white or colorless blood cell), and blood platelets (a type of cell that aids in blood clotting) in the blood.

Thrombocytopenia—A persistent decrease in the number of blood platelets usually associated with hemorrhaging.

Tryptophan—A crystalline amino acid widely distributed in proteins and essential to human life.

type. In acute severe cases, patients are healthy at birth but show symptoms between 1 to 14 days later. These symptoms include vomiting, refusal to eat, dehydration, listlessness, and lethargy. Other symptoms can include shaking, twitching, convulsions, low body temperature (under 97.8°F or 36.6°C), and a foul “sweaty feet” odor. If left untreated, the infant can lapse into a coma and die from severe ketoacidosis, hemorrhage, or infections. In the chronic intermittent type, symptoms typically occur within a year after birth and are usually preceded by upper respiratory infections or an increased consumption of protein-rich foods, such as meat and dairy products. Symptoms include vomiting, lethargy, “sweaty feet” odor, acidosis, and ketonuria. Additional symptoms may include diarrhea, thrombocytopenia, neutropenia, or pancytopenia.

There is a wide range of symptoms for 3-methylcrotonglycemia, which can occur in newborns, infants, and young children. These include irritability, drowsiness, unwillingness to eat, vomiting, and rapid breathing. Other symptoms can include hypoglycemia, alopecia, and involuntary body movements.

Approximately 30% of patients with hydroxymethylglutaric acidemia show symptoms within five days after birth and 60% between three and 24 months. Symptoms vary and can include vomiting, deficient muscle tone, lethargy, seizures, metabolic acidosis, hypoglycemia, and hyperammonemia.

Symptoms of methylmalonic acidemia (MA) due to methylmalonyl-CoA mutase (MCoAM) deficiency include lethargy, failure to thrive, vomiting, dehydration, trouble breathing, and deficient muscle tone, and they usually present themselves during infancy. In MA due to N-methyltetrahydrofolate, homocysteine methyltransferase deficiency and high homocysteine levels usually occur during the first two months after birth but have been reported in children as old as 14 years. General symptoms are the same as for MA due to MCoAM but can also include fatigue, delirium, dementia, spasms, and disorders of the spinal cord or bone marrow.

Symptoms of glutaric acidemia type I usually appear within two years after birth and generally become apparent when a minor infection is followed by deficient

muscle tone, seizures, loss of head control, grimacing, and dystonia of the face, tongue, neck, back, arms, and hands. Glutaric acidemia type II symptoms fall into three categories:

- Infants with congenital anomalies present symptoms within the first 24 hours after birth, with symptoms of deficient muscle tone, severe hypoglycemia, hepatomegaly (enlarged liver), metabolic acidosis, and sometimes a “sweaty feet” odor. In some patients, signs include a high forehead, low-set ears, enlarged kidneys, excessive width between the eyes, a mid-face below normal size, and genital anomalies.
- Infants without congenital anomalies have signs of deficient muscle tone, tachypnea (increased breathing rate), metabolic acidosis, hepatomegaly, and a “sweaty feet” odor.
- Mild or later onset symptoms in children include vomiting, hypoglycemia, hepatomegaly, and myopathy (a disorder of muscle or muscle tissue).

There are two types of propionic acidemia, one caused by propionyl-CoA carboxylase (PCoAC) deficiency and the other caused by multiple carboxylase (MC) deficiency. Symptoms of both disorders are generally the same and include vomiting, refusal to eat, lethargy, hypotonia, dehydration, and seizures. Other symptoms may include skin rash, ketoacidosis, irritability, metabolic acidosis, and strong smelling urine commonly described as “tom cats” urine.

There are five types of organic acidemias of fatty acid oxidation that involve deficiencies of acyl-CoA dehydrogenase enzymes: SCAD, MCAD, LCAD, VLCAD, and LCHAD. General symptoms for all five of these disorders include influenza- or cold-like symptoms, hyperammonemia, metabolic acidosis, hyperglycemia, vomiting, a “sweaty feet” odor, and delay in physical development. In young children, other symptoms can include loss of hair, involuntary or uncoordinated muscle movements (ataxia), and a scaly rash (seborrhea rash). Symptoms generally appear between two months and two years of age, but can appear as early as two days after birth up to six years of age.

There are two combined carboxylase deficiency organic acidemias: holocarboxylase synthetase deficiency and biotinidase deficiency. Symptoms of holocarboxylase deficiency include sleep and breathing difficulties, hypotonia, seizures, alopecia, developmental delay, skin rash, metabolic acidosis, ketolactic acidosis, organic aciduria, and hyperammonemia. Symptoms of biotinidase deficiency include seizures, involuntary muscular movements, hypotonia, rapid breathing, developmental delay, hearing loss, and visual problems. Skin

rash, alopecia, metabolic acidosis, organic acidemia, and hyperammonemia can also occur.

Symptoms of beta-ketothiolase deficiency vary. In infants, the most common symptoms include severe metabolic acidosis, ketosis, vomiting, diarrhea (often bloody), and upper respiratory or gastrointestinal infections. Adults with the disorder are usually asymptomatic (showing no outward signs of the disease).

Diagnosis

In all types of organic acidemia, diagnosis cannot be made by simply recognizing the outward appearance of symptoms. Instead, diagnosis is usually made by detecting abnormal levels of organic acid cells in the urine through a urinalysis. The specific test used is called combined gas chromatography-mass spectrometry. In gas chromatography, a sample is vaporized and its components separated and identified. Mass spectrometry electronically weighs molecules. Every molecule has a unique weight (or mass). In newborn screening, mass spectrometry analyzes blood to identify what amino acids and fatty acids are present and the amount present. The results can identify if the person tested has a specific organic acidemia. Many organic acidemias also can be diagnosed in the uterus by using an enzyme assay of cultured cells, or by demonstrating abnormal organic acids in the fluid surrounding the fetus. In some laboratories, analysis is done on blood, skin, liver, or muscle tissue. Molecular DNA testing is also available for common mutations of MCAD and LCHAD.

Since most organic acidemias are rare, routine screening of fetuses or newborns is not usually done and is not widely available. In MCAD, a more common organic acidemia, abnormal organic acids are excreted in the urine intermittently so a diagnosis is made by detecting the compound phenylpropionylglycine in the urine.

Treatment and management

There are few medications available to treat organic acidemias. The primary treatments are dietary restrictions tailored to each disorder, primarily restrictions on the intake of certain amino acids. For example, patients with some acidemias, such as isovaleric and beta-ketothiolase deficiency, must restrict their intake of leucine by cutting back on foods high in protein. Patients with propionic or methylmalonic acidemias must restrict their intake of threonine, valine, methionine, and isoleucine. The intake of the restricted amino acids is based on the percentage of lean body mass rather than body weight. Some patients also benefit from growth hormones. Patients with combined carboxylase deficiency are sometimes treated with

large doses of biotin. Some patients with methylmalonic acidemia are treated with large doses of vitamin B12.

Glucose infusion (to provide calories and reduce the destructive metabolism of proteins) and bicarbonate infusion (to control acidosis) are often used to treat acute episodes of some acidemias, including isovaleric, 3-methylcrotonylglycemia, and hydroxymethylglutaric.

The primary treatment for MCAD is to not go without food for more than 10 or 12 hours. Children should eat foods high in carbohydrates, such as pasta, rice, cereal, and non-diet drinks, when they are ill. A low fat diet is also recommended. The drug L-carnitine is sometimes used by physicians to prevent low blood sugar when patients have infections or are not eating regularly.

The treatment of LCHAD is similar to that of MCAD, except that L-carnitine is usually not prescribed. Children with LCHAD are often treated with medium chain triglycerides oil.

Holocarboxylase synthetase deficiency is generally treated by administering 10 milligrams (mg) of biotin daily. Eating large amounts of yeast, liver, and egg yolks, which naturally contain biotin, did not improve the condition. Biotinidase deficiency is usually treated successfully with pharmacological doses of between 5 and 20 mg of biotin daily. However, hearing and vision problems appear to be less reversible.

Prognosis

The prognosis of patients with organic acidemias varies with each disorder and usually depends on how quickly and accurately the condition is diagnosed and treated. Some patients with organic acidemias are incorrectly diagnosed with other conditions, such as sudden infant death syndrome (SIDS) or Reye syndrome. Without a quick and accurate diagnosis, the survival rate decreases with each episode of the disorder. Death occurs within the first few years of life, often within the first few months. With a quick diagnosis and aggressive monitoring and treatment, patients can often live relatively normal lives. For example, children with either biotinidase deficiency or holocarboxylase synthetase deficiency, when detected early and treated with biotin, have generally shown resolution of the clinical symptoms and biochemical abnormalities.

Resources

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ORGANIZATIONS

- Fatty Oxidation Disorders (FOD) Family Support Group, PO Box 54, Okemos, MI 48805-0054, (517) 381-1940, (866) 290-5206, deb@fodsupport.org, <http://www.fodsupport.org>
- National Newborn Screening and Genetics Resource Center (NNSGRC), 3907 Galacia Dr., Austin, TX 78759, (512) 921-1400, therell@uthscsa.edu, <http://genes-r-us.uthscsa.edu>
- Organic Acidemia Association, 9040 Duluth St., Golden Valley, MN 55427, (763) 559-1797, (866) 539-4060, mkstagni@gmail.com, <http://www.oaanews.org>

Ken R. Wells

Ornithine transcarbamylase deficiency

Definition

Ornithine transcarbamylase deficiency is a disorder in which the body fails to properly process ammonia, which can lead to coma and death if left untreated.

Description

Persons with ornithine transcarbamylase deficiency (OTC deficiency) have a problem with nitrogen metabolism. Too much nitrogen in the blood in the form of ammonia can cause brain damage, coma, and death. Ammonia is made up of nitrogen and hydrogen. Ammonia found in humans mostly comes from the breakdown of protein—either protein broken down from muscles, organs, and tissues already in the body, or excess protein that is eaten in the diet. Since excess ammonia is harmful, it is immediately excreted in normal humans after passing through the urea cycle and becoming urea. *Ornithine transcarbamylase* is a gene involved in the urea cycle—the process of making ammonia into urea, which occurs in the liver.

It is important to make urea, because unlike ammonia, urea can be excreted by the kidney into the urine. Ammonia, on the other hand, cannot be effectively excreted by the kidney. So, if the *ornithine transcarbamylase* (OTC) function is reduced or impaired, ammonia builds up in the bloodstream. This buildup of ammonia in the bloodstream can lead to consequences as severe as coma and death. The amount of ammonia found in the bloodstream, and the severity of the disorder, depend on how well the OTC gene functions. If it functions reasonably well, the person should have a minor form of the disorder or no disorder. If the gene functions extremely poorly, or not at all, the disorder will be severe.

Synonyms for ornithine transcarbamylase deficiency include hyperammonemia type II, ornithine carbamyl transferase deficiency, OTC deficiency, UCE, urea cycle disorder, OTC Type, and hyperammonemia due to ornithine transcarbamylase deficiency.

Genetic profile

OTC deficiency is an X-linked recessive disorder. This means that it is found on the X chromosome (specifically, it is located on the short arm at Xp21.1). Recessive disorders require that only abnormal genes, and no normal genes, be present. For non-sex chromosomes, this means that both copies of a gene (one received from each parent) must be abnormal in order for that person to have the disorder.

In X-linked recessive disorders, however, only one abnormal copy of a gene must be present to cause the disorder in males. Males possess only one X chromosome, from their mother, and one Y chromosome, which they receive from their father. If the mother is a carrier for the disorder (she has one normal gene and one abnormal gene), a male child would have a 50% chance of receiving an abnormal gene from her. If he receives the abnormal gene, he will have the disorder.

A female child of a female carrier is much less likely to have the disorder. Unless the father has OTC deficiency, a female child will have one normal and one abnormal gene. Since recessive disorders require that both genes be mutated, the female child cannot have the disorder. Females with only one mutant OTC gene may have a mild form of the disorder because it is not purely recessive. Usually, the normal copy of the gene can sufficiently compensate for the poor functioning of the second, abnormal gene.

Some females do have the full-blown disorder, probably because of a phenomenon called X-inactivation. Although females have two X chromosomes in each cell, only one is active. Therefore, it is possible a female could have the disorder because only the abnormal gene was

active in each cell of the liver, which is where OTC function takes place. Not enough is known about X-inactivation to speculate on the likelihood of this occurring. OTC disease due to X-inactivation is not very common.

If the father has the gene for the disorder, he cannot pass it on to his male child (he does not give the male child an X chromosome, only a Y). He can give his female child one copy of the gene, which might result in a mild form of the disorder or the full-blown disorder due to X-inactivation.

Demographics

OTC affects infants at the rate of approximately 1 birth in every 70,000. As expected with an X-linked disorder, the disorder is more common in males.

Signs and symptoms

Before birth there are no symptoms of OTC deficiency because the exchange of nutrients and fluids between the mother and fetus allows the excess ammonia to leave the infant's blood and go into the mother's blood. The mother is then able to get rid of the ammonia as urea because she either lacks the disorder or her ammonia levels are medically well-controlled.

The most severe cases of OTC deficiency usually present in infants before they are a week old, typically in males. It may take several days for symptoms to appear, since it takes that long for protein, and therefore ammonia levels, to build up in the infant. Affected infants generally show periods of inactivity, a failure to feed, and vomiting. Unfortunately, many other disorders may also present with these same general symptoms, and new parents may not recognize these as abnormal in an infant. These symptoms are always accompanied in OTC deficiency by hyperammonemia, or high levels of ammonia in the blood.

Hyperammonemia is the most important symptom for identification and treatment of ornithine transcarbamylase deficiency. It is the cause of all other symptoms seen in OTC deficiency. Additionally, hepatomegaly (an enlarged liver) and seizures may also be present. If the disorder, or at least the hyperammonemia, is not recognized and treated, the symptoms may progress into coma and eventually death. A failure to quickly resolve the hyperammonemia once an infant lapses into a coma may also lead to severe intellectual disability or death.

Patients with milder forms of the disorder may show symptoms later in life such as failure to grow at a normal rate or they may experience developmental delay. Developmental delay is an inability to reach recognized

milestones like speaking or grasping objects at an appropriate age. These milder symptoms would be accompanied by hyperammonemia, but the levels of ammonia would be much lower than in an episodic attack of hyperammonemia or in the severely ill infant. Other persons with mild forms of the disorder may have no symptoms, or may only experience nausea after a meal with large protein content.

Persons with a mild form of the disorder and no other symptoms may also learn they have the disorder from an episode of acute hyperammonemia. Acute conditions are brief and immediate, whereas chronic conditions are long-lasting.

An episodic attack of acute hyperammonemia, then, is an episode where levels of ammonia climb above what may be already high levels of ammonia. A person with an episode of acute hyperammonemia can have symptoms including some, or all, of the following: vomiting, lack of appetite, drowsiness, hepatomegaly, seizures, coma, and death. These episodes can be life-threatening and may require hospitalization depending on their severity and response to medication.

These episodic attacks are probably related to a large increase in the amount of protein being broken down in the body, which results in too much ammonia being produced. This ammonia cannot be immediately excreted, which results in hyperammonemia. The most common reasons for a change in the amount of protein broken down are probably starvation, illness, and surgery. Even persons with no previous symptoms can experience a fatal episode of acute hyperammonemia brought on by an increase in protein breakdown. Since an episodic attack of hyperammonemia can be fatal without any previous symptoms, persons who have at least one family member with OTC deficiency should consider testing to determine whether they have the gene for the disorder. If the disorder is known to be present, an episode of hyperammonemia might be anticipated and its effect lessened.

Diagnosis

A definitive diagnosis of OTC deficiency is made via laboratory testing, since physical symptoms are very general and common to a large number of disorders. A high level of ammonia in the blood is the hallmark of this disorder and other disorders that affect the urea cycle. In the short term, the levels of two amino acids in the urine, orotate and citrulline, should distinguish between OTC deficiency and other urea cycle deficiencies. In OTC deficiency, citrulline levels are normal or low, and orotate levels are usually high. In the long term, however, the most definitive diagnosis can be made through DNA

analysis, or through a test of OTC activity in a small piece of liver tissue (a biopsy) taken from the patient.

Prenatal diagnosis of the disorder is difficult and not indicated unless there is an affected family member with the disorder. In that case, if the mutation is known, DNA analysis would reveal the same mutation as in the family member with OTC deficiency. If the mutation is not known, a method called linkage analysis may be used. In linkage analysis, the OTC gene itself is not analyzed, but the DNA near the gene is analyzed. The “near DNA” can then be compared to the “near DNA” of the affected family member. If the DNAs are different, then the fetus should not have the disorder. If they are the same, then the fetus probably has the disorder.

Treatment and management

Long-term management

The severity of the disorder is the most important factor in determining long-term treatment of OTC deficiency. Individuals most severely affected by OTC deficiency, usually infant males, should have liver transplants. As previously mentioned, the urea cycle and OTC functions occur in the liver. The transplantation immediately corrects OTC deficiency. Episodes of life-threatening ammonemia are prevented, although monitoring of tissue levels of ammonia is suggested. Another important benefit is that the transplant allows the child to develop and grow in a normal manner, without the threat of developmental delay or intellectual disability. Transplants are now recommended even for children less than one year of age with a severe form of the disorder.

Two problems with liver transplants exist, however. First, it is difficult to obtain a liver from among the limited supply of donors, especially if the child is not currently hospitalized. The second problem arises from the way in which organs are assigned. Persons who are critically ill receive priority in organ donor lists. This means children whose disease is manageable may not be able to receive a transplant.

Second, children with transplants must have their immune system suppressed. The immune system fights off and lets one recover from infections like colds, flu, and chicken pox. However, it also fights the introduction of an organ from someone else's body, even a relative—except identical twins. Thus, as long as a person has a transplant, that person must have their immune system suppressed so that the transplanted organ is not killed by the body it is in. The problem with immune suppression is that a person is much more likely to become sick. This disadvantage is far outweighed by the advantages of normal mental development and the prevention of death in patients with severe OTC deficiency.

KEY TERMS

Developmental delay—When children do not reach certain milestones at appropriate ages. For example, a child should be able to speak by the time he or she is five years old.

Hyperammonemia—An excess of ammonia in the blood.

Urea—A nitrogen-containing compound that can be excreted through the kidney.

Urea cycle—A series of complex biochemical reactions that remove nitrogen from the blood so ammonia does not accumulate.

Patients in rural areas, or areas where there is no immediate access to a hospital equipped to care for a patient with an acute attack of hyperammonemia, should also be strongly considered for a liver transplant if the patient is predisposed to attacks of life-threatening hyperammonemia.

For less severely affected children, or children unable to obtain a liver transplant, long-term therapy consists of a combination of drugs, usually oral; sodium phenylbutyrate; and diet. This bypasses the normal process of the breakdown of protein into urea in the liver, which is the usual way that ammonia leaves the body. Children with OTC deficiency are placed on a low-protein diet so their protein breakdown system does not become overwhelmed and lead to hyperammonemia. Children with OTC deficiency are also given arginine, an amino acid, which, for reasons that are unclear, causes more nitrogen, which is part of ammonia, to be excreted in the urine, and lowers blood ammonia. Dietary regimens vary from patient to patient based on their age, size, and the severity of the disorder. A nutrition expert must be consulted when developing an appropriate diet. The strictest diet consists of vitamin supplements and no protein other than essential amino acids. Essential amino acids are those that cannot be made by the body and must be obtained through food. Since proteins are made up of amino acids, and only amino acids, that means this diet is extremely restrictive. It also means that very little ammonia is left in the bloodstream since most of the otherwise free ammonia is tied up in the synthesis of the non-essential amino acids, amino acids made by the body itself.

Any chronic disease is stressful for a family. Parents and patients should consider support and information groups like the National Urea Cycle Disorders Foundation.

Short-term management

Short-term management of attacks of crisis hyperammonemia (severe acute hyperammonemia) consists of dialysis and drug therapy. Dialysis and large doses of the drugs sodium benzoate and sodium phenylacetate and doses of arginine are used to decrease the levels of ammonia in the blood. These methods are used together due to their synergistic effect.

Dialysis is a process where a toxic substance is removed from the blood. This can best be understood by pouring a small amount of cola into a glass. Now pour a large amount of water into it. In this way, the cola is “watered down” or diluted. Ammonia is diluted in a similar way using dialysis. Blood is removed from a patient and run through a hose. At one point, this hose runs through a tank made up of liquid that contains all the components of blood, but no ammonia (this liquid is like the water in the water and cola example). Thus, ammonia spreads throughout the blood and the liquid surrounding the hose (the same way cola will spread throughout water added to the glass) and the amount of ammonia in the blood is reduced. By continuously pumping blood through the hose and changing the liquid around the hose, most of the ammonia can be removed from the blood. All of the really large particles, like red blood cells, are also kept in the blood because the hose has holes that are only large enough to let smaller particles like ammonia out while keeping red blood cells in.

The future

The future treatment of OTC deficiency will likely come from experiments in gene therapy. OTC deficiency is a disorder particularly amenable to gene therapy because only one gene is affected and only one organ, the liver, would need the new gene. However, gene therapy has not been successfully demonstrated in human beings. Many technical problems must still be solved in order to successfully treat OTC deficiency and other disorders like it with gene therapy.

Prognosis

Only 50% of the most severely affected patients live beyond the time they first attend school. Of those receiving liver transplants, 82% of patients survive five years after receiving the transplant. Children with the severe disorder that receive drug therapy are much more likely to experience intellectual disability, developmental delay, and a lack of growth. Also, many infants who experience hyperammonemic comas have severe mental damage.

For individuals not identified at birth or soon after, the prognosis varies widely. The consequences of the disorder are affected by the severity of the disorder and how

it is managed, although anyone with the disorder may experience life-threatening attacks of acute hyperammonemia. In terms of long-term survival, puberty appears to be a difficult time for those with OTC deficiency, and persons who survive until after puberty have improved outcomes. The prognosis for this disorder can vary from quite hopeful to very distressing based upon its severity and how well the disorder can be controlled. A severe disorder that is well controlled may still have a positive outcome.

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- "Ornithine Transcarbamylase-Deficiency." NORD. <https://rarediseases.org/rare-diseases/ornithine-transcarbamylase-deficiency/> (accessed June 15, 2021).

ORGANIZATIONS

- National Urea Cycle Disorders Foundation (NUCDF), 75 S. Grand Ave., Pasadena, CA 91005, (800) 386-8233 or (626) 578-0833, (626) 578-0823, info@nucdf.org, <http://www.NUCDF.org>

Michael V. Zuck, PhD

Osteoarthritis

Definition

Osteoarthritis is a degenerative joint disease characterized by the breakdown of the joint's cartilage.

Description

Osteoarthritis is a degenerative joint disease and one of the oldest, most common types of arthritis. It is characterized by the breakdown of cartilage, which can allow bones to rub against each other, causing pain and loss of movement. Often called "wear-and-tear arthritis,"

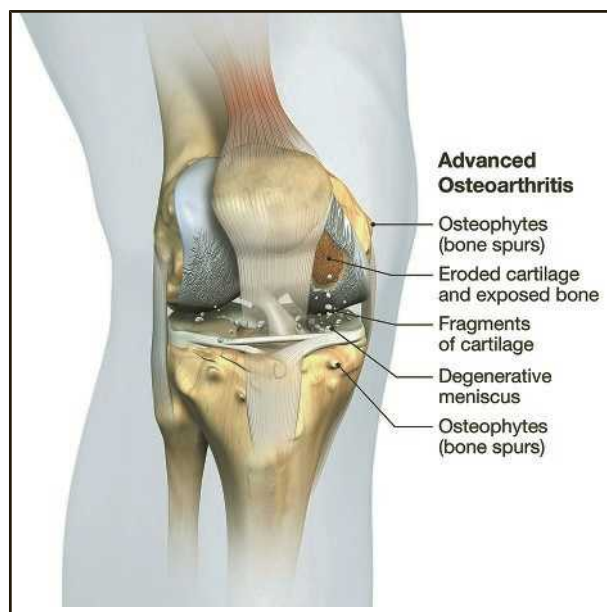


Illustration showing an advanced case of osteoarthritis in a knee joint. (BSIP/Science Source)

osteoarthritis can be caused by injury, abnormal growth, and inherited factors.

The biological causes of the disorder are currently unknown; however, osteoarthritis is thought to be due to mechanical stress and chronic, low-grade inflammation in joints. As osteoarthritis progresses, the collagen matrix becomes disorganized and begins to break down, allowing for both decreased support of the joints and increased inflammation at the joints.

In many cases, certain conditions seem to trigger osteoarthritis. People with joint injuries from sports, work-related activity, or accidents may be at increased risk, and obesity may lead to osteoarthritis of the knees and other weight-bearing joints. Individuals with mismatched surfaces on the joints that could be damaged over time by abnormal stress may be prone to osteoarthritis.

As collagen and cartilage are lost, tendons may thicken to compensate at bone and muscle junctions, which can lead to stiffness and pain associated with the disease. New bone outgrowths, or "spurs," can form at the periphery of joints to improve the congruence of joint surfaces in the absence of normal cartilage support.

Demographics

Osteoarthritis is the most common form of arthritis. It is estimated to affect more than 32.5 million Americans, mostly after age 45. Women are more commonly affected than men.

In the United States, 13.5% of men and 18.7% of women older than 45 have osteoarthritis of the knee and more than 3% of adults 45 and older have osteoarthritis of the hip. Prevalence of osteoarthritis in most joints is higher in men than women under age 50. After that age, more women are affected by osteoarthritis, and the occurrence of the disease increases with age. In men, the hip is affected more often, while in women, the hands, fingers, and knees are more problematic.

Some forms of osteoarthritis are more prevalent in African American men and women than in Caucasians, possibly because they tend to have a higher bone mineral density. In the case of knee osteoarthritis, it may be related to occupational and physical demands. African American women also have a higher risk of developing bilateral knee osteoarthritis and hip osteoarthritis, compared to women of other races.

Osteoarthritis is common worldwide, although the risk varies among ethnic groups. Caucasians have a higher risk than Asians, and the risk of osteoarthritis in the hips is lower in Asia and some Middle East countries than in the United States. Asians appear to have a higher incidence of osteoarthritis in the knees than Caucasians do, but an equal risk in the spine. Location of affected joints and inherited forms of the disorder can influence the age of onset.

Genetic profile

Genetics play a role in the development of osteoarthritis, particularly in the hands and hips. One study found that heredity might be involved in 30% of people with osteoarthritic hands and in 65% of those with osteoarthritic knees. Another study found a higher correlation of osteoarthritis between parents and children, and between siblings, than between spouses. Other research has shown that a genetic abnormality may promote a breakdown in the protective structure of cartilage.

Abnormal collagen genes have been identified in some families with osteoarthritis. One recent study found that the type IX collagen gene (*COL9A1*) located on chromosome 6 might be a susceptibility locus for female hip osteoarthritis. Other research has suggested that mutations in the *COL2A1* gene may be associated with osteoarthritis. While there is some evidence of other genetic factors in the development of osteoarthritis, the heritability and genes involved are not well documented.

A 2021 review reported new insights into the way genetics affect bone mass. Although bone mineral density is typically associated with osteoporosis, investigators also found a link between bone mineral density and the risk of developing osteoarthritis. They found genetic

markers suggesting that low bone mass combines with other factors to develop osteoarthritis.

Because osteoarthritis follows a complex disease process, further understanding of genes related to bone mass and other risk factors can help better understand how these genetic factors interact with other causes, such as obesity. As many as 86 genetic loci might be associated with inheritance of osteoarthritis risk. Current study includes determining which genes might play a protective role in the disease. As of 2021, multiple studies were under way to look at genomics, genetics, and epigenetics of osteoarthritis, as well as the role of specific genes. These more recent studies are beginning to connect genetic information with risk factors to determine how the genes affect development. These efforts eventually can lead to appropriate, even targeted, interventions.

Signs and symptoms

Although up to 85% of people over 65 show evidence of osteoarthritis on x-ray, only 35%–50% experience symptoms. Symptoms range from very mild to very severe and can affect the hands and weight-bearing joints such as knees, hips, feet, and the back. The pain of osteoarthritis usually begins gradually and progresses slowly over many years.

Osteoarthritis is commonly identified by aching pain in one or more joints, stiffness, and loss of mobility. The disease can cause significant trouble walking and stair-climbing. Inflammation may or may not be present.



Illustration of a healthy joint (left) and one affected by osteoarthritis (right). (Designua/Shutterstock)

KEY TERMS

Cartilage—Supportive connective tissue that cushions bone at joints or connects muscle to bone.

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Corticosteroids—Anti-inflammatory medications. They are related to cortisol, a naturally produced hormone that controls many bodily functions.

Extensive use of the joint(s) often exacerbates pain there. Osteoarthritis is often more bothersome at night than in the morning, and in humid weather rather than dry weather. Periods of inactivity, such as sleeping or sitting, may result in stiffness, which can be eased by stretching and exercise.

Bony lumps on the end joint of the finger, called Heberden's nodes, and on the middle joint of the finger, called Bouchard's nodes, may also develop, and collagen support at the joints is depleted.

Diagnosis

A diagnosis of osteoarthritis is made based on a physical exam and history of symptoms.

X-rays are used to confirm the diagnosis. In people over age 60, the disease can often be observed on x-ray. An indication of cartilage loss arises if the normal space between the bones in a joint is narrowed, if there is an abnormal increase in bone density, or if bony projections or erosions are evident. Any cysts that might develop in osteoarthritic joints are also detectable by x-ray.

Additional tests can be performed if other conditions are suspected or if the diagnosis is uncertain. Blood tests can rule out rheumatoid arthritis or other forms of arthritis.

It is possible to distinguish osteoarthritis from other joint diseases by considering a number of factors together:

- Osteoarthritis usually occurs in older people.
- It is usually located in only one or a few joints.
- The joints are less inflamed than in other arthritic conditions.
- Progression of pain is almost always gradual.
- A few of the most common disorders that might be confused with osteoarthritis are rheumatoid arthritis, chondrocalcinosis, and Charcot's joints.

Treatment and management

There is no known way to prevent osteoarthritis or slow its progression. Some lifestyle changes can reduce or delay symptoms, but treatment often focuses on decreasing pain and improving joint movement. Prevention and treatment measures may include the following:

- Exercises to maintain joint flexibility and improve muscle strength. By strengthening the supporting muscles, tendons, and ligaments, regular weight-bearing exercise helps protect joints, even possibly stimulating growth of the cartilage.
- Joint protection, which prevents strain and stress on painful joints.
- Heat/cold therapy for temporary pain relief.
- Various pain-control medications including corticosteroids and NSAIDs (nonsteroidal anti-inflammatory drugs, such as aspirin, ibuprofen, and naproxen). For inflamed joints that are not responsive to NSAIDs, injectable glucocorticoids may be used. For mild pain without inflammation, acetaminophen may be used.
- Weight control can prevent extra stress on weight-bearing joints. One study reported that weight loss seemed to reduce the risk for symptomatic osteoarthritis of the knee in women; in another study, women who lost 11 pounds or more cut their risk for developing osteoarthritis in half.
- Surgery may be needed to relieve chronic pain in damaged joints. Osteoarthritis is the most common indication for total joint replacement of the hip and knee.

New treatment findings

Studies have found that estrogen may promote healthy joints in women. Hormone replacement therapy may significantly reduce the risk in postmenopausal women, particularly in the knees.

It has been reported that deficiencies in vitamin D in older people may worsen their condition, so individuals with osteoarthritis should strive to take the recommended 400 IU per day. To protect bones, adults should also consume at least 1,000 mg of calcium daily.

Glucosamine and chondroitin sulfate are popular nutritional supplements that may diminish the symptoms of osteoarthritis. According to some reports, a daily dose of 750–1,500 mg of glucosamine and chondroitin sulfate may reduce joint pain, stiffness, and swelling; however, these supplements are not approved by the Food and Drug Administration as effective treatment of osteoarthritis. A person with osteoarthritis should consult with a doctor before using dietary supplements to treat symptoms.

QUESTIONS TO ASK YOUR DOCTOR

- Please describe the bodily changes that take place as a result of osteoarthritis.
- Why is osteoarthritis considered a genetic disorder?
- Is there a way to prevent developing osteoarthritis?
- How is osteoarthritis likely to affect my quality of life?

Prognosis

Osteoarthritis is not life-threatening, but quality of life can deteriorate significantly due to the pain and loss of mobility that it causes. Advanced osteoarthritis can force the patient to forgo activities, even walking, unless the condition is alleviated by medication or corrected by surgery.

There is no cure for osteoarthritis, and no treatment alters its progression with any certainty. Only heart disease has a greater impact on work, and 5% of those who leave the workforce do so because of osteoarthritis.

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"What Is Osteoarthritis?" National Arthritis and Musculoskeletal and Skin Disease. <https://www.niams.nih.gov/health-topics/osteoarthritis> (accessed May 20, 2021).

ORGANIZATIONS

Arthritis Foundation, 1355 Peachtree Street NE, Suite 600, Atlanta, GA 30309, (800) 283-7800, <http://www.arthritis.org>

Arthritis Research Institute of America, 300 South Duncan Avenue, Suite 188, Clearwater, FL 33755, (727) 461-4054, info@awlife.org, <http://www.preventarthritis.org>

National Institute of Arthritis and Musculoskeletal and Skin Diseases, 1 AMS Circle, Bethesda, MD 20892-3675, (301) 495-4484 or (877) 226-4267, (301) 718-6366, <http://www.niams.nih.gov>

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Revised by Teresa G. Odle, BA, ELS

Osteogenesis imperfecta

Definition

Osteogenesis imperfecta (OI) is a group of genetic diseases of collagen in which the bones are formed improperly, making them fragile and prone to breaking.

Description

Collagen is a fibrous protein material. It serves as the structural foundation of skin, bone, cartilage, and ligaments. In osteogenesis imperfecta, the collagen produced is abnormal and disorganized. This results in a number of abnormalities throughout the body, the most notable being fragile, easily broken bones. Another cardinal sign of OI is a blue-grey tint to the sclera of the eye, which otherwise is normally white.

There are eight forms of OI, types I through VIII. Of these, type II is the most severe and is usually fatal within a short time after birth. Most types have some overlapping and some distinctive symptoms, particularly weak bones.

Genetic profile

Evidence suggests that OI results from mutations in the *COL1A1*, *COL1A2*, *CRTAP*, and *P3H1* genes. Some studies note additional mutations in genes *EPRE1* and *FKBP10* being responsible for OI. Mutations in the *COL1A1* gene, located on 17q21.3–q22.1, and in *COL1A2*, located on 7q22.1, are responsible for more than 90% of all cases of OI. These two genes provide instructions for making proteins that are used to assemble type I collagen, the most abundant protein in bone, skin,

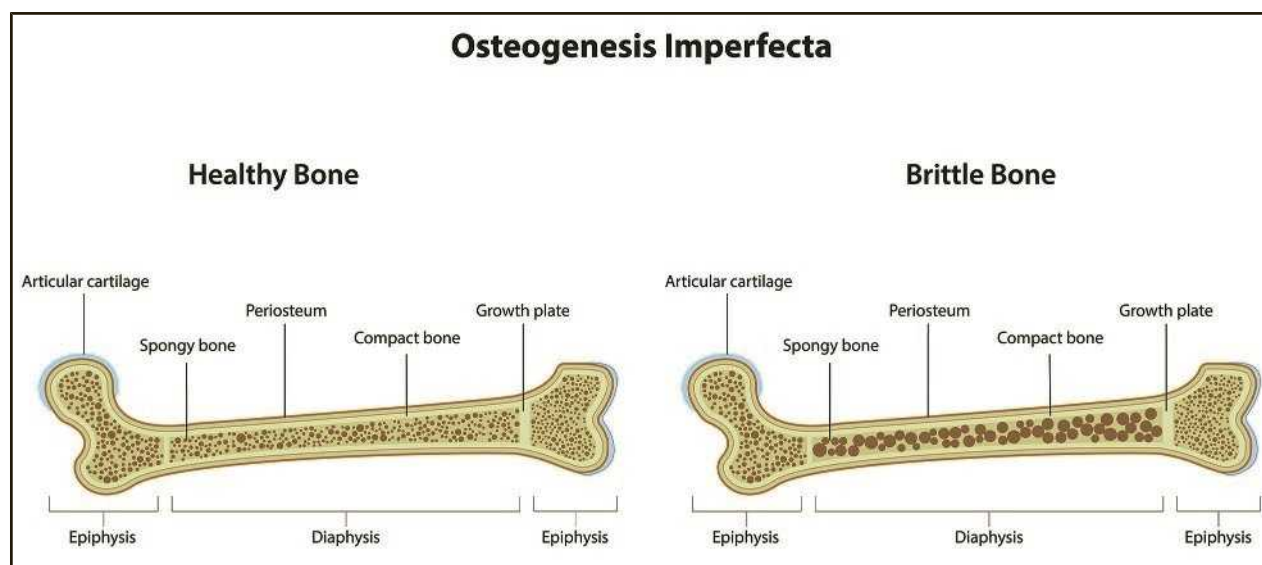


Illustration of a healthy bone (left) and one made brittle by osteogenesis imperfecta. (joshya/Shutterstock)

and other connective tissues. *COL1A1* and *COL1A2* gene mutations are due to an autosomal dominant pattern of inheritance and are responsible for OI types I–VI. The *CRTAP* gene, located on 3p22.3, provides instructions for making a protein called “cartilage associated protein,” required for normal bone development. Mutations in the *CRTAP* gene are responsible for type VII and are inherited in an autosomal recessive pattern. The *P3H1* gene, located on 1p34.1, instructs the making of the enzyme prolyl-3 hydroxylase 1, which modifies proline, an amino acid that is critical for the normal folding and assembly of collagen as it is being made. If the collagen molecule is not formed correctly due to the lack of or improper function of this enzyme, the function of the collagen will not be correct, leading to connective tissue abnormalities as seen in OI, particularly type VIII. Mutations in the *P3H1* gene, like mutations in the *CRTAP* gene, are inherited in an autosomal recessive pattern.

OI is usually inherited as an autosomal dominant condition, and 90% of OI cases are due to a mutation in the *COL1A1* or *COL1A2* genes. In autosomal dominant inheritance, a single abnormal gene on one of the autosomal chromosomes (one of the first 22 “nonsex” chromosomes) from either parent can cause the disease. One of the parents will have the disease (since it is dominant) and is the carrier. Only one parent needs to be a carrier in order for the child to inherit the disease. A child who has one parent with the disease has a 50% chance of also being a carrier and a 50% chance of not inheriting the dominant gene and, thus, not having the disorder.

In OI, the genetic abnormality may direct cells to make an altered collagen protein, and the presence of this altered

collagen causes OI types II, III, or IV. Alternately, the dominant altered gene may fail to direct cells to make any collagen protein. Although some collagen is produced by instructions from the normal gene, an overall decrease in the total amount of collagen produced results in OI type I.

If both parents have OI caused by an autosomal dominant gene change, there is a 75% chance that the child will inherit one or both OI genes. In other words, there is a 25% chance the child will inherit only the mother’s OI gene (and the father’s unaffected gene), a 25% chance the child will inherit only the father’s OI gene (and the mother’s unaffected gene), and a 25% chance the child will inherit both parents’ OI genes. Because this situation is uncommon, the outcome of a child inheriting two OI genes is hard to predict. It is likely that the child would have a severe, possibly lethal, form of the disorder.

About 25% of children with OI are born into a family with no history of the disorder. This occurs when the *COL1A1* or *COL1A2* gene spontaneously mutates in either the sperm or the egg before the child’s conception. No triggers for this type of mutation are known. This is called a new dominant mutation. This is most common in the more severe types of OI such as type II or type III. The affected child has a 50% chance of passing the disorder on to his or her children. In most cases, when a family with no history of OI has a child with OI, they are not at greater risk than the general population for having a second child with OI, and unaffected siblings of a person with OI are at no greater risk of having children with OI than the general population.

In studies of families into which infants with OI type II were born, most of the babies had a new dominant

mutation in a collagen gene. In some of these families, however, more than one infant was born with OI. Previously, researchers had seen this recurrence as evidence of recessive inheritance of this form of OI. More recently, however, researchers have concluded that the rare recurrence of OI to a couple with a child with autosomal dominant OI is more likely due to gonadal mosaicism. Instead of a mutation occurring in an individual sperm or egg, it occurs in a percentage of the cells that give rise to a parent's multiple sperm or eggs. This mutation, present in a percentage of the person's reproductive cells, can result in more than one affected child without affecting the parent with the disorder. An estimated 2%–4% of families into which an infant with OI type II is born are at risk of having another affected child because of gonadal mosaicism.

Demographics

The prevalence of OI was reported to be 6 to 7 in 100,000 people worldwide in 2015, with types I and IV being the most commonly seen out of the eight types, with a prevalence of 4 to 5 in 100,000 people.

Signs and symptoms

Type I

This is the most common and mildest type. Among the common features of type I are the following:

- Bones are predisposed to fracture, with most fractures occurring before puberty. People with OI type I typically have about 20–40 fractures before puberty.
- Stature is normal or near normal.
- Joints are loose, and muscle tone is low.
- Usually sclera (whites of the eyes) have a blue, purple, or gray tint.
- Face shape is triangular.
- There is a tendency toward scoliosis (a curvature of the spine).
- Bone deformity is absent or minimal.
- Dentinogenesis imperfecta may occur, causing brittle teeth.
- Hearing loss is a possible symptom, often beginning in the early 20s or 30s.
- Structure of collagen is normal, but the amount is less than normal.

Type II

Sometimes called the lethal form, type II is the most severe form of OI. Among the common features of Type II are the following:

- Frequently, OI type II is lethal at or shortly after birth, often as a result of respiratory problems.
- Fractures are numerous, and bone deformity is severe.
- Stature is small with underdeveloped lungs.
- Collagen is formed improperly.

Type III

Among the common features of type III are the following:

- Bones fracture easily. Fractures are often present at birth, and x-rays may reveal healed fractures that occurred before birth. People with OI type III may have more than 100 fractures before puberty.
- Stature is significantly shorter than normal.
- Sclera (whites of the eyes) have a blue, purple, or gray tint.
- Joints are loose, and muscle development is poor in arms and legs.
- Rib cage is barrel-shaped.
- Face shape is triangular.
- Scoliosis (a curvature of the spine) is present.
- Respiratory problems are possible.
- Bones are deformed, and deformity is often severe.
- Dentinogenesis imperfecta may occur, causing brittle teeth.
- Hearing loss is possible.
- Collagen is formed improperly.

Type IV

OI type IV falls between type I and type III in severity. Among the common features of type IV are the following:

- Bones fracture easily, with most fractures occurring before puberty.
- Stature is shorter than average.
- Sclera (whites of the eyes) are normal in color, appearing white or near white.
- Bone deformity is mild to moderate.
- Scoliosis (curvature of the spine) is likely.
- Rib cage is barrel-shaped.
- Face is triangular in shape.
- Dentinogenesis imperfecta may occur, causing brittle teeth.
- Hearing loss is possible.
- Collagen is formed improperly.

KEY TERMS

Collagen—The main supportive protein of cartilage, connective tissue, tendon, skin, and bone.

Ligament—A type of connective tissue that connects bones or cartilage and provides support and strength to joints.

Mutation—An inherited or *de novo* change in the DNA sequence of the genome.

Sclera—The tough white membrane that forms the outer layer of the eyeball.

Scoliosis—Abnormal curvature of the spine, usually defined as greater than ten degrees to the right or left as the doctor faces the patient.

Diagnosis

It is often possible to diagnose OI solely on clinical features and x-ray findings. Collagen or DNA tests may help confirm a diagnosis of OI. These tests generally require several weeks before results are known. Approximately 10%–15% of individuals with mild OI who have collagen testing, and approximately 5% of those who have genetic testing, test negative for OI despite having the disorder.

Diagnosis is usually suspected when a baby has bone fractures after having suffered no apparent injury. Another indication is small, irregular, isolated bones in the sutures between the bones of the skull (Wormian bones). Sometimes the bluish sclera serves as a diagnostic clue. Unfortunately, because of the unusual nature of the fractures occurring in a baby who cannot yet move, some parents have been accused of child abuse before the actual diagnosis of OI was reached.

Prenatal diagnosis

Testing is available to assist in prenatal diagnosis. Women with OI who become pregnant, or women who conceive a child with a man who has OI, may wish to explore prenatal diagnosis. Due to the wide range of potential mutations within a large genome, sequencing has been difficult for the detection of OI. With an increase in technology and the use of newer sequencing methods such as whole genome sequencing, next generation sequencing, and resequencing arrays, prenatal genetic testing is becoming more and more accurate. Because of the relatively small risk (2%–4%) of recurrence of OI type II in a family, families may opt for ultrasound studies to determine if a developing fetus has the disorder.

Ultrasound is the least invasive procedure for prenatal diagnosis and carries the least risk. Using ultrasound, a doctor can examine the fetus's skeleton for bowing of the leg or arm bones, fractures, shortening, or other bone abnormalities that may indicate OI. Different forms of OI may be detected by ultrasound in the second trimester. The reality is that when it occurs as a new dominant mutation, it is found inadvertently on ultrasound, and it may be difficult to know the diagnosis until after delivery since other genetic conditions can cause bowing and/or fractures prenatally.

Chorionic villus sampling is a procedure to obtain chorionic villi tissue for testing. Examination of fetal collagen proteins in the tissue can reveal information about the quantitative or qualitative collagen changes that lead to OI. When a parent has OI, it is necessary for him or her to have the results of a collagen test available. Chorionic villus sampling can be performed at 10–12 weeks of pregnancy.

Amniocentesis is a procedure that involves inserting a thin needle into the amniotic sac in the uterus and withdrawing a small amount of amniotic fluid. DNA can be extracted from the fetal cells contained in the amniotic fluid and tested for the specific mutation known to cause OI in a particular family. This technique is useful only when the mutation causing OI in a particular family has been identified through previous genetic testing of affected family members, including previous pregnancies involving a baby with OI. Amniocentesis is performed at 16–18 weeks of pregnancy.

Treatment and management

There are no treatments available to cure OI, nor to prevent most of its complications. Most treatments are aimed at correcting the fractures and bone abnormalities caused by OI. Splints, casts, braces, and rods are all used. Rodding refers to a surgical procedure in which a metal rod is implanted within a bone (usually the long bones of the thigh and leg). This is done when bowing or repeated fractures of these bones have interfered with a child's ability to begin to walk. Physical therapy and occupational therapy is also used for the treatment and management of OI to increase mobility and decrease muscle weakness and muscle wasting.

Medications have been evaluated for their potential use to treat OI. These include growth hormone treatment, treatment with intravenous and oral drugs called bisphosphonates, an injected drug called teriparatide (for adults only), and gene therapies. This type of pharmaceutical treatment has been shown to decrease the number of bone fractures and the frequency and intensity of pain.

Other treatments include hearing aids and early capping of teeth. Patients may require the use of a walker or wheelchair. Pain may be treated with a variety of medications. Exercise is encouraged as a means to promote muscle and bone strength. Swimming is a form of exercise that puts a minimal amount of strain on muscles, joints, and bones. Walking is encouraged for those who are able.

Smoking, excessive alcohol and caffeine consumption, and steroid medications may deplete bone and increase bone fragility.

Alternative treatments such as acupuncture, naturopathic therapies, hypnosis, relaxation training, visual imagery, and biofeedback have all been used to try to decrease the constant pain of fractures.

Prognosis

Lifespan for people with OI types I, III, and IV is not generally shortened. The prognosis for people with these types of OI is quite variable, depending on the severity of the disorder and the number and severity of the fractures and bony abnormalities.

Fifty percent of all babies with OI type II are still-born. The rest of these babies usually die within a very short time after birth. In recent years, some people with type II have lived into young adulthood.

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ORGANIZATIONS

- Little People of America, 250 El Camino Real, Suite 211, Tustin, CA 92780, (714) 368-3689 or (888) LPA-2001, (714) 368-3367, info@lpaonline.org, <http://www.lpaonline.org>
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), 1 AMS Circle, Bethesda, MD 20892-3675, (301) 495-4484 or (877) 226-4267, (301) 718-6366, NIAMInfo@mail.nih.gov, <http://www.niams.nih.gov>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>
- Osteogenesis Imperfecta Foundation, 804 W. Diamond Ave., Suite 210, Gaithersburg, MD 20878, (301) 947-0083 or (800) 981-2663, (301) 947-0456, bonelink@oif.org, <http://www.oif.org>

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Osteoporosis

Definition

Osteoporosis is a disease characterized by low bone mass and deterioration of bone tissues, leading to bone fragility and, consequently, an increase in fracture risk.

Description

The term "osteoporosis" comes from the Greek words "osteon," "meaning bone," and "porus," meaning "pore" or "passage." Osteoporosis literally makes bones porous. The amount of calcium stored in bones decreases over time, causing the skeleton to weaken.

In the bodies of younger adults, both the mineral portion and the framework of bone is in constant flux. Old tissue is broken down and reabsorbed, and new bone is created at approximately the same rate. In later years, this rate of renewal begins to slow behind the rate of removal. This slowing is what leaves the bones thinner and more fragile. The most typical sites of fractures related to osteoporosis are the hips, spine, wrists, and ribs, although the disease can affect any bone in the body.

The average woman acquires 98% of her skeletal mass by approximately age 20. Building strong bones during childhood and adolescence is a key defense against developing osteoporosis later. There are four main steps to preventing osteoporosis: consuming a balanced diet rich in calcium and vitamin D; participating in weight-bearing exercise; following a healthy lifestyle, including no smoking and limited alcohol intake; and testing bone density and taking medication when appropriate.



In compact bone, which forms the long bones of the body, concentric circles of bony material surround large channels that contain blood vessels, lymph vessels, and nerves. The sturdy but normally porous structure of a healthy bone can be weakened and leached away if its calcium content is not maintained. (Dee Breger/Science Source)

Type I, postmenopausal osteoporosis, is the most common. It is usually a consequence of reproductive hormone deficiency, and it afflicts mostly women over age 50. The disorder typically appears within the first 10 or 20 years after menopause.

Men may also develop the disorder, usually around 50 to 60 years of age, as a result of the following:

- Prolonged exposure to certain medications such as steroids used to treat asthma or arthritis, anticonvulsants, aluminum-containing antacids, and certain cancer treatments
- Chronic disease that affects the kidneys, lungs, stomach, and intestines and alters hormone levels
- Undiagnosed low levels of the sex hormone testosterone
- Lifestyle habits such as smoking, excessive alcohol use, low calcium intake, and inadequate physical exercise

Type II, senile osteoporosis, affects both men and women over the age of 70, although women are twice as likely to develop the disorder.

Juvenile primary osteoporosis is an inherited skeletal disorder. It causes bones to thin in children. Those with the disorder are susceptible to multiple fractures in the arms and legs, especially at the points at which new bone forms.

In some cases, osteoporosis is secondary to another cause. It can accompany endocrine disorders such as acromegaly and Cushing syndrome. It results from excessive use of drugs such as corticosteroids. In those cases, the treatment is directed at curing the principal ailment or at not using the offending drug. Blood or urine tests will diagnose other causes of bone loss or bone density.

Genetic profile

Osteoporosis results from a complex interaction between genetic and environmental factors throughout life. Evidence suggests that peak bone mass is inherited, but current genetic markers are only able to explain a small proportion of the variation in individual bone mass or fracture risk. As of 2021, no specific mode of inheritance had been identified. Heritability of bone mass has been estimated to account for 60% to 90% of its variance. Studies have shown reduced bone mass in daughters of osteoporotic women when compared with controls, in men and women who have first-degree relatives with osteoporosis, and in perimenopausal women who have a family history of hip fracture. Body weight in infancy may be a determinant of adult bone mineral area.

Some scientists believe that environmental influences during early life interact with the genome to establish the functional level of a variety of metabolic processes involved in skeletal growth.

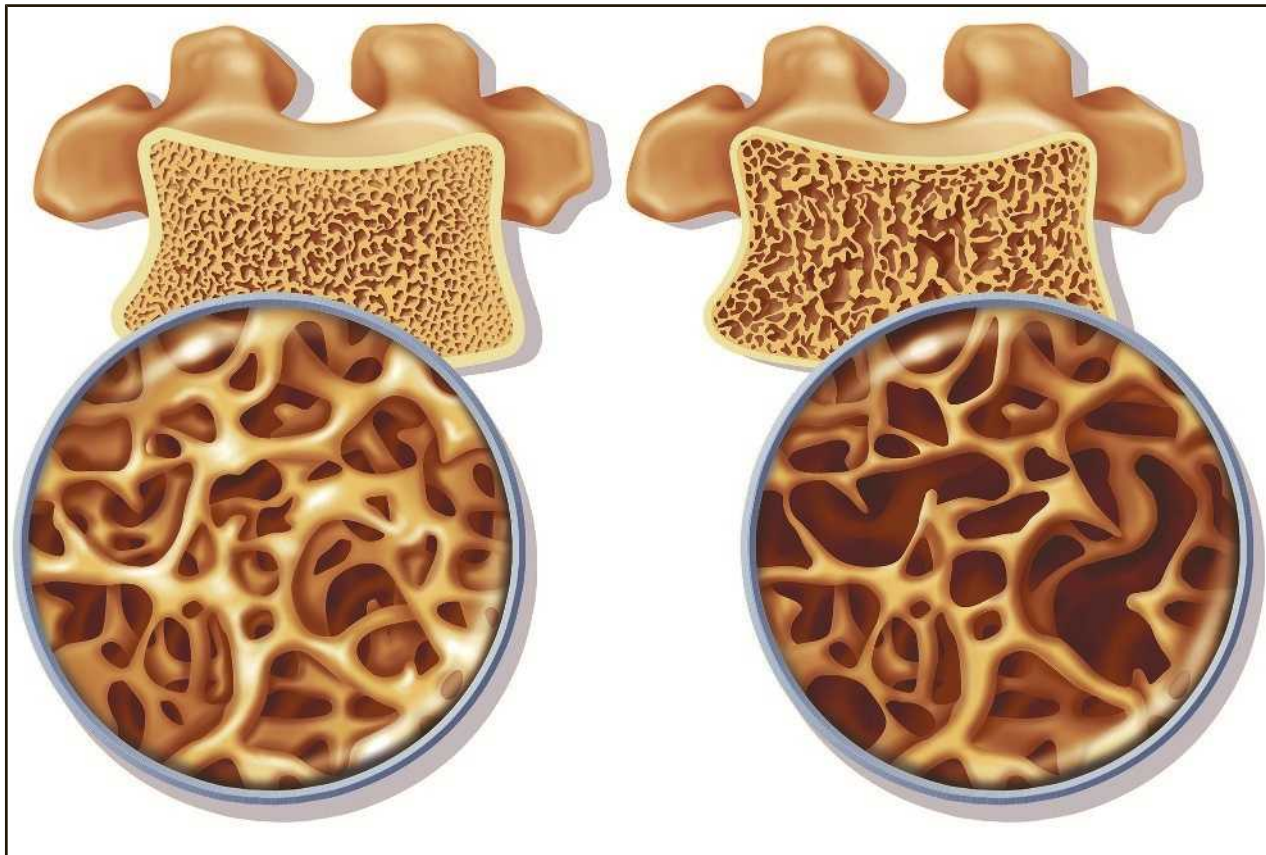
Many candidate genes exist for osteoporosis, but relatively few have been studied. The first candidate gene to be identified was the vitamin D receptor (*VDR*) gene, and

studies are ongoing as to how much this gene accounts for variance in bone mass. The response of bone mass to dietary supplementation with vitamin D and calcium is known to be dependent, in part, on *VDR* polymorphisms. A meta-analysis reported in 2020 that the *VDR BsmI* genotype is associated with increased risk of osteoporosis in Caucasians but not in Asians.

Other genes may aid in establishing who would benefit from treatments like hormone replacement therapy, bisphosphonates, or exercise. Associations between bone mass and polymorphisms have also been found in the estrogen receptor gene, the interleukin-6 genes, the transforming growth factor beta, and a binding site of the collagen type I alpha1 (*COL1A1*) gene.

Recently, T-Plastin (Plastin 3) (Xq23), an actin-bundling protein, has been implicated in X-linked osteoporosis with fractures. Further study in 2021 emphasized the role of plastin 2 with calcium ions in contributing to osteoporosis.

The risk of osteoporosis is greatly determined by peak bone mass, and any gene linked to fractures in the elderly might be associated with low bone mass in



Comparison of healthy dorsal vertebra (left) and one affected by osteoporosis (right). (BSIP/Science Source)

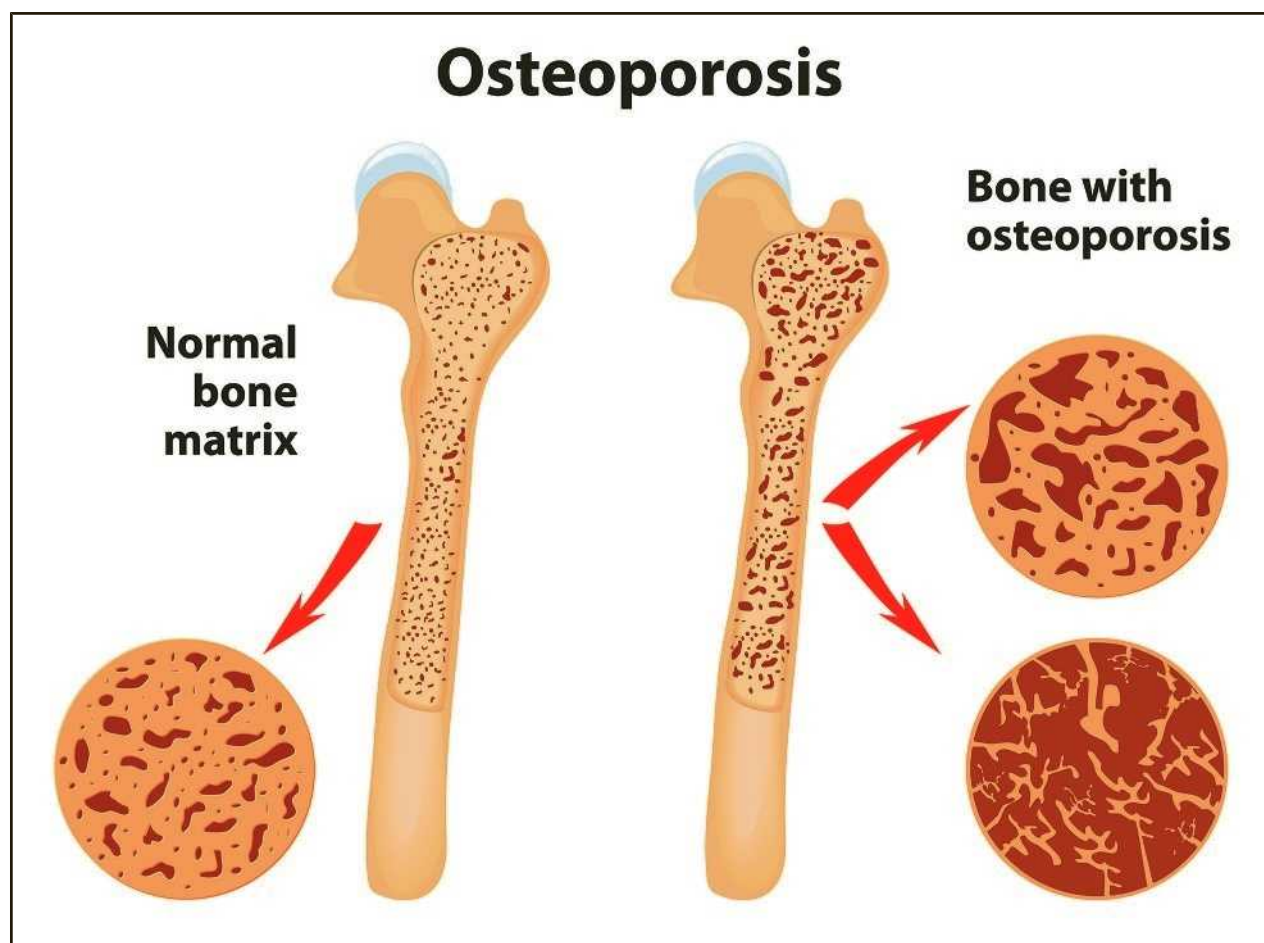


Illustration of a healthy bone (left) and one affected by osteoporosis. (Designua/Shutterstock)

children as well. Genetic studies continue to provide insights into shared genetic mechanisms between bone density mass and both osteoarthritis and osteoporosis.

Environmental influences such as diet, climate, and physical exercise may have significant impact on gene expression as well. In particular, malnutrition early in life is likely to have permanent effects resulting in lowered bone mass.

Juvenile primary osteoporosis is inherited in an autosomal dominant pattern. It is associated with mutations in the *LRP5* gene, which provides protein-making instructions that affect how cells develop, and in regulation of bone mineral density.

Demographics

Significant risk has been reported in people of all ethnic backgrounds. Asian and white women are at greatest risk of bone thinning, because they generally have the lowest bone density. Although the risk is smaller, African-American and Hispanic American women should

also take precaution. An estimated 10% of African-American women over age 50 have osteoporosis, and an additional 30% have low bone density that puts them at risk of developing osteoporosis.

Women in general have four times the risk of developing osteoporosis than men do, and 80% of those affected by osteoporosis are women. In the United States, an estimated eight million American women and two million men have osteoporosis.

An osteoporosis-related fracture will occur in one in two women and one in eight men over the age of 50.

Signs and symptoms

Osteoporosis is often called “the silent disease,” because bone loss occurs without symptoms. People might not know that they have osteoporosis until they have a fracture from a minor bump or fall, or a vertebra collapses. Physical signs of osteoporosis include back pain, loss of height over time, stooped posture, and fractures of vertebrae, wrists, or hips. Osteoporosis can be

detected by a bone mineral density test or even a regular x-ray.

Without preventive treatment, women can lose up to 20% of their bone mass in the first five to seven years following menopause, making them more susceptible to osteoporosis.

Over many years, a sequence of spinal compression fractures may cause kyphosis, the bent-over posture known as dowager's or widow's hump. These fractures rarely require surgery, and they can range from causing minor discomfort to severely painful episodes of back-ache. In either case, pain generally subsides gradually over one to two months.

Diagnosis

Since osteoporosis can develop undetected for decades until a fracture occurs, early diagnosis is important.

A bone mineral density test (BMD) is the only way to diagnose osteoporosis and determine risk for future fracture. The painless, noninvasive test measures bone density and helps determine whether medication is needed to help maintain bone mass, prevent further bone loss, and reduce fracture risk.

Several different machines measure bone density. Central machines, such as dual energy x-ray absorptiometry (DXA or DEXA) and quantitative computed tomography (QCT), measure density in the hip, spine, and total body. Peripheral machines, such as radiographic absorptiometry (RA), peripheral dual energy x-ray absorptiometry (pDXA), and peripheral quantitative computed tomography (pQCT), measure density in the finger, wrist, kneecap, shin bone, and heel.

A physician may be able to observe osteoporotic bone in a routine spinal x-ray; however, BMD tests are more accurate and can measure small percentages of lost bone density. In an x-ray, osteoporotic bone appears less dense, and the image is less distinct, suggesting weaker bone.

There are no official guidelines for osteoporosis screening. Some physicians recommend bone density testing at menopause to begin preventive treatment if necessary. The U.S. Preventive Services Task Force (USPTF) began to recommend in 2018 that women age 65 and older and postmenopausal women younger than 65 with increased risk of osteoporosis have bone measurement testing.

Testing is often recommended for post-menopausal women who have suffered a bone fracture after menopause or who have gone through menopause and have at least one risk factor for the disease. The major risk factors

are low body weight, low calcium intake, poor health, and a family history of osteoporosis.

Testing may also be recommended for elderly men with one of the following risk factors: bone fracture, poor health, or low testosterone levels.

Treatment and management

There are a number of options for preventing and treating bone loss.

Therapeutic options

Various therapies have been shown to be effective in preventing bone loss and increasing bone mass. These include the following:

- **Estrogen.** For women with postmenopausal osteoporosis, estrogen replacement therapy helps to halt bone loss and exerts a modest bone-building effect. Stopping estrogen therapy restarts bone loss, so long-term treatment is usually recommended. For women entering menopause, some physicians recommend estrogen replacement therapy to replace the decreasing supply of naturally occurring estrogen in the body and to enable the skeleton to slow its rate of absorption and to retain calcium. Estrogen is considered the best treatment against osteoporosis. Physicians may recommend combination estrogen and progesterone replacement therapy in women who have an intact uterus, in order to reduce endometrial cancer risk. Some studies indicate a relationship between estrogen use and breast cancer, while others indicate no relationship at all; the issue is still to be determined.
- **Raloxifene.** One of a class of drugs called selective estrogen receptor modulators (SERMs) that appear to prevent bone loss, raloxifene (Evista) produces small increases in bone mass. It is approved for the prevention and treatment of osteoporosis. Like estrogens, SERMs produce changes in blood lipids that may protect against heart disease, although the effects are not as potent as that of estrogen. Unlike estrogens, SERMs do not appear to stimulate uterine or breast tissue.
- **Alendronate.** One of a class of medications called bisphosphonates, alendronate (Fosamax) may prevent bone loss, increase bone mass, and reduce the risk of fractures.
- **Risedronate.** Also from the bisphosphonate family, risedronate (Actonel) has been shown to reduce bone loss, increase bone density, and reduce the risk of fractures.
- **Calcitonin.** A hormone that regulates calcium levels in the blood, calcitonin may prevent bone loss. It is approved for treatment of diagnosed osteoporosis.

QUESTIONS TO ASK YOUR DOCTOR

- If osteoporosis is a genetic disorder, is there anything I can do to prevent developing this disease as I grow older?
- What treatments are typically recommended for a person with osteoporosis?
- What is the probability that I will transmit my osteoporosis to my children?
- Are there books, articles, pamphlets, or other material that provide additional information about osteoporosis?

Preventive options

Measures have been identified that improve bone strength over the lifespan. Physicians recommend that all adult men and women, but particularly men and women over the age of 50, take the following measures to prevent osteoporosis:

- Consume at least 1,000 mg calcium. Foods high in calcium include dairy products, leafy green vegetables, beans, nuts, and whole-grain cereals. Supplements may be taken if adequate intake cannot be achieved through diet.
- Consume 400 IU of vitamin D to enhance calcium absorption.
- Participate in regular weight-bearing exercise, such as walking, jogging, tennis, weight-lifting, and cross-county skiing, to strengthen bones.
- Stop smoking.
- Reduce intake of caffeine to no more than three cups per day.
- Limit alcohol to no more than two drinks per day.
- Avoid excessive amounts of dietary fiber, because it binds to calcium and may interfere with absorption.

Making the house a safer place against falls can decrease risk of fracture in people with osteoporosis. Install handrails on the stairs; remove loose throw rugs; keep rooms and hallways well-lit, including the use of night lights; install handrails beside the tub, shower, and toilet; and place nonskid mats in the bathtub and shower and on tile bathroom floors.

If fractures occur, treatment may require casts, braces, physical therapy, and surgery to assist bone healing.

Prognosis

When osteoporosis is untreated, it can cause serious disability. Osteoporosis can be managed with proper medical care and self-care.

Osteoporosis is associated with 40,000 deaths annually, mostly from complications of surgery or immobilization after hip fractures.

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ORGANIZATIONS

- Foundation for Osteoporosis Research and Education, 300 27th Street, Oakland, CA 94612, (888) 266-3015, <http://www.fore.org>
- National Osteoporosis Foundation, 251 18th Street S, Suite 630, Arlington, VA 20036, (800) 231-4222, (202) 223-2237, <http://nof.org>
- NIH Osteoporosis and Related Bone Diseases National Resource Center, 2 AMS Circle, Bethesda, MD 20892-3676, (202) 223-0344 or (800) 624-2663, (202) 293-2356, NIHBoneInfo@mail.nih.gov, http://www.niams.nih.gov/Health_Info/Bone

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Osteosarcoma

Definition

Osteosarcoma, also called osteogenic sarcoma, is the most common type of bone cancer in young children. Osteosarcoma is destructive to bone development and can spread to other parts of the body.

Description

Osteosarcoma is a malignant tumor that arises from bone tissue and is thus called a primary bone cancer. Primary bone cancers are relatively rare overall; approximately 800 new cases of osteosarcoma occur in the United States every year.

Osteosarcoma occurs most frequently during childhood or adolescence with about 60% of the cases of the disease developing during the second decade of life. The incidence of osteosarcoma rises again among people in their 40s and 50s.



False-color CT scan of the knee joints showing osteosarcoma located in the tibia at left of image. The head of the tibia bone (center left) is cancerous (green). (GCa/Science Source)

Osteosarcoma may occur in any bone but develops most commonly in long bones, particularly near the knee or in the upper arm. The cancer starts growing within the bone and forms an expanding, ball-like mass called a tumor. The tumor eventually breaks through the surface of the bone and begins to invade adjoining structures, such as muscles. If untreated, the disease usually appears elsewhere in the same limb and metastasizes to distant parts of the body, such as the lungs.

Genetic profile

Some cases of osteosarcoma are likely to have a genetic basis, as numerous genetic abnormalities have been found in patients with osteosarcoma. Osteosarcoma is also the most common second cancer to develop in survivors of the genetic cancer retinoblastoma, suggesting that osteosarcoma may also have genetic contributions.

Other cancers are often associated with osteosarcoma. These are considered cancer syndromes, as the occurrence of more than one type of cancer is part of the syndrome's phenotype. The occurrence of osteosarcoma can be linked to a treatment for the primary disease, or it can be a result of a genetic predisposition, as is the case with Li-Fraumeni syndrome and retinoblastoma.

Li-Fraumeni syndrome (LFS) is an autosomal dominant disorder caused by a mutation in the *TP53* gene. Frederick Li and Joseph Fraumeni first described it in 1969 based on clinical phenotypes associated with other cancers. Germline mutations in the *TP53* gene have been identified among family members with LFS. *TP53* is a gene that functions in the regulation of the cell cycle, and mutations occur in 50% and 70% of cancer and LFP cases, respectively. Among those affected with LFS, osteosarcoma is the most common bone cancer to be associated with other symptoms of the syndrome.

Hereditary retinoblastoma is a rare, autosomal dominant disease that causes malignant eye tumors in children. It is caused by mutations in the *RBI* gene, which acts as a tumor suppressor by inhibiting proteins that are involved in cell replication. Individuals who have retinoblastoma often have increased risk of developing other cancers later on in life, including osteosarcoma. Heritable mutations of *RBI* occur in germ cells, but spontaneous mutations of *RBI* can also occur in somatic cells. These types of mutations in *RBI* are found in 30%–70% of osteosarcoma patients. It is thought that this may be because *RBI* is important in the inhibition of proteins that cause unregulated osteoblast proliferation or stimulate cell differentiation.

Demographics

Of the 800 new cases of osteosarcoma that are diagnosed in the United States each year, approximately 400

are in children and teens. Teens are most at risk for osteosarcoma, and it occurs more often in males than in females. It also appears that African Americans have a slightly higher risk than Caucasians.

Signs and symptoms

There are numerous theories regarding the causes of osteosarcoma. Many cases occur during a time of rapid bone growth, which is why it is often seen in teenagers. Individuals with Paget's disease are also more susceptible to osteosarcoma because of the associated constant breaking down and remodeling of their bones. This suggests that the cancer may develop when the body loses its ability to control the multiplication of certain bone cells. Other cases arise in people who have been exposed to radiation, either accidentally or as part of a medical treatment.

Common early symptoms of osteosarcoma are often hard to diagnose. There may be pain or swelling at the site of the tumor, but these symptoms may not initially seem serious in a young, active person. Thus, the patient or medical personnel may attribute the symptoms to growing pains or an injury from physical activity, and the diagnosis may be delayed. Eventually, it is usually possible to feel a firm lump on the bone and this lump will be sensitive to the touch.

Diagnosis

The complete diagnosis of osteosarcoma is a complicated process that requires a variety of tests and the help of several medical specialists. Physicians must first determine the stage of the cancer (the extent to which it has spread) and the grade of the cancer (the degree of cancerous qualities shown by cells in a biopsy specimen). A higher grade or stage indicates a more serious disease than a lower grade or stage.

Initial diagnosis begins with x-ray images of the affected area. These pictures will show a cancerous growth within the bone, which is often described as having a "moth-eaten appearance." The patient then needs further tests such as computed tomography (CT, CAT) or magnetic resonance (MR, MRI) imaging scans of the tumor, a chest x-ray series or chest CT, and a nuclear medicine scan of the entire skeleton (bone scan). This imaging will determine the parts of the body that are affected by the cancer and to what extent the cancer has spread from the initial areas. Blood tests, such as measurements of alkaline phosphatase (ALP), provide additional information. It is unclear why ALP levels are increased in cases of osteosarcoma, but it remains a diagnostic tool for determining the stage of the cancer.

KEY TERMS

Alkaline phosphatase (ALP)—An enzyme that is found in the blood and that helps to break down proteins in the body. ALP can be present in different forms depending on where it was synthesized. ALP can be made in the liver, kidneys, intestines, and bones.

Chemotherapy—Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of the cancerous cells or by killing the cancer cells.

Grade—As a noun: a classification of the cancerous qualities of an individual tumor. A higher grade indicates a more serious disease than does a lower grade. As a verb: to classify the cancerous qualities of an individual tumor.

Malignant—Cancerous.

Metastasize—To spread to another part of the body.

Monoclonal antibody (mAB)—A protein, produced in large quantities in a laboratory, designed to attack a specific target in the body.

Osteogenic—Derived from or containing bone cells.

Osteogenic sarcoma—A form of cancer that originates in the bone.

Paget's disease—A non-cancerous disease marked by excessive growth of abnormal bone material.

Retinoblastoma—A cancerous tumor of the eye.

Stage—As a noun: the extent to which an individual cancer has spread. A higher stage indicates a more serious disease than does a lower stage. As a verb: to determine the extent to which an individual cancer has spread.

Tumor—An abnormal growth of cells. Tumors may be benign (non-cancerous) or malignant (cancerous).

Finally, physicians require a biopsy sample of the diseased bone, obtained with a needle or by a surgical procedure, to be sure that the disease is truly cancer and to identify its grade. There are numerous tests, mostly involving examinations under the microscope, to perform on this biopsy specimen.

Treatment and management

Before the 1980s, limb amputation was the standard treatment for osteosarcoma. Usually, however, the tumor had already spread elsewhere in the body and the patient eventually died of the disease.

QUESTIONS TO ASK YOUR DOCTOR

- What type of osteosarcoma do I (or my family member) have? How does this affect treatment options?
- What stage is the cancer at and has it spread to other organs?
- When will treatment begin and how long will it last? What common side effects can I expect?
- Are there genetic or fertility decisions I should consider?
- Based on the treatment plan, what are the chances the cancer will come back?

Newer medical developments make it possible to avoid amputation and treat many patients with osteosarcoma successfully. Patients almost always receive chemotherapy with more than one drug (multi-drug therapy) before surgery to shrink the original tumors and reduce the likelihood of the cancer spreading to other areas of the body. Techniques known as limb-sparing surgery often allow removal of the tumor while saving the rest of the extremity. Afterward, patients usually continue to receive chemotherapy and may require bone grafts or prosthetic devices to replace parts of bones or joints that have been removed as part of their treatment.

Future treatments under investigation include the development of monoclonal antibodies that destroy specific cancer cells, techniques to slow cancer growth by controlling certain genes involved in cell growth or replication, and bone-specific chemicals that directly target areas of active bone growth and slow it down.

Alternative and complementary therapies

Current treatments with chemotherapy and surgery offer a substantial improvement over past therapies. While radiation therapy is often not as successful as chemotherapy in treating osteosarcoma generally, it can sometimes be helpful in keeping tumor growth under control before other treatments can be put into place.

Alternative therapies often include clinical trials that are testing new medications or technologies, but these are normally only provided when a patient's cancer is not responding to traditional forms of treatment.

Complementary methods of therapy are not considered curative but can often be helpful in minimizing pain or suffering caused by traditional treatment. These

methods can focus on stress relief through talk or art therapy, or use of acupuncture to treat pain or nausea.

Prevention of osteosarcoma is difficult since doctors do not know the cause of most cases. Until research can provide information and tools that make prevention possible, early detection of the disease remains vital. Anyone with persistent pain in a bone or limb should report this to a physician. People with special risk factors including Paget's disease, exposure to significant amounts of radiation, or a family history of certain types of cancer must be especially vigilant.

Prognosis

Early detection is extremely important. Prognosis for an individual patient reflects a complex balance among the extent to which the cancer has already spread at the time of diagnosis, the aggressiveness of the cancer, and the response to chemotherapy. The best chance of a cure occurs when a tumor shows no sign of metastasis at the time of original surgery, is well confined within a single bone, responds well to chemotherapy, and can be completely removed. The five-year survival rate for osteosarcoma in a long bone of a limb is about 70%. A physician must follow all patients closely to watch for cancer recurrence.

Resources

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- "Osteosarcoma." MedlinePlus. October 16, 2020. <https://medlineplus.gov/ency/article/001650.htm> (accessed July 9, 2021).

ORGANIZATIONS

- American Cancer Society, PO Box 22718, Oklahoma City, OK 73123-1718, (800) 227-2345, <http://www.cancer.org>

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Otopalatodigital syndrome

Definition

Otopalatodigital (OPD) syndrome, also called digi-tootopalatal syndrome or palatootodigital syndrome, is a rare X-linked genetic disorder that affects bone and facial structure. OPD is fully expressed in males. Females are only mildly affected.

Description

There are two forms of OPD syndrome. Type I is inherited through an X-linked trait with intermediate expression in females, while type II is inherited through an X-linked recessive trait. OPD syndrome type I is also called Taybi syndrome. OPD syndrome type II is alternatively called Andre syndrome, cranioorodigital syndrome, or faciopalatoosseous (FPO) syndrome.

A genetic disorder called frontometaphyseal dysplasia, or FMD, has very similar features to type I OPD syndrome.

There are three recognized forms of a genetic disorder called Larsen syndrome: an autosomal dominant type, a recessive type, and a lethal type. All three of these syndromes have similar symptoms to those seen in individuals affected with OPD syndrome. Some research has suggested that Larsen syndrome, recessive type, may in fact be type II OPD syndrome.

As the various names of OPD syndrome suggest, this disorder is characterized by malformations and/or dysfunctions of the ears (-oto-), palate (-palato-), fingers and toes (-digito-), skull (-cranio-), mouth (-oro-), face (-facio-), and bones (-osseo-). Some of the characteristics common to both types of OPD syndrome include: a cleft palate, a prominent forehead, a broad nose, widely spaced eyes (hypertelorism), a downward slanting of the opening between the upper and lower eyelids (palpebral fissures), conductive hearing loss, short fingers and toes (brachydactyly), an abnormal inward curving of the fingers (clinodactyly), a caved in chest at birth (pectus excavatum), short stature (dwarfism), and a congenital dislocation of the elbows caused by a misalignment of the head of the large bone in the forearm (radius).

Genetic profile

Both forms of OPD syndrome are X-linked. The gene mutation responsible for the appearance of type I OPD syndrome has been tentatively assigned to the Xq28 band. It is also believed that type II OPD syndrome is an allelic variant of type I OPD, which is to say that each form of OPD syndrome is caused by different mutations in the same gene or in overlapping genes at the same

KEY TERMS

Brachydactyly—Abnormal shortness of the fingers and toes.

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Clinodactyly—An abnormal inward curving of the fingers or toes.

Conductive hearing loss—Hearing loss that is the result of a dysfunction of the parts of the ear responsible for collecting sound. In this type of hearing loss, the auditory nerve is generally not damaged.

Hypertelorism—A wider-than-normal space between the eyes.

Hypospadias—An abnormality of the penis in which the urethral opening is located on the underside of the penis rather than at its tip.

Omphalocele—A birth defect where the bowel and sometimes the liver protrudes through an opening in the baby's abdomen near the umbilical cord.

Palpebral fissures—The opening between the upper and lower eyelids.

Pectus excavatum—An abnormality of the chest in which the sternum (breastbone) sinks inward; sometimes called "funnel chest."

chromosomal location. Recessive type Larsen syndrome is also believed to be either another allelic variant of OPD syndrome, or identical to type II OPD syndrome. Another extremely rare genetic disorder, Melnick-Needles syndrome, also has an overlapping of symptoms with type II OPD syndrome. It is felt that this syndrome is also possibly an allelic variant of OPD syndrome.

OPD syndrome is transmitted via the X chromosome. A female generally possesses two X chromosomes, one from her mother and one from her father. A male generally possesses only a single X chromosome, that from his mother. He gets a Y chromosome from his father. Certain rare exceptions to these inheritance patterns are seen, but in general, a female is an XX and a male is an XY. It is for this reason that X-linked disorders are generally seen in greater numbers of males than females. The male does not possess a second X chromosome that can be expressed. A male either has a mutation on his X chromosome, or he does not. A female, on the other hand, can be either homozygous or heterozygous

for an X-linked trait. That is, she can either have two identical copies of this trait (homozygous) or only one copy of this trait (heterozygous).

Type I OPD syndrome is transmitted through a dominant trait. A child of a type I OPD syndrome affected parent has a 50% chance of also being affected with type I OPD syndrome.

Type II OPD syndrome is transmitted through an X-linked recessive trait. A child of a type II OPD syndrome affected parent has a 50% chance of also inheriting the gene for the type II OPD syndrome. Subsequently, if that child is male, he will have expression of the disorder. If it is a female child, then she generally will have milder features. Girls who are homozygous for type II OPD syndrome (inheriting the gene from each parent) will exhibit more severe symptoms than girls who are heterozygous for type II OPD syndrome. Males affected with type II OPD syndrome exhibit symptoms similar to those seen in homozygous girls.

Demographics

The incidence of occurrence of OPD syndrome types I and II in 2015 were each fewer than 1 in 100,000 people. However, type I OPD syndrome is more common than type II OPD syndrome and more than 100 cases had been reported in the medical literature. In 2015, only 40 detailed cases of type II OPD syndrome had been described in the medical literature.

Signs and symptoms

The severity of symptoms experienced by those people affected with OPD syndrome varies widely from practically asymptomatic to symptoms so severe that they cause infantile or prenatal death. In type II OPD syndrome, males are generally affected with far more severe symptoms than females.

There are six abnormalities of the face and head that characterize OPD syndrome: a cleft palate, downwardly slanting openings between the eyelids, widely spaced eyes (hypertelorism), a prominent forehead, a broad nose, and conductive hearing loss.

Conductive hearing loss results from a blockage of the auditory canal or some other dysfunction of the eardrum or one of the three small bones within the ear (the stapes, the malleus, and the incus) that are responsible for collecting sound. In this type of hearing loss, the auditory nerve is normal. In individuals affected with OPD syndrome, complete deafness from birth is often observed. In those individuals with partial hearing, speech disabilities related to this hearing loss are quite common.

QUESTIONS TO ASK YOUR DOCTOR

- How does the genetic basis of the two types of otopalatodigital syndrome differ from each other?
- What signs and symptoms are characteristic of this disorder?
- What kinds of treatment are available for otopalatodigital syndrome, and at what stage of a child's life should each treatment be used?
- Can you recommend any websites that have additional information about this disorder?

In addition to the abnormalities of the head, universal characteristics of OPD syndrome affected individuals also include: abnormally short fingers and toes (brachydactyly); abnormal inward curving of some fingers (clinodactyly); short nails; a congenital dislocation of the elbows, and sometimes the knees; a caved in chest (pectus excavatum) at birth; and growth retardation.

Symptoms that are characteristic of type I OPD syndrome include curvature of the spine (scoliosis); generalized bone malformation, particularly in the bones of the limbs and ribcage; broad distal digits, malformed or missing teeth (hypodontia); and mild intellectual disability.

Symptoms that are characteristic of type II OPD syndrome include: low-set ears, flattened vertebrae in the spine, bowing of the bones of the limbs, flexed overlapping digits, a malformation or complete absence of the large bone in the shin (fibula), malformations of the hips, a small opening in the abdominal wall (hernia) at the navel (omphalocele), and a malformation of the male genitalia in which the opening of the urethra is located on the underside of the penis, rather than at the tip of the penis (hypospadias).

Diagnosis

A diagnosis of OPD syndrome is suggested when a patient presents the five characteristic abnormalities of the head and face accompanied by conductive hearing loss. This diagnosis is confirmed by the observance of brachydactyly and congenital dislocation of the elbows and/or knees.

Type I OPD syndrome is differentially diagnosed from type II OPD syndrome by the appearance of scoliosis. Type II OPD syndrome is differentially diagnosed from type I OPD by the presence of an omphalocele and greater malformations of the bones of the ribcage.

Treatment and management

There are currently no treatments aimed specifically at OPD syndrome. Instead, treatment is on a case-by-case and symptom-by-symptom basis.

Malformations of the head and face can generally be corrected, if necessary, by surgeries. In certain instances, the conductive hearing loss experienced by individuals with OPD syndrome may also be corrected through surgery. When it cannot, hearing aids may be required.

Many of the skeletal abnormalities seen in OPD syndrome affected individuals can either be corrected by surgery or can be alleviated through the use of braces until the bones become more fully developed.

Malformations of the male genitalia and the omphalocele observed in type II OPD syndrome affected infants can also be corrected by surgery.

Certain OPD affected individuals may also benefit from treatments with growth hormone.

In cases of mild intellectual disability or speech problems, early intervention programs for these types of developmental delays may also be of benefit.

Prognosis

Most individuals affected with type I OPD syndrome can expect to lead full lives if medical treatments, including corrective surgeries, are sought. Many individuals affected with type II OPD syndrome die either prior to birth or as infants due to respiratory failure associated with the malformation of the bones of the ribcage. If these individuals survive infancy, they also may expect to live full lives after corrective surgeries and other medical treatments.

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ORGANIZATIONS

- Children's Craniofacial Association (CCA), 13140 Coit Rd., Suite 517, Dallas, TX 75240, (214) 570-9909 or (800) 535-3643, (214) 570-8811, contactCCA@ccakids.com, <http://www.ccakids.com>
- FACES: The National Craniofacial Association, PO Box 11082, Chattanooga, TN 37401, (423) 266-1632 or (800) 332-2373, faces@faces-cranio.org, <http://www.faces-cranio.org>
- Let's Face It, 72 Victoria Ave., Westgate on Sea, Kent UK CT8 8BH, 01843 833724, chrisletsfaceit@aol.com, <http://www.lets-face-it.org.uk>
- My Face, 333 E. 30th St., Lobby Unit, New York, NY 10016, (212) 263-6656, (212) 263-7534, info@myface.org, <http://myface.org>

Paul A. Johnson

Ovarian cancer

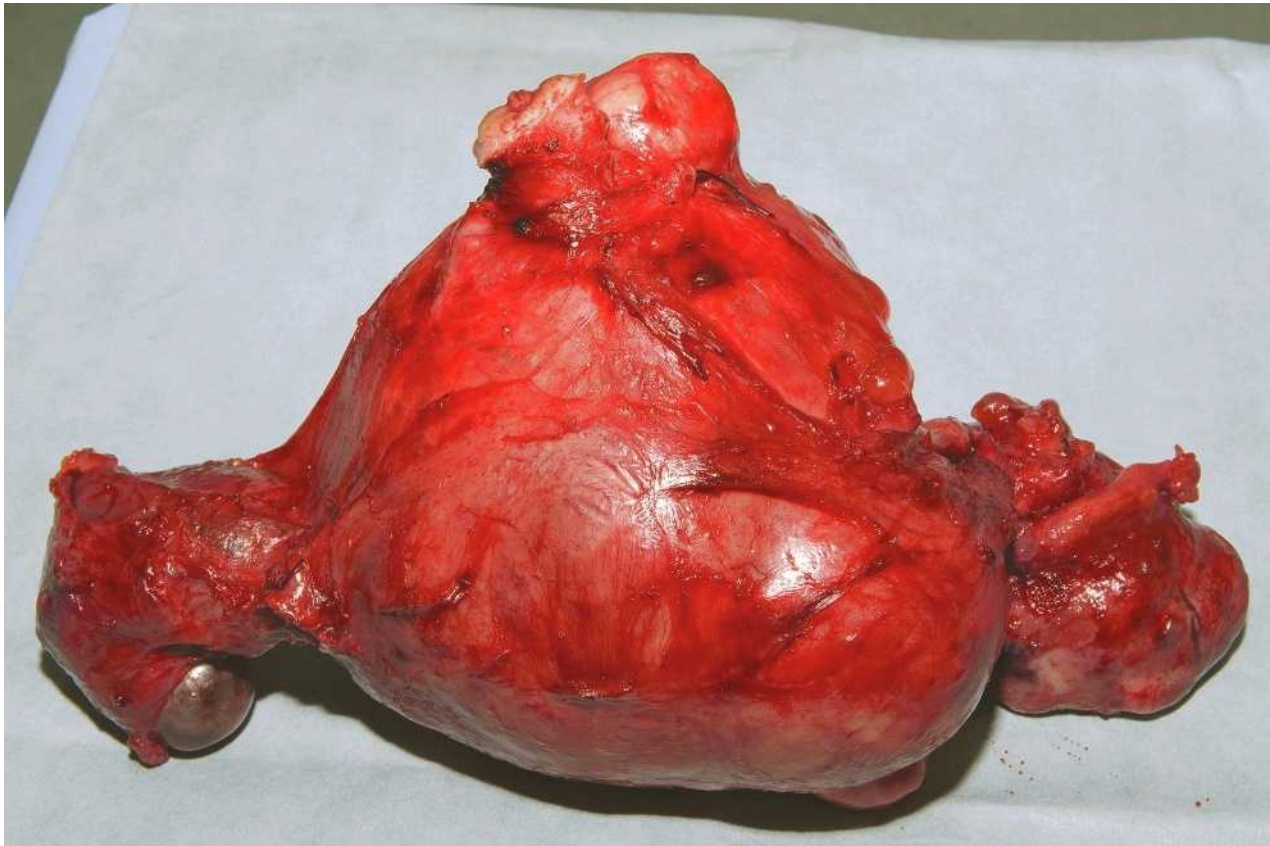
Definition

Ovarian cancer is a disease in which the cells in the ovaries become abnormal and start to grow uncontrollably, forming tumors. Ninety percent of all ovarian cancers develop in the cells that line the surface of the ovaries and are called "epithelial cell tumors." Despite advances in treatment, ovarian cancer remains one of the most lethal cancers.

Description

The ovaries are a pair of almond-shaped organs that lie in the pelvis on either side of the uterus. The fallopian tubes connect the ovaries to the uterus. The ovaries produce and release an egg each month during a woman's menstrual cycle. In addition, they produce the female hormones estrogen and progesterone, which regulate and maintain the proper growth and development of female sexual characteristics.

Ovarian cancer is the fifth most common cancer among women in the United States. It accounts for 4% of all cancers in women but is very difficult to discover in the early stages, often because there are no obvious warning signs, and the disease can progress relatively quickly. In addition, the ovaries are situated deep in the abdomen, and small tumors might not be detected easily during a routine



Enlarged uterus removed from a 60 year old woman with ovarian cancer and uterine fibroids. Fibroids are benign (non-cancerous) tumors of fibrous and muscular tissue. (Dr P. Marazzi/Science Source)

physical examination. The death rate due to ovarian cancer is higher than that of any other cancer among women, since it often is detected at advanced stages.

Ovarian cancer can develop at any age, but more than half the diagnoses are among women who are 63 years or older. It is more common in white women than in African American women. The vast majority of women with ovarian cancer have no family history of the disease, but for about 5% to 10% of individuals there may be a very strong family history of ovarian cancer or other cancers such as breast cancer. In those cases, a specific genetic alteration may run in the family, causing a predisposition to ovarian cancer and other associated cancers.

Genetic profile

Cells in ovarian tissue normally divide and grow according to controls and instructions by various genes. If these genes have changes (mutations) within them, the instructions for cellular growth and division may be altered, causing abnormal or uncontrolled cell growth that can lead to ovarian cancer. In this way, all ovarian cancers are genetic, because they all result from changes within genes.

The difference is that most ovarian cancers are caused by sporadic changes within the genes, and only a minority are caused by inherited genetic alterations. Most ovarian cancers occur later in life after years of exposure to various environmental factors (e.g., asbestos exposure, or smoking) that can cause sporadic genetic alterations.

A small proportion of ovarian cancer is caused by inherited genetic mutations. In 1994, a breast and ovarian cancer susceptibility gene, known as *BRCA1* (location 17q21), was identified, and the discovery of *BRCA2* (location 13q12) followed shortly in 1995. Women with mutations in these genes have an increased risk for breast and ovarian cancer, and men have an increased risk for prostate cancer. Men with a *BRCA2* mutation also have an increased risk for breast cancer. Slightly increased risks for colon and pancreatic cancers in men and women are also associated with *BRCA2* mutations.

BRCA1 and *BRCA2* mutations are inherited in an autosomal dominant manner. People who have one copy of a *BRCA* alteration have a 50% chance of passing it on to each of their children, regardless of that child's gender. Nearly all individuals with mutated *BRCA* have a family

history of the mutation, usually a parent with it. In turn, they also may have a very strong family history of breast, ovarian, prostate, colon, and/or pancreatic cancers. Aside from *BRCA1* and *BRCA2*, there likely are other cancer susceptibility genes that are still unknown.

In addition to *BRCA1* and *BRCA2*, ovarian cancer may be present in rare genetic cancer syndromes. In those instances, an individual may have other health problems that are unrelated to cancer as well as a family history of a wide variety of cancers and symptoms. For example, hereditary non-polyposis colorectal cancer (HNPCC) is a syndrome that often involves cancers of the colon, uterus, ovaries, and stomach. HNPCC is due to changes in several genes, including *hMLH1*, *hMSH2*, *hMSH6*, and *hPMS2*. These genes are unrelated to *BRCA1* and *BRCA2* but are still correlated to the development of ovarian cancer.

Demographics

On average, a North American woman faces a lifetime risk of about one in 78 of developing ovarian cancer. The American Cancer Society (ACS) states that in 2021, about 21,410 new cases of ovarian cancer will be diagnosed in the United States and that 13,770 women will die from the disease. The ACS notes that the rate at which women are diagnosed with ovarian cancer has been slowly declining since 2000. Specific *BRCA* mutations are common in certain ethnic groups, which may make hereditary ovarian cancer more common in these populations. Certain *BRCA* mutations are more common in the

Ashkenazi (Eastern European) Jewish, Icelandic, Dutch, French Canadian, and West African populations.

Signs and symptoms

Ovarian cancer has no specific signs or symptoms in the early stages of the disease; however, some symptoms are commonly associated with it:

- Pain or swelling in the abdominal area
- Bloating and general feeling of abdominal discomfort
- Constipation, nausea, or vomiting
- Loss of appetite, fatigue
- Unexplained weight gain (generally due to fluid buildup from the cancer in the abdomen)
- Vaginal bleeding in women who have already gone through menopause

Only a physician can assess whether symptoms are an indication of early ovarian cancer, and it is important to seek medical care immediately if any of the above-mentioned symptoms is present.

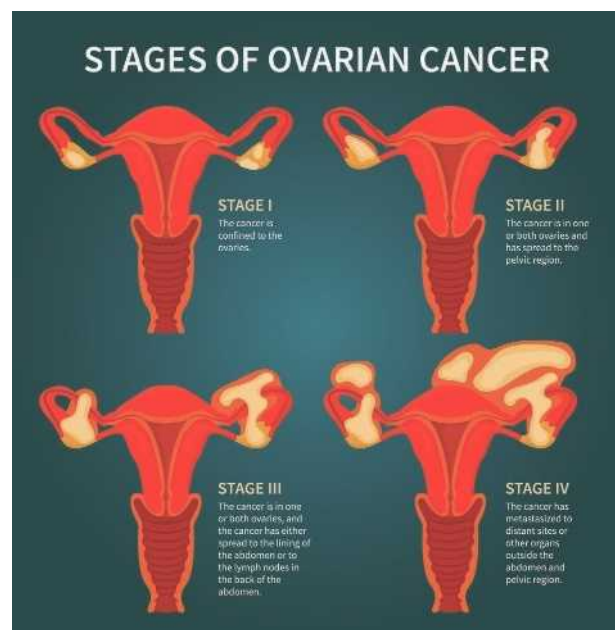
A family history of ovarian cancer puts a woman at an increased risk for developing the disease. In addition, if a woman has had, or has a family history of, breast cancer then she may be at an increased risk for ovarian cancer. Signs of possible mutations in *BRCA1* or *BRCA2* in a family signify hereditary breast or ovarian cancer and can include:

- Several relatives with cancer
- A larger number of relatives with cancer than unaffected relatives
- Close genetic relationships between people with cancer, such as parent-child, sibling-sibling
- Onset of cancer before the ages 45 to 50
- An individual with both breast and ovarian cancer
- An individual with bilateral or multi-focal breast cancer
- The presence of ovarian, prostate, colon, or pancreatic cancers in the same family
- Case(s) of breast cancer in men

BRCA mutations may be suspected if someone has the above features in his or her family, and he or she is of a particular ethnic group particularly at risk. This is because specific *BRCA1* and *BRCA2* mutations are known to be more common in some groups.

Diagnosis

If a woman has symptoms of ovarian cancer, a pelvic examination is conducted to feel the ovaries to determine whether they have enlarged, which is indicative of a tumor. Blood tests to determine the level of the protein carbohydrate antigen 125 (CA-125) may be done as well.



Ovarian cancer. (Shutterstock/kanvictory)

CA-125 blood levels may be high when a woman has ovarian cancer. Pelvic or transvaginal ultrasound also may be used to get several views of the ovaries and to carefully check their shapes and structures. A CT scan may be helpful if the ultrasound is technically unsatisfactory for accurate interpretation.

Biopsy and surgery are necessary in order to determine the type of tumor, as not all tumors are cancerous. If the tumor appears to be small, a procedure known as laparoscopy may be used to further investigate and make a diagnosis. A tiny incision is made in the abdomen, and a slender, hollow, lighted instrument is inserted to enable the doctor to view the ovary more closely and to obtain a biopsy. If the ovary has suspicious findings on laparoscopy and biopsy, a laparotomy to remove that ovary is usually performed. Large masses are normally investigated by open surgery.

Standard imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) could be used to determine whether the disease has metastasized (spread to other parts of the body).

There is DNA-based genetic testing to identify a *BRCA1* or *BRCA2* mutation in an individual. A blood sample is used, and both *BRCA* genes are studied for abnormalities in their sequences. There is also targeted testing for people in high-risk ethnic groups where the *BRCA* mutations common to that group can be tested for specifically.

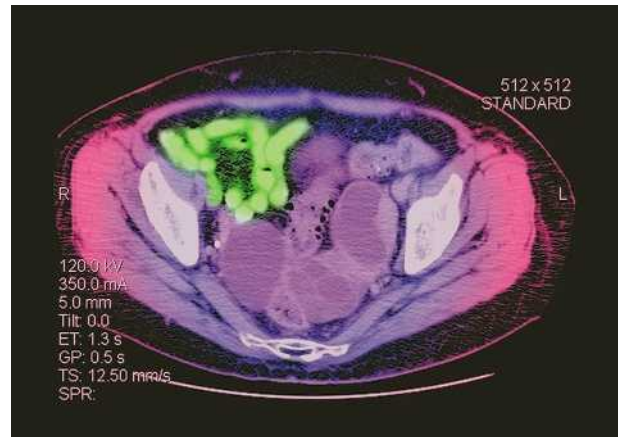
Women without cancer who test positive for a *BRCA* alteration are at a significantly increased risk to develop the associated cancers. A woman's risks associated with a mutant *BRCA1* are 40% to 60% for ovarian cancer by age 70 and 55% to 65% for breast cancer by age 70. A woman's risks with a *BRCA2* alteration are 16% to 27% for ovarian cancer by age 70 and approximately 45% for breast cancer by age 70.

Women with ovarian cancer who are found to have a *BRCA* mutation are at an increased risk to develop breast cancer. For some women, this may be a new risk that they were not aware of before the testing, particularly if they have no family history of breast cancer.

Women with a *BRCA2* mutation may be at slightly increased risk for colon and pancreatic cancers. Additionally, because the testing process and test results are quite complex, everyone should receive proper genetic counseling before pursuing any *BRCA1* and *BRCA2* testing. Prenatal *BRCA* testing is available but is rarely performed unless accompanied by extensive genetic and psychological counseling.

Treatment and management

As with many other cancers, treatment is determined by the exact size, type, and stage of ovarian cancer, and it



This CT scan of the pelvis shows a large multi-lobulated cystic mass (green), which is ovarian cancer. (Matthew Bologna/Medical Body Scans/Science Source)

is often unique to an individual. However, the cornerstone of treatment for ovarian cancer is debulking surgery, which removes as much of the cancer as is feasible. This may require a laparoscopic or open surgical procedure in order to remove as much cancerous tissue as possible. Other organs, such as the uterus and fallopian tubes, may also be removed, especially if the cancer has spread. Chemotherapy following surgery is used to destroy any remaining cancer cells. Hormone therapy may be used to suppress tumor growth of refractory stromal tumors rather than the more common epithelial cell tumors. Immunotherapy is used to enhance the activity of the immune system. Radiation therapy is not typically used for ovarian cancer, because it is not as effective as other treatments.

New Treatments

In 2021, promising research was underway to develop treatments that stop tumor growth in treatment-resistant cancer cells and kill cancer stem cells, which are cancer cells that act like stem cells. These cells self-renew, enabling tumor initiation, and they differentiate into rapidly proliferating non-stem cells that can accelerate tumor growth.

Preventing and Predicting Recurrence

Ovarian cancer has a high relapse rate: between 70% and 80% of patients who achieve remission will have a recurrence of disease. When it recurs, it often comes back within the first two years following treatment, sometimes as early as six months after treatment ends. Because recurrence risk is so high, researchers are focusing on identifying precision assays, which are biomarkers to detect the disease earlier, predict recurrence, and guide

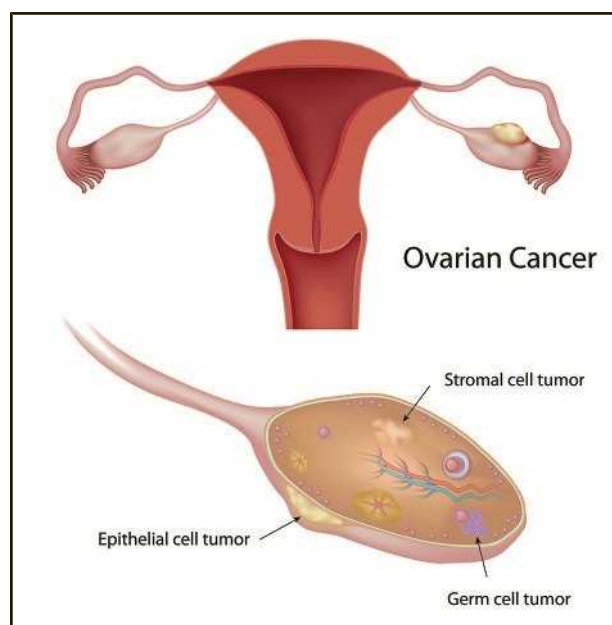


Illustration of ovarian cancer. (Alila Medical Media/Shutterstock)

treatment decision-making. In 2021, a clinical trial was launched to evaluate whether coffee products made using the leaves of the *Artemisia annua* plant can prevent ovarian cancer recurrence. The same year, Mijin Kim, PhD, a postdoctoral fellow in molecular pharmacology at Memorial Sloan Kettering Cancer Center in New York earned Marie-José Kravis Women in Science Endeavor fellowship grant for her work on a new sensor technology designed for early detection of ovarian cancer. The technology consists of carbon nanotubes that are able to detect and distinguish subtle differences in physiochemical properties of ovarian cancer biomarkers.

Screening

In 2021, the results of a British trial that followed more than 200,000 women ages 50 to 74 over the course of 16 years found that annual population screening for ovarian cancer detected cancers earlier, rather than in the later stages of the disease, but did not reduce deaths attributable to this aggressive disease. The investigators concluded that screening was not effective in women with no symptoms of ovarian cancer, but they asserted that for women who do have symptoms, and for those at high risk for ovarian cancer, screening and early detection can make a difference in terms of their quality of life. Screening recommendations for women at high risk of developing ovarian cancer may include:

- Pelvic examination every six months or yearly, starting at age 25 to 35

KEY TERMS

Alteration—Change or mutation in a gene, specifically in the DNA that codes for the gene.

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Laparoscopy—A diagnostic procedure in which a small incision is made in the abdomen, and a slender, hollow, lighted instrument is passed through it. The doctor can view the ovaries more closely through the laparoscope and, if necessary, obtain tissue samples for biopsy.

Laparotomy—An operation in which the abdominal cavity is opened up.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Pelvic examination—A physical examination performed by a physician, often associated with a Pap smear. The physician inserts a finger into a woman's vagina, attempting to feel the ovaries directly.

Transvaginal ultrasound—A probe is inserted into the vagina, and the ovaries are visualized using sound waves. Color Doppler imaging measures the amount of blood flow, as tumors sometimes have high levels of blood flow.

- Transvaginal ultrasound with color Doppler imaging every six months or yearly, beginning at age 25 to 35
- Yearly blood CA-125 testing, starting at age 25 to 35

Women with a *BRCA1* or *BRCA2* gene mutation are also at an increased risk for breast cancer. Screening recommendations for them may include:

- Monthly breast self-examination
- Examination of their breasts by a physician or nurse every six months or yearly, starting at age 25 to 35
- Mammograms (imaging of the breasts) yearly, starting at age 25 to 35

Specific screening programs may vary by physician. In addition to cancer screening, women with *BRCA1* or *BRCA2* gene mutations should know about preventive surgery options. They may consider having their healthy ovaries and/or breasts removed in order to reduce their risks

QUESTIONS TO ASK YOUR DOCTOR

- Ovarian cancer is common among the women in my family; what tests should I have to monitor my risk for the disease?
- What information is used to make a diagnosis of ovarian cancer?
- What determines the different stages of ovarian cancer?
- Which types of treatment are recommended for my ovarian cancer, and what side effects should I expect as a result of these treatments?

of developing ovarian and/or breast cancer in the future. Women may be more agreeable about having their ovaries removed, because ovarian cancer is difficult to detect; however, this surgery ends their ability to have children and automatically triggers the start of menopause. Both preventive surgeries greatly reduce a woman's cancer risk, but they can never eliminate it entirely.

For people with cancer or at high risk for it, support, education, and discussion groups are available.

Prognosis

Because ovarian cancer is not usually diagnosed until it is in an advanced stage, it is the most terminal of all the female cancers of the reproductive organs. As of 2021, it was estimated that only 48% of women diagnosed with ovarian cancer would survive past five years. When ovarian cancer is diagnosed before it has spread to other organs, about 93% of the patients will survive five years or more. Unfortunately, fewer than 20% of all cancers are found at this early stage.

There appears to be no difference in the survival rates of women who develop ovarian cancer because of *BRCA* mutations and those whose ovarian cancer is caused by another factor. Because unaffected people in a family with a *BRCA* mutation may be in high-risk screening programs, the hope is that they may be able to have any of their cancers detected earlier, which could give a better prognosis.

Resources

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- Bairi, Khalid El, ed. *Ovarian Cancer Biomarkers: Mapping to Improve Outcomes*. Springer, 2021.
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- "Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ®)—Patient Version." National Cancer Institute. April 9, 2021. <https://www.cancer.gov/types/ovarian/patient/ovarian-prevention-pdq> (accessed June 24, 2021).

ORGANIZATIONS

- American Cancer Society, 1599 Clifton Road NE, Atlanta, GA 30329, (800) 227-2345, <http://www.cancer.org>
- Facing Our Risk of Cancer Empowered (FORCE), 16057 Tampa Palms Boulevard W, PMB #373, Tampa, FL 33647, (954) 827-2200, info@facingourrisk.org, <http://www.facingourrisk.org>
- Gilda's Club, 195 West Houston Street, New York, NY 10014, (212) 647-9700, (212) 647-1151, <http://www.gildasclubnyc.org>
- National Cancer Institute. Office of Communications, 31 Center Drive, MSC 2580, Building 1 Room 10A16, Bethesda, MD 20892-2580, (800) 422-6237, <http://www.nci.nih.gov>
- National Ovarian Cancer Coalition, 12221 Merit Drive, Suite 1950, Dallas, TX 75251, (888) 682-7426, (214) 273-4201, <http://www.ovarian.org>

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and Emily R. Larson, PhD

Owren parahemophilia see **Factor V Leiden thrombophilia**

The GALE ENCyclopedia *of*
GENETIC DISORDERS

FIFTH EDITION

VOLUME

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BRIGHAM NARINS, EDITOR

P

Pallister-Hall syndrome

Definition

Pallister-Hall syndrome (PHS) is an extremely rare developmental disorder characterized by a spectrum of features ranging from mild (extra fingers or toes or a non-cancerous malformation in the hypothalamus region of the brain) to severe (laryngotracheal cleft, an opening between the windpipe and voice box that can cause death in newborns).

Description

First reported in 1980 by American geneticist Judith G. Hall and American medical doctor Philip D. Pallister, PHS is often diagnosed at birth. Some symptoms are immediately noticeable, including short limbs, extra digits, unusual facial features, or blockage of the anal opening. Some signs, such as intellectual disability and abnormalities of the heart, lung, or kidneys, must be diagnosed by a physician.

Newborn infants with PHS must be carefully monitored for signs of hypopituitarism (insufficient production of growth hormones by the pituitary gland), which can cause fatal complications if not promptly treated. Similarly, inadequate activity of the adrenal gland can be lethal in newborns. If not immediately recognized, an imperfectly formed anus can also develop serious complications in a newborn. PHS is sometimes inappropriately considered part of the CAVE (cerebro-acro-visceral early lethality) group of disorders.

Genetic profile

PHS has an autosomal dominant inheritance, meaning that it can occur in either sex and is passed from generation to generation when an abnormal gene is received from one parent and a normal gene is received from the other. Roughly 25% of diagnosed patients have a *de novo* mutation. Affected patients have a 50% chance

of passing the disorder to each offspring. In most such cases, signs and symptoms in affected offspring are similar to those of the parents. However, PHS is more commonly found in isolated cases involving individuals with no family history of the disorder. Truncating mutations in the middle portion of the *GLI3* gene affects zinc finger transcription factor leading to PHS (chromosomal locus 7p13). This gene provides instructions for making a protein that controls gene expression, the process that regulates whether genes are turned on or off in particular cells known as the sonic hedgehog signaling pathway. The *GLI3* mutations typically lead to the production of an abnormally short version of the GLI3 protein.

Demographics

Only about 100 cases of this very rare genetic disorder have been diagnosed worldwide. Males seem to be more affected than females. The disorder is not limited to particular ethnic groups. Some researchers have proposed that many patients with Pallister-Hall signs and symptoms have been misdiagnosed as having a related genetic disorder, isolated post-axial polydactyly type A (PAP-A).

Signs and symptoms

This disorder is noted for a wide range of signs and symptoms, including the following:

- Abnormalities of the head, neck, and facial areas including short neck, short midface, flat nasal bridge, small tongue, noticeable underdevelopment of one jaw compared to the other, asymmetric skull, cleft palate and other irregularities of the palate, cleft larynx or epiglottis, cysts on the gums, and ears that are small, low-set, and abnormally rotated toward the back of the head
- Hypothalamic hamartoblastoma, a noncancerous tumor in the hypothalamus. It grows at the same rate as nearby brain tissue, up to 4 cm across, taking the place of the hypothalamus. Most hypothalamic hamartomas have no symptoms, but in some cases they can cause

KEY TERMS

Adrenal gland—A triangle-shaped endocrine gland, located above each kidney, that synthesizes aldosterone, cortisol, and testosterone from cholesterol. The adrenal glands are responsible for salt and water levels in the body, as well as for protein, fat, and carbohydrate metabolism.

Hypothalamus—A part of the forebrain that controls heartbeat, thirst, hunger, body temperature and pressure, blood sugar levels, and other functions.

Pituitary gland—A small gland at the base of the brain that is responsible for releasing many hormones, including luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

neurological problems including gelastic epilepsy, which causes chest and diaphragm movements similar to those that occur during laughter.

- Inhibited flow of cerebrospinal fluid in the brain
- Limb abnormalities including short limbs, extra fingers or toes (central or postaxial polydactyly), webbing of fingers or toes (syndactyly), abnormally small fingernails or toenails, or absent nails
- Respiratory abnormalities including underdeveloped or abnormally developed lungs
- Anus lacking the usual opening
- Congenital heart defects
- Kidneys with abnormal development or placement
- Underdeveloped or abnormally developed adrenal, pituitary, or thyroid glands. This can lead to decreased activity of these glands. Some Pallister-Hall newborns cannot survive due to insufficient activity of the adrenal gland. An underdeveloped pituitary gland can also have lethal consequences. Symptoms of hypopituitarism may include hypoglycemia, jaundice, or unusual drowsiness.
- In males, unusually small penis, underdeveloped testicles, or failure of one or both testes to descend normally
- Retarded growth in most patients
- Mild intellectual disability
- Spinal abnormalities
- Dislocated hips
- Signs of puberty may appear unusually early.

Diagnosis

Both clinical examination and family history are used to diagnose PHS.

The hallmark clinical findings are hypothalamic hamartoma (a noncancerous tumor in the hypothalamus), as well as extra fingers or toes. Another sign useful for diagnostic purposes is bifid epiglottis, a cleft in the thin flap of cartilage behind the base of the tongue. This particular malformation is almost never seen except in cases of PHS. It rarely causes problems.

Prenatal testing may be conducted by ultrasound; however, its effectiveness in detecting PHS is not conclusive.

A molecular genetic test exists to scan the coding regions of the *GLI3* gene for mutations, as this is the only gene known to cause this disorder. The test can differentially diagnose a patient from other causes of polydactyly.

Treatment and management

Management depends on the specific signs and symptoms present.

Unless there are unusual complications, hamartoblastomas are usually left in place. However, it is sometimes necessary to surgically remove a hamartoblastoma when it causes undue pressure on the brain (hydrocephalus). Hamartoblastomas are usually monitored throughout the life of the patient. Typically, magnetic resonance imaging (MRI) is used because hypothalamic hamartomas are sometimes not visible on computerized tomography (CT) scans or cranial ultrasound examinations.

Because of the dangers posed by adrenal insufficiency, Pallister-Hall patients are often assessed for cortisol deficiency. Cortisol (hydrocortisone) is an important steroid hormone released by the adrenal glands. Patients are also likely to see an endocrinologist to evaluate their growth hormone, luteinizing hormone, follicle-stimulating hormone, and thyroid hormone levels. X-rays may be taken of limbs, and the kidneys may be examined by ultrasound. The epiglottis may be examined by laryngoscope, an instrument used to view the larynx through the mouth.

If patients show evidence of aspiration (when breathing forces foreign matter into the lungs) they should be seen immediately by an ear, nose, and throat specialist to determine whether laryngotracheal cleft is present.

Newborns with hypopituitarism should immediately be given hormone replacement therapy and watched closely for life-threatening complications.

A surgical procedure known as a colostomy may be needed to correct an imperforate anus.

QUESTIONS TO ASK YOUR DOCTOR

- What is the prognosis for my child?
- What will daily life be like for my child throughout his or her life?
- What are the treatment options available to us?
- Is there genetic testing available to us if we decide to have more children?
- How often should my child be monitored for signs/symptoms related to this disorder?

Similarly, extra toes or fingers can be surgically corrected on an elective basis.

Seizures, such as those caused by gelastic epilepsy, may require symptomatic treatment.

Whenever a new case of PHS is uncovered, it is advisable to also examine the parents and any offspring for the disorder. Evaluation for a parent is likely to include a cranial MRI, x-rays of hands and feet, and laryngoscopy.

In 2015, a clinical trial on PHS was sponsored by the National Human Genome Research Institute (NHGRI), seeking to evaluate the range of severity, natural history, molecular etiology, and pathophysiology of PHS. Researchers were investigating the relationship between Pallister-Hall and some disorders with similar characteristics, including Greig cephalopolysyndactyly syndrome (GCPS), McKusick-Kaufman syndrome (MKS), Bardet-Biedl syndrome (BBS), and oro-facial-digital syndromes (OFDs).

Prognosis

Because of the broad range and severity of Pallister-Hall signs and symptoms, the prognosis varies widely from case to case, though only a small percentage are known to have serious complications.

In families in which multiple cases of PHS exist, the prognosis for any new case is likely to be similar to the existing cases. Mild forms of the syndrome have been identified in a number of large, healthy families whose members are believed to have normal life expectancies.

In cases that occur in isolated individuals, the prognosis is based on the specific malformations present. Reviews of these malformations as reported in scientific literature have limited usefulness because published cases tend to be more severe than those normally encountered.

Unless there are life-threatening malformations such as hypopituitarism, the prognosis for these random cases is considered excellent.

There is a 50% chance that any child of a Pallister-Hall patient will be affected.

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American Brain Tumor Association, 8550 W. Bryn Mawr Ave., Suite 550, Chicago, IL 60631, (773) 557-8750 or (800) 886-2282, (773) 577-8738, info@abta.org, <http://www.abta.org>

Hope for Hypothalamic Hamartomas, PO Box 721, Waddell, AZ 85355, admin@hopeforhh.org, <http://hopeforhh.org>.

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>.

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Pallister-Killian syndrome

Definition

Pallister-Killian syndrome (PKS) is a rare chromosome abnormality in which a person has four copies of the short arm of chromosome 12 instead of the normal two copies. Affected individuals have unusual facial features, intellectual disabilities, seizures, patchy color differences in the skin, and various other physical

abnormalities. Many fetuses with PKS die during pregnancy or soon after birth.

Description

PKS was first described in 1977. The first two patients reported by Dr. Phillip Pallister, an American pediatrician and geneticist, were adults with severe intellectual disabilities, unusual facial features, severe lack of muscle strength, and pale areas on their skin. In 1981, Austrian Dr. Wolfgang Killian and his colleague Dr. Maria Teschler-Nicola described a child with intellectual disabilities, unusual facial features, pale skin on the face, and absence of hair at the front of the scalp.

PKS may also be called Killian syndrome, Killian/Teschler-Nicola syndrome, Pallister mosaic syndrome, or Teschler-Nicola/Killian syndrome. This syndrome is also known as tetrasomy 12p mosaicism or isochromosome 12p syndrome based on the characteristic chromosome abnormality detected via laboratory studies. PKS is called mosaic because the characteristic chromosome abnormality that causes the syndrome appears only in a fraction of the total cells examined.

Genetic profile

PKS is a sporadic disorder, which means that it appears to occur at random. The chromosome problem that causes PKS, tetrasomy 12p, does not appear to run in families. PKS is not specifically associated with any specific chemical or environmental exposures.

Tetrasomy 12p is characterized by the presence of four copies of the short arm of chromosome 12, instead of the normal two copies. This chromosome abnormality is not found throughout an affected person's body. Chromosome analysis performed on the blood of persons with PKS virtually always shows normal results. The characteristic chromosome abnormality can, however, be detected via chromosome analysis on skin cells. Through chromosome analysis, tetrasomy 12p is identified due to the presence of what appears to be an extra chromosome composed of two copies of the short arm of chromosome 12. This chromosome composed of two copies of the short arm of chromosome 12 is called an isochromosome. In tetrasomy 12p, there is a total of four copies of the short arm of chromosome 12: there are the two normal copies, plus the two abnormal copies located on the extra isochromosome.

Demographics

The incidence of PKS is uncertain and is estimated around 1 in 25,000. PKS occurs at random; however, an association with advanced maternal age (35 years or older) has long been documented. Though PKS may occur more frequently in babies born to mothers age 35

KEY TERMS

Bifid uvula—The uvula is the small, teardrop-shaped piece of flesh hanging in the back of the throat; the uvula is bifid if the bottom area is split in two parts.

Cystic hygroma—Birth defect that appears as a soft bulging under the skin at the neck; the bulging is actually abnormal growths of sac-like structures filled with lymphatic fluid.

Diaphragmatic hernia—An abnormal opening in the diaphragm, the layer of muscle that separates the chest cavity from the abdominal cavity.

Isochromosome—A chromosome is normally composed of two sections referred to as p and q; instead, an isochromosome is an abnormal chromosome made up of two p sections or two q sections.

Mosaic—Refers to a person or organ composed of two or more genetically different cell types.

Tetrasomy—Refers to the presence of four parts or copies of a chromosome or part of a chromosome.

or older, the syndrome still may occur in babies born to mothers of any age. PKS occurs strictly due to an abnormality of the chromosomes.

Signs and symptoms

Many infants with more severe physical defects associated with PKS die *in utero* or shortly after birth. Other persons with PKS have lived at least into their 20s. All persons with PKS have some level of intellectual disability or developmental delay.

The features of PKS may vary significantly between affected persons. The most typical person with PKS will have profound intellectual disabilities, delayed development, lack of muscle tone, light- and/or dark-colored areas of skin, lack of scalp hair above the temples, and unusual facial features. The facial features characteristic for PKS include a large forehead, widely spaced eyes with vertical folds of skin at the inner corners, droopy eyelids, short and upturned nose, full cheeks, lengthened distance between the nose and upper lip, and small chin.

Persons with PKS often have deafness, absent or minimal speech, poor vision, and seizures. Additionally, individuals with PKS have been reported as having short, wide hands with short fingers, while others have extra fingers or toes. Some affected persons have had cleft palate and some have had a bifid uvula (cleft, or split, uvula). The teeth come in later than normal in persons with PKS.

Heart defects may be present, and the sac normally surrounding the heart, the pericardium, may be missing. Additionally, there may be small patches of exposed tissue where the skin did not develop.

Many individuals with PKS have been reported to have extra nipples, and some have a hernia around the navel. Some persons with PKS have problems with the intestines or anus. Many have birth defects involving the genitals or internal reproductive organs and others have disorganized or cyst-filled kidneys. A small tail-like stub at the bottom of the spine was reported in at least one person affected with PKS.

The features of PKS change over time. The lack of hair above the temples, which is common in younger persons with PKS, mostly resolves by age five. Additionally, an affected individual's initial lack of muscle tone gives way to fixation of the joints later in life.

Diagnosis

PKS may be suspected from a person's physical features, but a diagnosis requires that a person has the characteristic chromosome abnormality, tetrasomy 12p. PKS is different from many types of chromosomal syndromes in that the causative chromosome abnormality is not found from chromosome studies on the blood. Chromosome testing on skin cells will show the characteristic chromosome abnormality in at least some of the cells. It is believed that the characteristic chromosome abnormality, the isochromosome 12p, does not show up in the blood cells because the abnormal isochromosome is lost in the rapid cell division that creates these blood cells. Diagnosis of PKS has traditionally required a skin biopsy, but recent reports indicate that the diagnosis can be made using cells scraped from the inside of the cheek.

Many cases of PKS may be diagnosed prenatally. PKS is detectable by amniocentesis, a routine test offered in pregnancies suspected to be at risk for chromosome problems. PKS may be suspected when certain physical abnormalities are detected on an ultrasound during pregnancy. In pregnancies where PKS has been diagnosed in an unborn baby, many ultrasounds have shown an increased amount of fluid around the baby, in addition to other physical abnormalities, including short arms and legs, heart malformations, diaphragmatic hernia, cystic hygroma, and unusually flat profile of the face.

Treatment and management

There is no treatment or cure for PKS or for the intellectual disabilities and developmental delays associated with this syndrome. Persons with PKS are treated for the symptoms they display. Individuals with PKS often take medications for seizures; some may have surgeries due

to birth defects involving the diaphragm, intestines, anus, kidneys, genitals, or heart. Physical therapy and occupational therapy may be helpful for development of muscle tone and reduction of joint fixation.

Prognosis

Many infants with PKS die before they are born (*in utero*), or soon after birth. Some affected individuals have been reported to live into their 20s. Many have severe to profound intellectual disabilities and have difficulties with self-care. A few reports have described affected persons with milder intellectual impairment.

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ORGANIZATIONS

- Chromosome Disorder Outreach, PO Box 724, Boca Raton, FL 33429-0724, (561) 395-4252, info@chromodisorder.org, <http://www.chromodisorder.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06180, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>
- PKS Kids, PO Box 12211, Green Bay, WI 54307, gpeters@pkskids.net, <http://www.pkskids.net>

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Pancreatic beta cell agenesis

Definition

Pancreatic beta cell agenesis is a rare disorder in which a child is born with no beta cells—the cells in the pancreas that produce insulin—resulting in diabetes.

Description

Diabetes mellitus is a disease caused by elevated blood sugar and can result in numerous medical problems that can affect the kidney, eyes, cardiovascular system, skin, and joints. There are two common types. Type 1 results from the destruction of the insulin-producing cells (beta cells) of the pancreas and usually occurs in children of at least one year of age or young adults. Injected insulin is required to allow glucose (sugar) to enter the body's cells to be used for energy. Type 2 diabetes results from the body cells' decreased ability to respond to the insulin the body produces. In contrast to these two types, neonatal diabetes is extremely rare. Neonatal diabetes is usually transient, meaning that it goes away after some time. It appears to be caused by immaturity of the beta cells; about half of all babies with this form of the disease recover and do not require insulin earlier than three months of age. Fewer than 40 cases of permanent neonatal diabetes had been reported. Reported causes of neonatal diabetes have included absence of the whole pancreas, absence of the clusters (called islets) that contain the beta cells, and absence of the beta cells themselves. This last form is known as pancreatic beta cell agenesis.

Only one confirmed case of pancreatic beta cell agenesis has been reported (1993). This was in an infant girl who had a low birth weight and showed high glucose (sugar) in her blood during a routine test. She was pale, with a low body temperature, rapid breathing, and low muscle tone. Her health was further complicated by a diagnosis of an additional metabolic disorder, methylmalonic acidemia (MMA). She died at the age of 16 days. An autopsy showed that her pancreas had islets, which are the bundles of cells that typically contain insulin-producing cells as well as cells that produce other hormones. However, the islets in her pancreas did not contain the insulin-producing cells.

Genetic profile

Pancreatic beta cell agenesis may be an autosomal recessive disorder. This means that a child would have to inherit two abnormal copies of a specific gene, one from each parent, in order to have the disorder. The infant described had both pancreatic beta cell agenesis and MMA, also known to be an autosomal recessive disorder. A gene causing MMA is located on chromosome 6, and studies of this child's genes and chromosomes showed that she inherited two identical copies of at least part of chromosome 6 from her father, a condition known as paternal uniparental isodisomy, instead of one copy of this region from each parent. The MMA was caused by the inheritance of two identical abnormal *MMA* genes from her father, and the beta cell agenesis was then

KEY TERMS

Agenesis—Failure of an organ, tissue, or cell to develop or grow.

Beta cells—Specialized cells of the pancreas that make insulin.

Diabetes mellitus—The clinical name for common diabetes. It is a chronic disease characterized by inadequate production or use of insulin.

Insulin—A hormone produced by the pancreas that is secreted into the bloodstream and regulates blood sugar levels.

Metabolic disorder—A disorder that affects the metabolism of the body.

Metabolism—The total combination of all the chemical processes that occur within cells and tissues of a living body.

Pancreas—An organ located in the abdomen that secretes pancreatic juices for digestion and hormones for maintaining blood sugar levels.

believed to have been caused by the inheritance of two abnormal copies of another gene. On other chromosomes, it has been shown that certain genes work only when they come from the mother and others only from the father. Several cases of transient neonatal diabetes have also featured two identical copies of paternal chromosome 6 or other abnormalities of chromosome 6. This suggests that there may be a connection between pancreatic beta cell agenesis and transient neonatal diabetes. It is believed that the relevant region of chromosome 6 contains a gene that delays the production of insulin and works only when inherited from the father. As of 2015, there were no reports in the literature describing the status of the beta cells in infants with transient neonatal diabetes. Presumably, this is because a pancreatic biopsy would be required, and this procedure would be too strenuous for a fragile baby.

Demographics

The overall incidence of neonatal, or newborn, diabetes mellitus is approximately 1 in 400,000 to 1 in 600,000 live births, and many cases are transient, with the infants requiring insulin for an average of three months. These infants do appear to be at an increased risk of developing type 2 diabetes in young adulthood. Fewer than 40 cases of well-documented permanent neonatal diabetes have been reported. Only two infants with neonatal diabetes have demonstrated (by autopsy) a complete

lack of insulin-producing cells in the pancreas at birth. The first child had both pancreatic beta cell agenesis and another disorder called methylmalonic acidemia. She also had low birth weight, typical of children with neonatal diabetes because of the inability to metabolize glucose. The second child was of normal birth weight, suggesting that she originally had beta cells that were subsequently destroyed, perhaps by an autoimmune process as in type 1 diabetes. Both of these infants died in the newborn period.

Signs and symptoms

Symptoms of neonatal diabetes include lethargy, dehydration, and breathing difficulties. In the laboratory, high levels of glucose (sugar) in the blood and urine are demonstrated. Children with neonatal diabetes, including the child with pancreatic beta cell agenesis, are generally of low birth weight.

Diagnosis

Neonatal diabetes, like other forms of diabetes, is diagnosed by high blood sugar levels. Permanent and transient forms of neonatal diabetes are indistinguishable at initial diagnosis. Determining if the cause of neonatal diabetes is pancreatic beta cell agenesis was done after death in the published cases by studying the pancreas from an autopsy; a pancreatic biopsy would be required to make this diagnosis in a living child.

Treatment and management

Pancreatic beta cell agenesis, like type 1 and some cases of type 2 diabetes mellitus, is treated by insulin injection.

Prognosis

Both children that were reported to have an absence of beta cells were diagnosed through autopsy, because they died at birth. The second child's prognosis was complicated by the fact that she had the additional MMA disorder. As of 2015, it remained unknown if any living children had pancreatic beta cell agenesis.

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- American Diabetes Association. Attn: Center for Information, 1701 N. Beauregard St., Alexandria, VA 22311, (800) 342-2383, askada@diabetes.org, <http://www.diabetes.org>
- Juvenile Diabetes Research Foundation International (JDRF), 26 Broadway, New York, NY 10004, (212) 785-9500 or (800) 533-2873, (212) 785-9595, info@jdrf.org, <http://www.jdrf.org>

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Pancreatic cancer

Definition

The pancreas is an important gland found in the abdomen behind the stomach. The pancreas secretes a fluid that breaks down fats and proteins and also releases hormones such as insulin to control blood sugar levels. Pancreatic cancer is the uncontrolled growth of malignant cells of the pancreas. A higher than average number of pancreatic cancer cases occurring in the same family is known as familial pancreatic cancer. However, according to the American Society of Clinical Oncology, more than 90% of families who meet the criteria for genetic testing for pancreatic cancer and have such testing will not have the mutation. This means that shared environmental factors also contribute to the risk for pancreatic cancer.

Description

Most pancreatic cancer grows from cells from the exocrine pancreas, the secreting portion of the pancreas. The most common appearance of pancreatic cancer cells is gland-like, which is termed adenocarcinoma. According to Natalia Khalaf and colleagues, more than 85% of all pancreatic cancers are adenocarcinomas.

In most cases, it is difficult to determine the cause of pancreatic cancer. Both environmental as well as genetic

risk factors have been implicated in pancreatic cancer. A high-fat diet has been linked to increased pancreatic cancer risk, whereas diets high in vegetables and fruits seem to lower the risk. Smoking is known to increase the risk of pancreatic cancer; it is estimated that as many as 20% of pancreatic cancer cases are linked to smoking. Smokeless tobacco products have also been associated with an increased risk for pancreatic cancer. Alcohol use has been linked with increased pancreatic cancer risk. Obesity is another risk factor for pancreatic cancer.

Certain occupations, such as farming or manufacturing, may increase the risk of pancreatic cancer. Multiple studies have shown that exposure to pesticides increases the risk. The relationship of diabetes to pancreatic cancer has been closely studied. It is uncertain whether diabetes is the cause or the symptom of pancreatic cancer. Long-term inflammation of the pancreas, chronic pancreatitis, increases the risk of pancreatic cancer. Genetic risk factors have also been reported.

Genetic profile

Several studies have reported a higher rate of pancreatic cancer in relatives of individuals with the disease. Characteristic features of a hereditary form of pancreatic cancer include having two or more first-degree relatives diagnosed with pancreatic cancer or one first-degree relative diagnosed with pancreatic cancer under the age of 50. Some risk is thought to be due to known hereditary conditions, whereas, in other cases, a known genetic syndrome has not been determined.

There are several known hereditary cancer syndromes that increase the risk of pancreatic cancer. Mutations in the *BRCA1* and *BRCA2* genes have been clearly

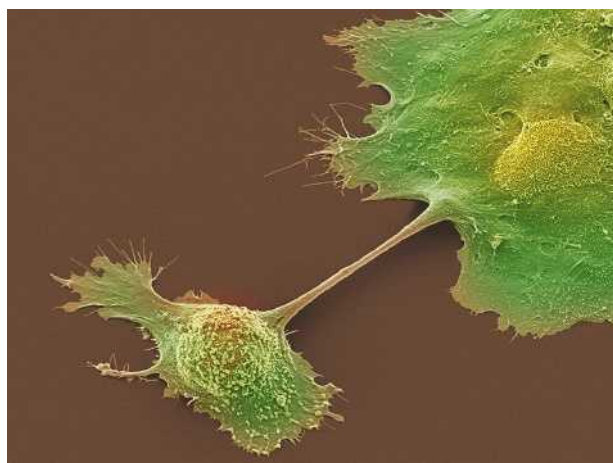
linked to increases in breast and ovarian cancer, as well as an increased risk for pancreatic cancer. Mutations in the *PALB2*, *FANCC*, *FANCG*, and *ATM* genes have also been linked to increased risks for pancreatic cancer. Changes, or mutations, in the *CDKN2A* (p16) gene responsible for familial atypical multiple mole melanoma syndrome (FAMMM) can increase risks of melanoma, a type of skin cancer, and also incur a 20-fold to 47-fold increased risk for pancreatic cancer. Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome, is caused by mutation in several genes, including the (*MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*) gene. These genes increase the risk for colon cancer and other cancers, including pancreatic cancer, in some families. Another colon cancer syndrome caused by mutations in the *APC* gene has been linked to pancreatic cancer. Peutz-Jeghers syndrome, juvenile polyposis syndrome (JPS), and Li-Fraumeni syndrome cause slightly increased risks of pancreatic cancer, in addition to the other symptoms of the disorders.

Another hereditary syndrome believed to be associated with pancreatic cancer is hereditary pancreatitis, caused by mutations in several different genes: *PRSS1*, *SPINK1*, and *CFTR*. Hereditary pancreatitis causes long-term, recurrent inflammation of the pancreas. Individuals with hereditary pancreatitis are estimated to have a 40% risk of pancreatic cancer by age 70.

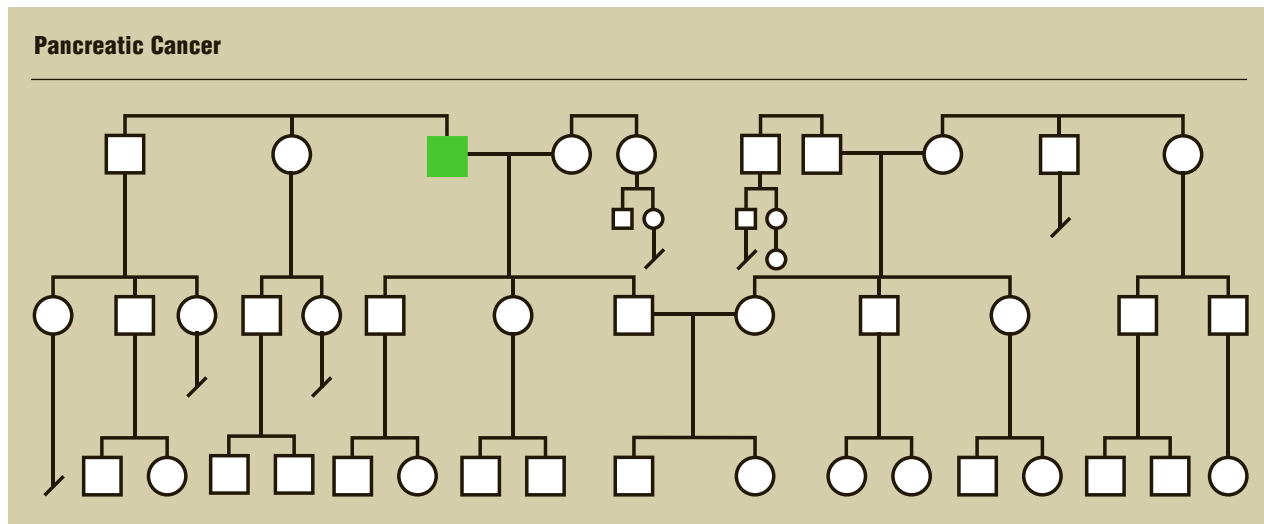
All of these disorders are inherited in an autosomal dominant pattern. With autosomal dominant inheritance, men and women are equally likely to inherit the syndrome, and children of affected individuals are at 50% risk of inheriting the gene alteration.

Genetic testing is available for many of these known syndromes, but due to the complexity of the disorders, genetic counseling should be considered before testing. Some experts believe that the heritability of pancreatic cancer is as high as 21%. For example, in a study of nearly 3,568 people with pancreatic cancer and 3,363 controls, all of European descent and who were genotyped by Fei Chen and colleagues, the researchers found that chromosome 9 had the highest levels of genetic variations, followed by chromosomes 7, 8, and 1.

Some families with increased pancreatic cancer rates do not have a known genetic syndrome as the cause. It is possible that environmental factors or chance could explain some cases of pancreatic cancer in families; however, it is also possible that other as yet unknown genetic causes could explain some cases of familial pancreatic cancer. While genetic testing may not be available in all cases, families may participate in collections, or registries, of familial pancreatic cancer cases for research purposes.



Colored scanning electron micrograph of pancreatic cancer cells. (Steve Gschmeissner/Science Source)



Pancreatic cancer: pedigree analysis chart (Gale)

Demographics

The American Cancer Society (ACS) estimated that 60,430 people, including 31,950 men and 28,480 women, would be diagnosed with pancreatic cancer in 2021. The ACS also estimated the deaths from pancreatic cancer at 48,220 deaths in 2021, including 25,270 men and 22,950 women. Pancreatic cancer was the fourth leading cause of death in both men and women, representing 8% of all deaths from cancer in the United States in 2021. The ACS also estimates that the lifetime risk of a person in the United States developing pancreatic cancer is 1 in 64. Survival rates for pancreatic cancer depend on whether the cancer is localized, regional, or distant (metastasized far from the original tumor). For example, according to the ACS, the 5 year survival rate for localized cancer is 39%, while the regional survival rate in 5 years is 13%. However, many pancreatic cancers have metastasized at the time of diagnosis, and the 5 year survival rate at this stage is only 3%.

Signs and symptoms

Since the symptoms of pancreatic cancer typically do not develop until the cancer has progressed to an advanced state, it is difficult to diagnose pancreatic cancer at an early and much more treatable stage, and this is a key problem. In the future, genetic testing may identify individuals at risk for pancreatic cancer before they are symptomatic, so that these individuals can be closely followed and tested for possible cancer. For example, according to the American Society of Clinical Oncology (ASCO), all individuals with pancreatic adenocarcinoma should undergo genetic testing, as well as receive a complete review of their family cancer history. ASCO says

that up to 10% of all pancreatic adenocarcinomas are familial and some genes increase the risk for pancreatic cancer from 4 to 40%. Individuals with a known family history for pancreatic cancer should be carefully followed by their physicians. For example, the *BRCA2* gene, which is associated with cancer of the breast, ovary, melanoma, and the prostate, also increases the risk for pancreatic cancer. Some researchers are seeking laboratory or genetic markers that may indicate an increased risk for pancreatic cancer. For example, machine learning, also known as artificial intelligence, was engaged by Ananya Malhotra and colleagues in a study in which the medical records of about a thousand patients with pancreatic cancer over the period 2005-2009 were input to the computer, along with data from about 4,500 patients who did not have pancreatic cancer. The goal was to find patterns among the patients with pancreatic cancer, and 57 such patterns were found. The new data was able to correctly predict 41% of the patients at high risk for pancreatic cancer up to 20 months before their actual diagnosis. This information could not help patients who were already diagnosed, but it theoretically could help individuals in the general clinical population. The experts said that their algorithm could provide an early diagnosis in many patients with pancreatic cancer. The future goal is to apply this learned information to primary care patients not yet diagnosed with pancreatic cancer but who may be unknowingly at risk for the disease.

The symptoms of pancreatic cancer may include the following:

- unintended weight loss
- loss of appetite
- fatigue

- abdominal or back pain
- jaundice (yellowish color to skin and eyes)
- digestive problems, including greasy stool
- sudden diabetes onset
- nausea and vomiting

Diagnosis

If pancreatic cancer is suspected, a physical examination often is done first, and certain body imaging tests may be recommended. One imaging test that may be done is a computed tomography (CT) scan. This exam creates pictures of the interior of the body from computer-analyzed differences in x-rays passing through the body. Evidence of substantial tumors or any metastasis (spreading of cancer) can be detected by CT scanning. Once a biopsy is taken, the tissue sample is examined by CT for evidence of cancer and this typically determines the diagnosis.

Ultrasound is another method of viewing internal body structures. The type of ultrasound used to look at the pancreas (and other parts of the upper intestine) is called endoscopic ultrasonography (EUS). In ultrasound, sound waves are passed into the body and a computer develops an image based on the returned sound waves. Ultrasound is generally less expensive and more easily available than CT; however, there are limitations to the use of ultrasound in viewing the pancreas. Ultrasound may be used in addition to CT. MRI/magnetic resonance cholangiopancreatography (MCRP) and endoscopic retrograde cholangiopancreatography (ERCP) are methods of viewing the pancreas by inserting a thin tube down the throat, injecting of dye into the pancreatic and bile ducts, and visualizing with an MRI or an x-ray.

Once the tumor and any metastasis have been identified and the biopsy tissue evaluation has been done, the tumor can be staged. Staging is a ranking system that provides a method of describing the extent and characteristics of a cancer. Staging can be used to help determine the treatment and prognosis for a given cancer.

Unfortunately, it is very difficult to diagnose pancreatic cancer at an early stage, which makes screening for this cancer especially challenging.

Treatment and management

Surgery may provide the best chance of a cure, though surgery is not often possible due to the spread of cancer by the time it is diagnosed. Removal of all or part of the pancreas and other areas, such as the duodenum (the first part of the small intestine), is known as the Whipple procedure. Complications of this surgery

include infection and bleeding. Fewer than 20% of newly diagnosed pancreatic cancers are operable.

Chemotherapy is cancer-killing medicine that has been found to increase survival in some patients. This drug can be given intravenously or orally. Once in the bloodstream, chemotherapy agents reach other parts of the body. There are different chemotherapy agents and the side effects may be different as well, including nausea, hair loss, low blood counts, and other effects.

Recent improvements in radiation, high-energy rays directed at cancer cells, have made this therapy more effective. Although cures due to radiation therapy are uncommon, relief from pain and increased survival are possible. Side effects of radiation therapy may include skin changes, upset stomach, and other effects.

Sometimes, surgery, radiation, or other therapies are performed to relieve symptoms rather than cure the cancer. This is known as palliative treatment.

Involvement in research as part of clinical trials may be offered to certain patients. Although treatments through clinical trials may not be proven, it is an opportunity to potentially benefit from new therapies.

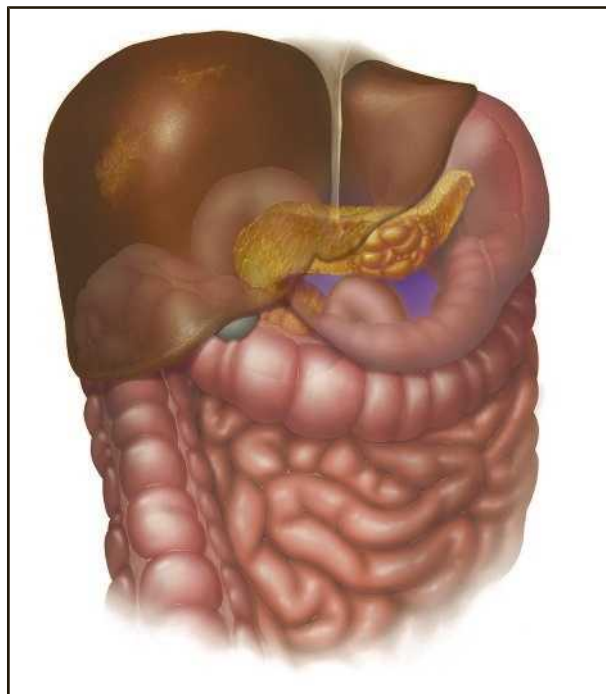
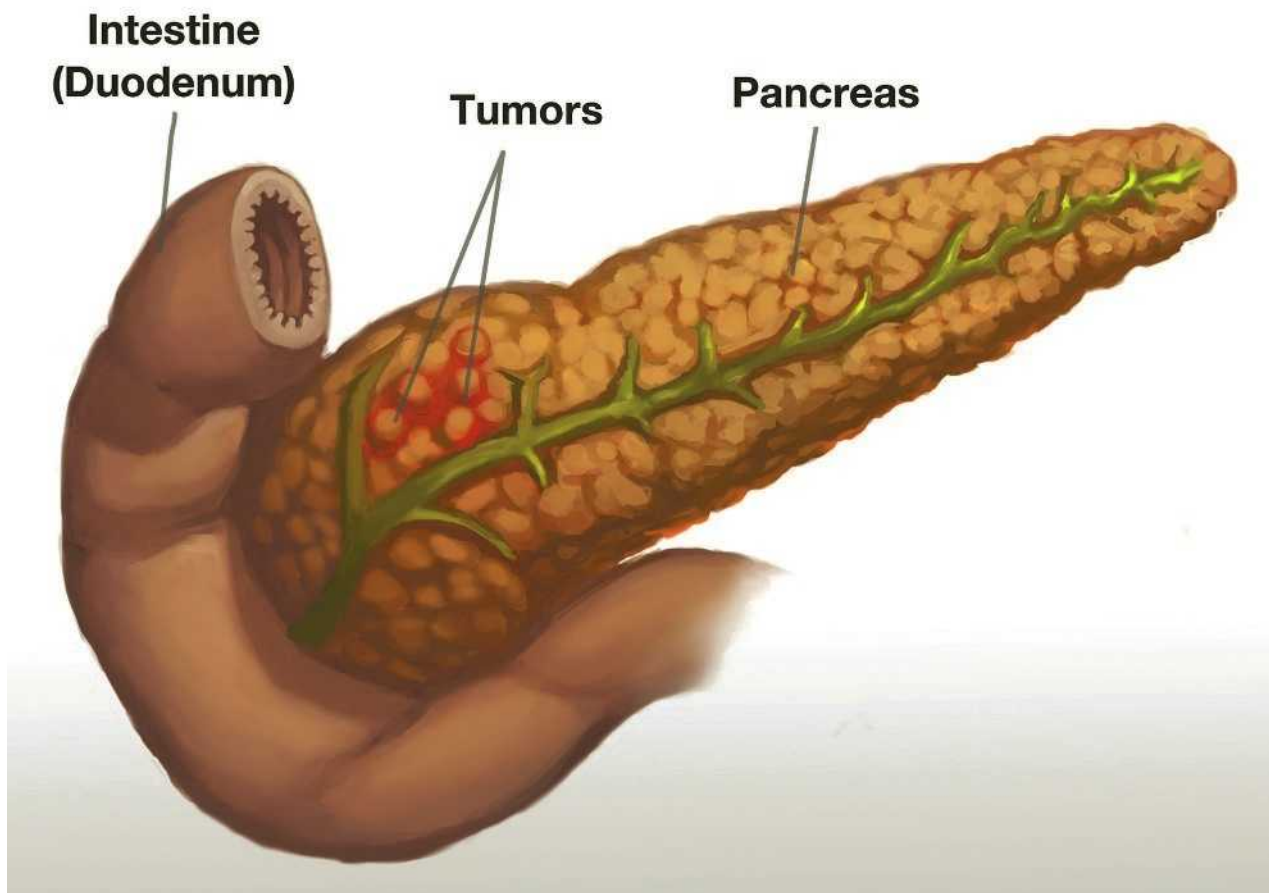


Illustration of pancreatic cancer and the location of the pancreas (between the stomach, liver, spleen, hepatobiliary system, and large and small intestines). Metastatic cancer is common among people with pancreatic cancer, most commonly spreading to the liver. (Molecule Medical Arts/ Science Source)

Pancreatic Cancer



Tumors are shown in reddish tint on the left end of the pancreas. The pancreatic duct is in green and the duodenum is reddish brown. (Spencer Sutton/Science Source)

Screening before cancer development may be considered for patients with a higher risk of the disease either due to a known genetic syndrome or to a family history of pancreatic cancer. ERCP, MCRP, and ultrasound have been used for screening purposes; however, the usefulness and cost-effectiveness of these tests for screening needs further evaluation. Surveillance may be considered for persons with two or more close relatives (first-degree family members) with pancreatic cancer, or with one close relative (first-degree) with pancreatic cancer at an early age (before age 50), or with two or more distant relatives (second-degree), one of which was affected before age 50.

Prophylactic pancreatectomy, surgical removal of the pancreas before any cancer development, has been considered in cases with a hereditary risk. The concern with prophylactic pancreatectomy is that there is a risk

of serious complications, and consequently the decision must be weighed carefully. Some experts are seeking possible preventive measures against pancreatic cancer; for example, Daoyan Wei and colleagues report that vitamin D supplementation is an area of current research in 2021. Many people with pancreatic cancer are deficient in vitamin D, which may be a related factor, and further research is needed.

Clinical trials

Clinical trials on pancreatic cancer are currently sponsored by the National Institutes of Health (NIH) and other agencies, such as the National Cancer Institute (NCI). In 2021, the NIH reported there were 890 active studies on pancreatic cancer, and many of these studies included screening, treatment, and genetic studies.

KEY TERMS

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

BRCA2—Gene, when mutated, known to cause increased risks of breast, ovarian, and, possibly, pancreatic cancer.

Cationic trypsinogen gene—Gene known to cause hereditary pancreatitis when significantly altered.

CDKN2A, or p16—Gene, when altered, known to cause familial atypical multiple mole melanoma (FAMMM) syndrome and possibly increased pancreatic cancer risk.

Chemotherapy—Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of the cancerous cells or by killing the cancer cells.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Duct—Tube-like structure that carries secretions from glands.

Duodenum—Portion of the small intestine nearest the stomach; the first of three parts of the small intestine.

Endoscopic retrograde cholangiopancreatography (ERCP)—A method of viewing the pancreas by inserting a thin tube down the throat into the pancreatic and bile ducts, injection of dye, and performing x-rays.

Exocrine pancreas—The secreting part of the pancreas.

First-degree relative—A closely related family member. Examples are parent/child, brother/sister, brother/brother, or sister/sister. First-degree relatives share 50% of their genes in common.

Hereditary nonpolyposis colon cancer (HNPCC)—A genetic syndrome causing increased cancer risks,

most notably colon cancer; also called Lynch syndrome.

Insulin—A hormone produced by the pancreas that is secreted into the bloodstream and regulates blood sugar levels.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Li-Fraumeni syndrome—Inherited syndrome known to cause increased risk of different cancers, most notably sarcomas.

Melanoma—Cancerous tumor, usually of the skin.

Metastasis—The spreading of cancer from the original site to other locations in the body.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual or manifest as a disease and can be transmitted to offspring.

Palliative—Treatment done for relief of symptoms rather than a cure.

Pancreas—An organ located in the abdomen that secretes pancreatic juices for digestion and hormones for maintaining blood sugar levels.

Pancreatitis—Inflammation of the pancreas.

Peutz-Jeghers syndrome—Inherited syndrome causing polyps of the digestive tract and spots on the mouth, as well as increased risk of cancer.

Radiation—High-energy rays used in cancer treatment to kill or shrink cancer cells.

Second-degree relative—Two relatives (grandmother/father and grandchild or aunt/uncle and niece/nephew) who share 25% of their genes in common.

Staging—A method of describing the degree and location of cancer.

Whipple procedure—Surgical removal of the pancreas and surrounding areas, including a portion of the small intestine, the duodenum.

Examples include:

- RNA precision oncology in advanced pancreatic cancer. (NCT04476537)
- Systematic hereditary pancreatic cancer risk assessment and implications for personalized therapy. (NCT03060720)
- Biomarkers in patients with pancreatic cancer. (NCT03311776)

Clinical trial information is constantly updated by the NIH, and the most recent information on pancreatic cancer trials can be found at: <http://clinicaltrials.gov>

Prognosis

It is difficult to diagnose pancreatic cancer early, and, therefore, the cancer frequently has spread to other

QUESTIONS TO ASK YOUR DOCTOR

- What stage is my pancreatic cancer?
- What are the best treatment options for my newly diagnosed pancreatic cancer?
- Where can I learn more about clinical trials for pancreatic cancer patients, and how can I find out if I will qualify for a trial?
- Are there any screening options for healthy individuals with a known increased risk for pancreatic cancer?

locations in the body, such as the liver or lymph nodes (part of the immune system). Most long-term survivors originally had smaller tumors and no spreading of the cancer. Of course, every case of pancreatic cancer is different, and it is difficult to predict the course and survival for each individual patient. The prognosis of individuals with hereditary risk factors is dependent on the syndrome, if any, and the aggressiveness of the particular cancer.

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- American Cancer Society (ACS), 250 Williams St., NW, Atlanta, GA 30303-1002, (404) 320-3333, <http://www.cancer.org>
- Canadian Cancer Society (CCS), Suite 200, 10 Alcorn Ave., Toronto, ON, Canada M4V 3B1, (416) 961-7223, (416) 961-4189, ccs@cancer.ca, <http://www.cancer.ca>
- National Cancer Institute (NCI), 6116 Executive Blvd., Suite 3036A, MSC 8322, Bethesda, MD 20892-8322, (800) 422-6237, cancergovstaff@mail.nih.gov, <http://cancer.gov>
- National Comprehensive Cancer Network (NCCN), 275 Commerce Dr., Suite 300, Fort Washington, PA 19034, (215) 690-0300, (215) 690-0280, <http://www.nccn.org>

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Pancreatic carcinoma see **Pancreatic cancer**

Panic disorder

Definition

A panic disorder is a psychological state characterized by acute and rapid onset feelings that engulf and overwhelm the affected person with a deep sense of helplessness and impending doom. Panic disorder is an anxiety disorder characterized by worry and fear, as well as by physiological changes such as a rapid pulse and elevated blood pressure. The main feature of panic disorder (PD) is a history of previous panic attacks (PA). However, the first time individuals experience a panic attack, they may feel certain they are having a heart attack and risking death. As a result, they often present to a hospital emergency room, where they are evaluated for a possible heart attack, cleared from that diagnosis, and diagnosed instead with a panic disorder (PD). PA symptoms are pronounced, and the affected person may gasp for air, have a rapid rate of breathing (hyperventilate), feel dizzy or light-headed, and develop a loss of sensation (paresthesia). Most panic attacks last three to ten minutes, and it is rare for one to extend in duration more than 30 minutes.

Description

The essential characteristics of panic disorder (PD) consist of specific and common criteria. The affected person usually has recurrent, uncontrollable, and unexpected panic attacks, which are the active presentation of panic disorder. The panic attack is characterized by a discrete, rapid onset of feeling intense fear or discomfort and a feeling of unreality. Affected persons have several physical signs and cognitive symptoms, and they usually react in a manner showing fear of imminent death or disaster. Individuals having a PA commonly exhibit signs of heavy sweating, a racing heartbeat, chest pain, shortness of breath, and the perception of feeling smothered. The PA is usually followed by a period of one or more months of thought processes that focus on irrational fears.

Genetic profile

Panic disorder can run in families, and twin studies suggest that about 20% of patients who meet the criteria for diagnosis have first-degree relatives with the disorder. In families with no history of affected first-degree relatives, the prevalence decreases to 4%. The ratio between monozygotic twins (identical) to dizygotic (nonidentical) twins is 5:1 for PD. British researchers have also found more than 500 genes linking anxiety and depression in some individuals, and this genetic finding affects at least 1.4 million people in the United Kingdom who report suffering from both depression and anxiety. Recent evidence suggests that there is a genetic mutation in the *SLC6A4* gene. This gene encodes for a molecule that is related to a brain chemical called serotonin, which is known to affect mood. If the transport of serotonin is imbalanced, certain parts of the brain may not receive the correct stimulus, causing alterations in mood.

Another gene possibly associated with PD is the *COMT* gene that encodes the enzyme catechol-O-methyltransferase. Mutations in this gene have been associated with other disorders that affect thought and emotion, with studies suggesting that these conditions may be due to inefficient degradation of catecholamines, a family of neurotransmitters that include adrenaline and dopamine.

Demographics

PD usually begins during the affected person's late teens or 20s and is uncommon after the age of 35 years. Global studies suggest that the lifetime prevalence of PD is between 1.5% and 3.5% of the population. In the United States, the National Institute of Mental Health (NIMH) estimates that about 12.5 million American adults have ever experienced a PA, and PD is twice as common in women as men.

Agoraphobia (an anxiety state about being in situations or places that might make escape embarrassing or difficult) is seen in approximately one-third to one-half of persons who meet the criteria for PD diagnosis. Other reports indicate that about 95% of persons affected with agoraphobia also have a previous history or current diagnosis of PD.

Signs and symptoms

Criteria for panic disorder

- Recurrent and unexpected PA.
- Worry about the consequences, implications, or behavioral changes associated with PA.
- PA is not caused by, or associated with, a medical condition. It is not associated with another mental disorder, such as phobia (an exaggerated fear of something like spiders or heights).
- Exposure to a specific phobia situation or object can promote a PA.

Criteria for panic attack

- Cardiac palpitations (pounding, racing, or accelerated heart rate)
- Sweating
- Shaking (trembling)
- Breathing difficulties, including shortness of breath or perceptions of being smothered
- Feeling of choking
- Chest discomfort or pain
- Feeling light-headed (faint, dizzy, or unsteady)
- Stomach discomfort or nausea
- Loss of contact with reality during the attack
- A feeling of being detached and out of contact with oneself
- Fear of losing control of oneself (going "crazy")
- Fear of dying
- Tingling or numbness sensations

Criteria for agoraphobia

The essential feature of agoraphobia is anxiety about being in situations or places that make escape embarrassing or difficult. These fears usually involve characteristic clusters of situations that include being on a bridge, being in a crowd, standing in line in a department store, or traveling in a train, bus, or automobile. Elevators are another common cause promoting the occurrence of PA. These situations, which lead to the PA, are often difficult or embarrassing to flee from abruptly. Avoidance of the

affected person's fear, which usually limits travel away from home, causes impaired functioning.

Criteria for PD without agoraphobia

Recurrent unexpected PA is characterized by at least one attack, followed by a month or more of one or more of the following symptoms:

- Persistent concern about having future attacks
- Worry about consequences associated with attacks
- A change in behavioral patterns related to the attacks (e.g., the affected person avoids travel)
- Absence of agoraphobia
- PA not due to a medical condition
- PA not associated with another mental disorder (e.g., phobias)

Diagnosis

There are no specific laboratory findings associated with diagnosing PD. However, evidence suggests that some affected persons may have low levels of carbon dioxide and an important ion in the human body called bicarbonate that helps in regulating blood from becoming too acidic or alkaline. These chemical changes may hypersensitize nerve cells, which can increase the activity of other structures throughout the body, such as sweat glands and the heart and therefore contribute to symptoms of PD. Additionally, lactic acid (a chemical made in the body from sugar) plays a role in nerve cell hypersensitivity. The diagnosis of PD can be made accurately if the specific symptoms and criteria are established.

Neuroimaging studies indicate that the arteries, the vessels that deliver oxygen-rich blood to cells and tissues, are constricted as a result of increased breathing rates during a PA. The consulting clinician must exclude other possible causes of panic attacks, such as intoxication with stimulant drugs such as cocaine, caffeine, and amphetamines. Withdrawal from alcohol and barbiturates can also induce panic-like behaviors. Additionally, the consulting therapist should obtain a comprehensive medical history and examination to determine whether the PA is caused by a medical condition frequently observed in hormonal diseases like overactive thyroid or tumors that secrete chemicals causing a person to have pronounced "hyper" changes like racing heartbeat, sweating, and shaking. Other causes include a possible cardiac disease, such as arrhythmia, when the heart beats irregularly.

Treatment and management

Moderate to severe PD is characterized by frequent PA ranging from five to seven times per week or with significant disability associated with anxiety among

KEY TERMS

Cognitive-behavioral therapy—A therapy technique that works toward diminishing the irrational fears that are causing panic attacks by confronting the triggers that cause the attacks. Therapy includes breathing techniques and noting physical changes and sensations during anxiety and attacks.

Palpitation—An irregular heartbeat.

Phobia—An exaggerated fear.

Recurrent—Tending to repeat.

episodes. In addition to cognitive-behavioral therapy (CBT), an affected person will usually require medications. There are four classes of medications commonly prescribed for PD patients.

Tricyclic antidepressants

Tricyclic antidepressants are a class of older medications used to treat depression and other closely related mental disorders such as PD. Individuals affected with PD who are treated with tricyclics are usually given imipramine, which has been shown in some studies to be effective in approximately 70% of cases. Medications in this category usually have a prolonged lag time until a positive response is observed. This is primarily due to adverse side effects, which prevent rapid increases of dosage, and also because they act on specific chemical imbalances in the brain that take time to stabilize.

Choices of tricyclic antidepressants for PD may include imipramine, desipramine, and nortriptyline. These medications require careful dosing and monitoring. The actual dosage can vary from case to case. Elderly patients may require a smaller dose due to decrease in metabolism of large chemicals and in kidney function, which are part of aging. Some patients may develop gastrointestinal side effects, which may interfere with absorption from the gut, thereby decreasing beneficial blood levels. More common side effects experienced by patients who are prescribed tricyclics are dry mouth and low blood pressure. The heart may be adversely affected, especially in patients with pre-existing diseases, causing direct damage or strain on the heart. People taking tricyclics also commonly experience changes in sexual functioning. Adverse side effects can make patients not want to take the medication at its proper dosage, which decreases its effectiveness.

Selective serotonin reuptake inhibitors

A newer group of antidepressants compared to tricyclics, the selective serotonin reuptake inhibitor

(SSRI) is another medication option. Some SSRIs are approved by the Food and Drug Administration (FDA) to treat panic disorder, including fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft). These medications act on specific areas in the brain to brain levels of serotonin, a neurotransmitter. However, as with all medications, SSRIs have potential side effects, such as nausea, difficulty sleeping, sweating, fatigue, and sexual problems.

Monoamine oxidase inhibitors (MAOIs)

A second line category of medications used to treat PD is the monoamine oxidase inhibitors (MAOIs). Monoamine oxidase is a protein that assists in storing certain chemicals in nerve cells. MAOIs will stop the action of this protein, thereby decreasing the amount of certain chemicals in the brain that may influence PAs. This group of medications is effective in approximately 75% to 80% of cases, especially for nonactive depression. Affected individuals using MAOIs must avoid specific foods in order to prevent a hypertensive crisis (when the blood pressure rapidly increases). These foods include some cheeses, liver of all types, meat and yeast extracts, fermented or aged meats like salami and bologna, broad and Chinese bean pods, all types of alcohol-containing products, soy sauce, shrimp and shrimp paste, and sauerkraut. Although MAOIs are effective medications for treatment of PD, they are underutilized due to strict dietary limitations.

Benzodiazepines

Benzodiazepines are another class of medications used to treat PD; however, these drugs carry a risk for addiction according to the Drug Enforcement Administration (DEA). They are also sedating medications, and individuals who take them should not drive or engage in arduous or challenging tasks. Individuals who have issues with alcohol or drug abuse should avoid these medications, which may interact with other drugs. They include medications such as alprazolam (Xanax), diazepam (Valium), lorazepam, (Ativan) clonazepam (Klonopin), and others. Benzodiazepines have been reported to be effective in 70% to 90% of patients with PD; however, the effective dose of shorter-acting drugs is approximately two to three times higher for PD than for milder forms of simple anxiety, and these medications are usually indicated for mild anxiety. This increased dosing in patients with PD is undesirable, since there is risk of physical dependence and withdrawal, commonly exhibited when the medication is rapidly tapered down or stopped. However, they are indicated when PD-affected patients respond poorly to tricyclics or have a fear of taking MAOIs due to dietary restrictions and problems associated with eating the wrong foods accidentally. Some

researchers have tested experimental drugs for panic disorder, such as orexin receptor (OXR) antagonists, with promising results.

Long-term management

Reassuring the PD patient that anticipated panic attacks are unlikely while taking medication is essential for long-term maintenance. Cognitive-behavioral therapy is also important for long-term treatment. Weaning off medications must be done slowly, since patients develop a sense of security that they will not have an attack while decreasing their dosage. It is also best if people with PD avoid caffeine, because researchers have found that nearly half of those with PD are triggered by caffeinated beverages or foods. Coffee and tea contain caffeine, as do chocolate and many soft drinks.

Clinical trials

The National Institutes of Health (NIH) and other agencies currently sponsor clinical trials on panic disorder. In 2021, NIH reported 200 ongoing and completed studies, including:

- The role of Orexin in human panic disorder. (NCT02593682)
- The effect of transcranial direct current stimulation in panic disorder (PDstim). (NCT04160806)
- Breathing regulation training for individuals with panic disorder. (NCT00183521)
- Changes of cerebral glucose metabolism after 12 weeks of paroxetine treatment in panic disorder. (NCT00767754)

Clinical trial information is constantly updated by the NIH, and the most recent information on panic disorder trials can be found at: <http://clinicaltrials.gov>.

Prognosis

The courses of PD and agoraphobia vary considerably over time. Some affected people may experience spontaneous remissions, where the disorder is present but not active. The course of PD can be so variable that an affected person may go on for years without a PA, have several attacks, and then enter a second phase of remission that may last for years. In some cases, a decrease in PA may be closely related to a decrease and avoidance of anxiety-associated situations that promote agoraphobia. Agoraphobia itself may become chronic with or without PA. In general, approximately 50% to 60% will recover substantially five to 20 years after the initial attack. Approximately 20% will still have long-term impairment, which will stay the same or worsen slightly. Generally, the earlier treatment is sought, the better the outcome. The course in children and

QUESTIONS TO ASK YOUR DOCTOR

- Are the symptoms I have described typical of panic disorder?
- If my spouse and I decide to have children, are they likely to inherit this condition from one of us?
- What medications are appropriate to relieve the symptoms I am experiencing from panic disorder?
- What side effects, if any, should I expect from these medications?

adolescents is chronic, usually lasting about three years. Generally, PD shows the highest risk of developing new psychological disorders during follow-up visits. If PA is treated early, anticipatory anxiety and phobia may be more manageable and responsive to treatment.

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ORGANIZATIONS

- American Psychiatric Association, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209, (888) 35-77924, apa@psych.org, <http://www.psych.org>
- American Psychological Association (APA), 750 First Street NE, Washington, DC 20002-4242, (800) 374-2721, (202) 336-5568, <http://www.apa.org>
- Mental Health America, 2000 N. Beauregard Street, 6th Floor, Alexandria, VA 22311, (703) 684-7722, (800) 969-6642, (703) 684-5968, <http://www.nmha.org>
- National Institute of Mental Health (NIMH), 6001 Executive Boulevard, Bethesda, MD 20892-9663, (301) 443-4513, (866) 615-6464, (301) 443-4279, nimhinfor@nih.gov, <http://www.nimh.nih.gov/index.shtml>

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Revised by Christine A. Adamec

Pantothenate kinase-associated neurodegeneration

Definition

Pantothenate kinase-associated neurodegeneration (PKAN) is a genetic disorder of the nervous system. It is characterized by prolonged movement difficulties and an accumulation of iron in the brain.

Alternate names associated with pantothenate kinase-associated neurodegeneration include neurodegeneration with brain iron accumulation (NBIA), juvenile-onset neuroaxonal dystrophy, Hallervorden-Spatz syndrome or disease, and hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration (HARP). Hallervorden-Spatz disease and HARP were once considered separate disorders. HARP is now considered to be a part of PKAN, and both are associated with dysfunction of movement, dementia, and eye disorders.

Description

PKAN is a genetic disorder that usually results when an individual inherits a mutation in a gene that makes a protein called pantothenate kinase 2. Ten gene mutations have been identified that cause this disorder. Eight are autosomal recessive, one is autosomal dominant, and

one is X-linked dominant. These mutated genes cause iron to build up in parts of the brain, particularly in the basal ganglia. This region is a collection of three clusters of nerve cells (neurons) that control movement. These three clusters are known as the caudate nucleus, putamen, and globus pallidus and are located deep in the brain. When iron accumulates in the basal ganglia, involuntary movements can result. These include tremors and jerking movements or rigidity of the limbs.

Two forms of the disease exist:

- Classic form, in which symptoms arise in early childhood. Symptoms are usually severe and worsen rapidly.
- Atypical form, which appears later in childhood or in adolescence. Symptoms are generally less severe and advance more slowly than those in the classic form. The atypical form is less common than the classic form.

Genetic profile

PKAN results from a mutation in the *pantothenate kinase 2* gene, which is generally abbreviated *PANK2*. This disorder is an autosomal recessive one, so it occurs when an individual inherits a mutated *PANK2* gene from each parent. The parents may not have the condition themselves but may instead only be carriers. A carrier is an individual who does not develop the disorder but may pass the gene for the disorder onto a child. If both parents are carriers, each of their children has a 50% chance of being a carrier and a 25% chance of acquiring the disorder. If both parents have PKAN, all of their children will also acquire the disorder.

Located on the short arm of chromosome 20, the *PANK2* gene carries the blueprint for making the enzyme pantothenate kinase 2, which is active in the mitochondria (the powerhouses of cells) in nerve cells within the brain. Pantothenate kinase 2 is part of the process that makes the molecule called coenzyme A, which is important in converting carbohydrates and fats into energy.

Individuals who have inherited the mutated *PANK2* gene from both parents experience a disruption in the production of coenzyme A, iron begins to accumulate in the brain, and a range of symptoms develop.

Scientists know of some 100 different mutations in the *PANK2* gene that are associated with PKAN. Commonly, the *PANK2* mutation results from a substitution in amino acids, the building blocks of proteins. The amino acid glycine is often substituted with the amino acid arginine at a single position in the enzyme. In some patients, usually including those with the classic form of the disease, the mutation completely cuts off production of functional pantothenate kinase 2. In other patients,

usually those with the atypical form of the disorder, the enzyme is produced, but it does not function as it should. Either way, the manufacture of coenzyme A is compromised, and symptoms arise.

Demographics

PKAN is estimated to affect 1 to 3 people per million (an incidence rate of 0.001%–0.0003%). Its incidence does not appear to be related to ethnicity, gender, or geographic area. The classic form is more common and accounts for about three-fourths of all cases.

Signs and symptoms

Individuals with PKAN typically begin to experience symptoms as children, and they worsen as they age. Symptoms may include the following:

- Involuntary muscle contractions (dystonia)
- Tremors
- Muscle spasms
- Stiffness or rigidity in the arms and legs
- Difficulty walking
- Weakness
- Abnormal posture
- Repeated words, rapid speech, or slurred speech, particularly in the atypical form
- Swallowing problems (dysphagia)
- Night blindness followed by increasingly impaired vision
- Dementia
- Behavioral problems, particularly in the atypical form
- Personality changes, particularly in the atypical form
- Depression, particularly in the atypical form

Diagnosis

Patients and/or their parents should inform the doctor of any family history of this (and other inherited neurological or muscular disorders), which will be helpful in making a diagnosis.

Examination

The doctor will typically conduct or order a neurological examination to check for muscle weakness, rigidity of the limbs, involuntary muscle contractions, and other movement abnormalities.

Tests

Although not widely available, genetic testing can confirm the presence of the mutation associated with PKAN.

QUESTIONS TO ASK YOUR DOCTOR

- Who is at risk for PKAN/NBIA disorders?
- What treatment options do I have if I am diagnosed with PKAN/NBIA?
- What changes can I make in my lifestyle to help diminish the effects of the disorder?
- Should I seek genetic counseling before deciding to have children?

Procedures

A particularly telling diagnostic tool for this disorder is a magnetic resonance imaging (MRI) scan, which can detect a pattern of iron accumulation in the brain that is characteristic to this disorder. This pattern is known as the *eye of the tiger*.

Treatment and management

No cure for PKAN is available, but treatments exist for a number of the symptoms. Some are as follows:

- Nerve-blocking botulinum toxin, the muscle relaxant baclofen, or other surgical treatments for dystonia
- Evaluations and possible treatments for feeding problems
- Pain medications when necessary

In addition, recent clinical trial results have shown efficacy of Deferiprone (an iron chelator) in decreasing iron accumulation in the brain and improving the motor function in patients with NBIA. Medical professionals may also recommend physical therapy for movement issues or occupational therapy to assist the day-to-day life of those individuals who have visual, motor, or other impairments. There is no way to prevent PKAN. It is an inherited disorder.

Adults who are carriers may wish to undergo genetic counseling before deciding to have children so that they understand the risks. Brothers and sisters of a child with the disorder have a 25% chance of having the disorder themselves, and a 50-50 chance of being a carrier for the disorder.

Prognosis

Individuals with the classic form of this disease generally experience their first symptoms before they reach ten years of age, whereas those with the atypical form usually do not have symptoms until they are more than ten years of age, sometimes not until they reach their

20s. In both cases, the disease worsens over time, but the classic form progresses more quickly. In individuals with the classic form, the ability to walk on their own is lost within 10 to 15 years of the onset of symptoms. Those with the atypical form generally lose the ability to walk unassisted within 15 to 40 years after the onset of symptoms. Many individuals with this disorder live long lives, but some die young due to secondary problems (such as aspiration pneumonia that results from inhaling an inappropriate substance such as saliva or vomit) associated with the illness.

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National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

NBIA Disorders Association, 2082 Monaco Court, El Cajon, CA 92019-4235, (619) 588-2315, info@NBIAdisorders.org, <http://www.NBIAdisorders.org>

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Parkes Weber syndrome

Definition

Parkes Weber syndrome is a disorder of the vascular system characterized by anomalies in the arteries and veins that can cause skin discoloration, disproportionate growth of one limb compared to the other, and, in the

most serious cases, heart failure due to poor regulation of blood flow.

Description

British dermatologist Frederick Parkes Weber first described Parkes Weber syndrome in 1907. The syndrome is characterized by the occurrence of vascular anomalies called capillary malformations and arteriovenous fistulas (AVFs). Capillary malformations increase blood flow to the surface of the skin, producing large, flat splotches on the skin that are often referred to as port wine stains due to their pink-to-red color. Slow-flowing capillary lesions that dilate or increase in number near the surface of the skin cause these stains. AVFs are faulty connections between arteries and veins that can cause bleeding in the skin, muscle, bone, brain, and other organs. This bleeding can have dangerous neurological effects and can also lead to heart failure, making Parkes Weber syndrome a potentially life-threatening disorder. These malformations are usually present at birth and can progress during development.

In some cases, one limb can grow larger than the other; most commonly this occurs in the leg. This deformity is due to uneven growth in the soft tissue of the legs.

Genetic profile

Parkes Weber syndrome can be caused by mutations in the *RASA1* gene, which codes for the p120-RasGAP protein. The Ras genes code for a family of GTPase proteins that are involved in the regulation of cell division and differentiation in a number of tissue types, including blood vessels. GTPases are enzymes that hydrolyze the molecule GTP to provide energy for molecular interactions and protein activity. The activity of Ras proteins is modulated by GTPase activating proteins (GAP) that serve as enhancers for the GTPase protein function. The *RASA1* protein is a GAP that modulates Ras GTPases and is involved in regulating Ras activity during cell development.

Mutations in *RASA1* can be inherited, normally in an autosomal dominant pattern, but they can also occur in individuals with no family history of the syndrome. Because some cases of Parkes Weber syndrome are caused by other, unknown genetic mutations, occurrence of the disease is often sporadic and difficult to predict.

Demographics

Parkes Weber syndrome is very rare, and the prevalence is unknown; however, it is estimated that it may affect approximately 0.3% of the world's population.

KEY TERMS

Artery—A blood vessel that carries blood away from the heart to peripheral tissues.

Capillary—A very narrow tube that carries liquid like blood or lymphatic fluid.

Debulking—The removal of abnormal tissue.

Lesion—A defective or injured section or region of the brain (or other body organ).

Vascular system—The network of blood vessels in the body.

Vein—A vessel that carries oxygen-poor blood from the tissues and extremities back toward the heart to be reoxygenated.

Signs and symptoms

The presence of capillary malformations and AVF are what distinguishes this congenital vascular syndrome from other, similar disorders. Parkes Weber syndrome is potentially more serious than similar disorders because of the stress AVF and the increased blood flow to overgrown limbs can put on the heart.

Klippel-Trenaunay syndrome (KTS) is another congenital vascular disorder that has similar symptoms to those of Parkes Weber syndrome but is less life-threatening. KTS also presents with port wine stains and increased growth of bone and soft tissues, but not AVF. Capillary malformation-arteriovenous malformation (CM-AVM) also has similar vascular abnormalities to those of Parkes Weber syndrome. Similarities in genetic anomalies or mutations between all three syndromes may be the reason for the overlap of symptoms.

Diagnosis

The diagnosis for Parkes Weber syndrome is based on clinical and molecular genetic testing. Since mutations in *RASA1* are known to cause the syndrome, individuals who are suspected to have it can be tested directly for changes in the *RASA1* gene.

Treatment and management

There is no one treatment regimen generalized for all patients with Parkes Weber syndrome because the symptoms can be complex and vary in severity. Most treatments are considered on a case-by-case basis depending on the individual condition. In some cases, debulking can remove excess or damaged vasculature. This can decrease or limit problematic blood flow or lesions. Debulking is invasive

QUESTIONS TO ASK YOUR DOCTOR

- Why is Parkes Weber syndrome more dangerous than other vascular disorders?
- Can I pass this disease to my children?
- What tests or other procedures are used to diagnose this condition?
- Can Parkes Weber syndrome be cured and, if not, what kinds of treatment are available?

and can cause complications; therefore, it is often used only as a last resort. There is also a high rate of recurrence of lesions, and in the long term, debulking may not have a lasting benefit to the patient. In the most extreme cases where tissue or limbs are compromised by the vascular abnormalities, amputation is utilized. This was more common in the early days of treatment and is now avoided as much as possible.

Nonsurgical treatment options include sclerotherapy, in which medicines are injected into affected vessels to shrink them and allow for more normal blood flow. Compression therapies and garments can alleviate blood flow impediments, providing pain relief and decreasing some risks of infection that are linked to inflammation and circulation problems. Combined with elevating the affected areas, compression therapy can be useful in the management of discomfort caused by the symptoms of Parkes Weber syndrome.

Prognosis

While the symptoms can be treated, there is no cure for Parkes Weber syndrome.

Resources

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American Pediatric Surgical Association, 1061 E. Main St., Suite 300, East Dundee, IL 60118, (309) 733-7874, info@apsapedsurg.org, <http://www.apsapedsurg.org>

Emily R. Larson, PhD

Parkinsonism see **Parkinson's disease**

Parkinson disease—juvenile see **Parkinson's disease**

Parkinson's disease

Definition

Parkinson's disease (PD) is a progressive neurological movement disorder that can cause tremors, slow movement (bradykinesia), rigidity, and balance problems. It can also cause memory problems, depression, and other symptoms. PD results when the brain cells (neurons) that make the chemical dopamine die or stop working. Dopamine is a neurotransmitter that sends signals to other nerve cells (neurons).

Description

PD was first noted by British physician James Parkinson in the early 1800s. It is a degenerative neurological disorder that causes movement problems like tremor, slowness, stiffness, and walking and balance problems. It causes a progressive decline in movement control, affecting the ability to control initiation, speed, and smoothness of motion. It is associated with a variety of other symptoms like depression, memory problems, and effects on the automatic functions that our body performs. PD is associated with aging, and symptoms are seen in up to 15% of people aged 65 to 74 and almost 30% of people aged 75 to 84.

PD affects the basal ganglia and substantia nigra of the brain. Nerve cells (neurons) in the substantia nigra, which produce dopamine, are responsible for passing on messages that control movement. In a person with PD, dopamine-producing neurons of the substantia nigra die off or stop working properly. The dying brain cells contain Lewy bodies, which can help with diagnosing PD. PD symptoms occur when around 80% of dopamine is lost. When that happens, dopamine receptors in the central part of the brain called the striatum are not properly stimulated, which causes the basal ganglia of the brain to become over- or under-stimulated. When it is over-

stimulated, tremors result. When it is under-stimulated, slowness of movement and rigidity result. What causes the neuron death is largely unknown.

When no cause for nigral cell degeneration can be found, the disorder is called idiopathic Parkinsonism, or Parkinson's disease (PD). Parkinsonism symptoms may be seen in other degenerative conditions, known as the "Parkinsonism plus" syndromes, such as progressive supranuclear palsy.

Usually, PD only happens in one family member. Only about 15% of people with PD have a familial form in which multiple family members are affected. Late-onset adult PD is the most common type of PD, and it usually starts in the late 50s or early 60s. About 10% to 20% of people have an early-onset type of adult PD before the age of 50. Juvenile-onset PD usually starts before age 20. The early-onset adult and juvenile types of PD are more likely to result from a pathogenic variant in a single gene (mutation).

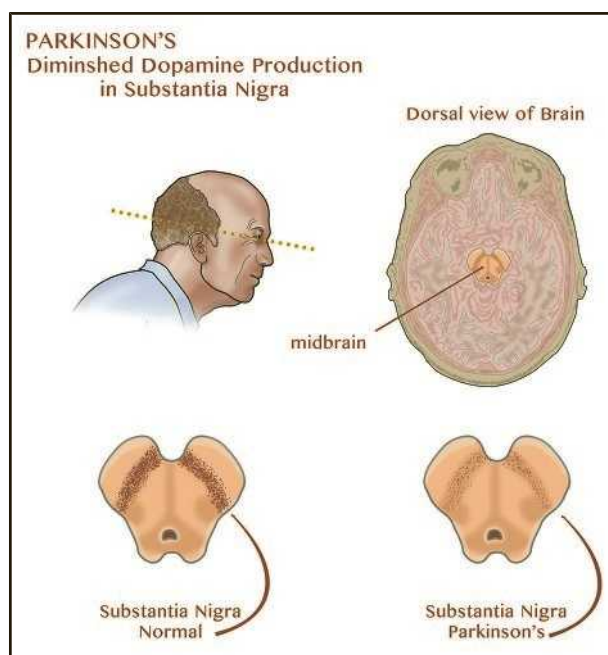
Genetic profile

For most people, the cause of PD is unknown, but it seems to result from a combination of genetic and environmental factors. About 5% to 10% of people with PD have monogenic PD, meaning that it is caused by a pathogenic variant in a single gene. There are a number of different genes that cause monogenic PD.

Monogenic PD is usually inherited in an autosomal dominant or autosomal recessive manner. Rarely, it can be inherited in an X-linked manner. Someone with autosomal dominant PD has a pathological variant (mutation) in one copy of a PD gene and one copy without a variant. They have a 50% chance of passing PD on to their children. Someone has autosomal recessive PD if both copies of their PD gene have a variant. Autosomal recessive PD can only be passed on if both parents are at least carriers, meaning that they have a variant in one copy of the same PD gene. Two carriers have a 25% chance of having a child with PD. X-linked PD results from a variant of a PD gene on the X chromosome. Males have one X chromosome and one Y chromosome, while females have two X chromosomes. X-linked PD usually affects males who inherit the variant from their mother. Carrier females who have one copy with a variant and one normal copy usually do not have symptoms. Carrier females have a 50% chance of passing it on to their children. Daughters born to fathers with X-linked PD will all be carriers, and sons will not have a PD variant.

Monogenic Early and Late Onset PD (Adult Onset)

The most common monogenic genes that cause adult onset PD are:



Degeneration of dopaminergic neurons in the substantia nigra of the midbrain. The image at top depicts where the substantia nigra lies in the brain. At bottom right is a normal substantia nigra and at bottom left is a diminished substantia nigra. Degeneration of this structure is characteristic of Parkinson's disease. (Monica Schroeder/ Science Source)

- PARK-GBA, found in 3% to 7% of adult onset PD and 20% of adult onset PD in those of Ashkenazi Jewish ancestry.
- PARK-LRRK2, found in 1% to 2% of adult onset PD and 13% to 30% of adult onset PD in those of Ashkenazi Jewish ancestry and 41% in those of African Berber ancestry.
- PARK-PINK1 found in 3.7% of early onset adult PD
- PARK-Parkin found in 1% of adult onset and 4.6% to 10.5% of early onset adult PD

Monogenic Juvenile Onset PD

Monogenic Juvenile Onset PD is usually inherited in an autosomal recessive manner where both parents are carriers of a variant of a PD gene. Two carriers have a 25% chance of having a child with PD. Variants in at least six genes can cause monogenic juvenile onset PD. Each of these variants is rare.

Susceptibility Genes for PD

There are also gene variants that appear to play a smaller role in predisposing people to PD. Unlike the genes that cause monogenic PD, these genes may slightly increase the lifetime risk of PD or may influence things

like age of onset and the progression of the symptoms. Most of these genes are still being researched and are not typically included in clinical genetic testing or diagnosis of PD.

Environmental risk factors in PD

Increasing age is one of the most important environmental risk factors for PD. Aging causes a normal decline in dopamine-producing neurons. It is possible that some people who develop PD at an older age are born with fewer dopamine-producing neurons and are therefore more susceptible to age related PD. Environmental risk factors decrease the number of dopamine neurons, making the brain more susceptible to the age-related decline in neurons.

Some environmental risk factors that seem to increase the risk of PD are: pesticide exposure, head injury, rural living, and infectious agents. A chemical called MPTP, which is found as an impurity in some illegal drugs, can cause permanent symptoms of PD within hours of ingestion. MPTP may exert its effects through generation of toxic molecular fragments called free radicals. Reducing free radicals has been a target of several experimental treatments for PD using antioxidants. Some environment factors that seem to decrease the risk of PD are: tobacco smoking, caffeine, use of nonsteroidal anti-inflammatory drugs like ibuprofen, high blood urate levels, and physical activity.

Demographics

PD affects approximately 500,000 people in the United States—both men and women—with as many as 50,000 new cases each year.

Signs and symptoms

Different people with PD have different symptoms. Some are obvious, and others are hard to detect. People with PD often have motor symptoms that are related to movement and other non-motor related symptoms. People with juvenile-onset PD often have involuntary muscle contractions (dystonia), abnormal muscle tightness (spasticity), and dementia.

Motor Symptoms

The three main motor symptoms of PD are

- **Resting tremors:** a rhythmic, involuntary shaking that occurs in a finger, hand, arm, or leg when it is at rest. It usually disappears during voluntary movement. The classic tremor of PD is called a “pill-rolling tremor” because the movement resembles rolling a pill between the thumb and forefinger.

- **Slow movements (bradykinesia)** occur, which may involve slowing down or stopping in the middle of familiar tasks such as walking, eating, or shaving. They may include freezing in place during movements (akinesia).
- **Muscle rigidity or stiffness**, occurring with jerky movements replacing smooth motion. This can also result in a “masked face,” with little facial expression and decreased eye-blinking.

Everyone with PD has bradykinesia, but they might not have the other two motor symptoms. Tremor is the most common symptom when PD is diagnosed, but not everyone with PD has tremor. Some people with PD have problems walking or difficulties with balance and coordination, which may lead to a rapid, shuffling gait (festination) to prevent falling. Usually these happen later on as the disease advances.

Non-motor Symptoms

People with PD can experience a wide-range of non-motor symptoms, which are very common and can affect



Colored 3D magnetic resonance imaging (MRI) scan of the brain of a patient who has had an electrode (grey line) inserted into the brain. The electrodes stimulate the brain to help to control the tremors associated with Parkinson's.
(Zephyr/Science Source)

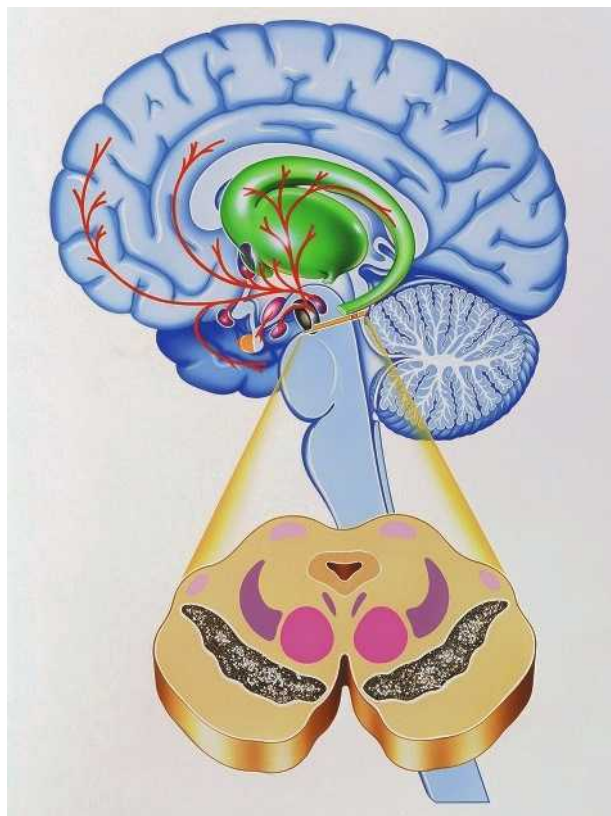


Illustration of a brain with Parkinson's disease. (J. Bavosi/ Science Source)

almost every part of the body and can happen at any time. The severity of these symptoms varies from person to person. Some of the non-motor problems can be:

- Mood and thinking problems. Like depression, anxiety, lack of motivation and interest in activities, memory or thinking problems, and hallucinations or paranoid beliefs.
- Effects on the automatic functions that our body performs: constipation, low blood pressure, sexual problems, excessive perspiration, and problems with urination.
- Other physical changes like drooling, sleepiness, speech problems, pain, skin changes, sleep problems, loss of smell, swallowing problems, vision problems, and weight loss.

Diagnosis

The diagnosis of PD involves a careful medical history and a neurological exam to look for characteristic symptoms. There are no definitive tests for PD, although a variety of lab tests may be done to rule out other causes of symptoms, especially if only some of the major symptoms are present. Tests for other causes of Parkinsonism

symptoms may include brain scans, blood tests, lumbar puncture, and x-rays.

Genetic testing would be indicated in cases where there is an early onset or multiple family members affected with PD. Testing should be done first on a family member affected with PD. It could include a multigene panel that looks for variants in known PD genes or exome or genome sequencing that looks for any gene variants in the genome that might explain the PD. If a variant in a PD gene is founded, then testing of other family members can be done. If a variant is not found, then this does not rule out a genetic cause.

Treatment and management

There is no cure for PD. Most drugs treat the symptoms of the disease only, although one drug, selegiline (Eldepryl), may slow degeneration of the substantia nigra.

Drugs

The pharmacological treatment of PD is complex. While there are a large number of drugs that can be effective, their effectiveness varies by patient, disease progression, and the length of time the drug has been used. Dose-related side effects may preclude using the most effective dose or require the introduction of a new drug to counteract them. There are five classes of drugs currently used to treat PD.

DRUGS THAT REPLACE DOPAMINE. One drug that helps replace dopamine, levodopa (L-dopa), is the single most effective treatment for the symptoms of PD. L-dopa is a derivative of dopamine and is converted into dopamine by the brain. It may be started when symptoms begin or when they become serious enough to interfere with work or daily living.

L-dopa therapy usually remains effective for five years or longer. Following this, many patients develop motor fluctuations, including peak-dose “dyskinesias” (abnormal movements such as tics, twisting, or restlessness), rapid loss of response after dosing (known as the “on-off” phenomenon), and unpredictable drug response. Higher doses are usually tried, but they may lead to an increase in dyskinesias. In addition, side effects of L-dopa include nausea, vomiting, and low blood pressure upon standing (orthostatic hypotension), which can cause dizziness. These effects usually lessen after several weeks of therapy.

ENZYME INHIBITORS. Dopamine is broken down by several enzyme systems in the brain and elsewhere in the body; blocking these enzymes is a key strategy to prolonging the effect of dopamine. The two most commonly prescribed forms of L-dopa contain a drug to

inhibit the amino acid decarboxylase (an AADC inhibitor), one type of enzyme that breaks down dopamine. These combination drugs are Sinemet (L-dopa plus carbidopa) and Madopar (L-dopa plus benserazide). Controlled-release formulations also aid in prolonging the effective interval of an L-dopa dose.

The enzyme MAO-B inhibitor selegiline may be given as add-on therapy for L-dopa. Research indicates that selegiline may have a neuroprotective effect, sparing nigral cells from damage by free radicals. Because of this and the fact that it has few side effects, it is also frequently prescribed early in the disease before L-dopa is begun. Entacapone and tolcapone, two inhibitors of another enzyme system called catechol-O-methyltransferase (COMT), may reach the market, as early studies suggest that they effectively treat PD symptoms with fewer motor fluctuations and decreased daily L-dopa requirements.

DOPAMINE AGONISTS. Dopamine works by stimulating receptors on the surface of corpus striatum cells. Drugs that also stimulate these cells are called dopamine agonists, or DAs. DAs may be used before L-dopa therapy or added on to avoid requirements for higher L-dopa doses late in the disease. DAs available in the United States include pramipexole (Mirapex), ropinirole (Requip), apomorphine, and bromocriptine (Parlodel). Other dopamine agonists in use outside the United States include cabergoline (Dostinex) and lisuride (Dopergine). The previously used pergolide (Permax) was removed from the market in 2007. Side effects of all the DAs are similar to those of dopamine, plus confusion and hallucinations at higher doses.

ANTICHOLINERGIC DRUGS. Anticholinergics maintain dopamine balance as levels decrease. However, the side effects of anticholinergics (dry mouth, constipation, confusion, and blurred vision) are usually too severe in older patients or in patients with dementia. In addition, anticholinergics rarely work for very long. They are often prescribed for younger patients who have predominant shaking. Trihexyphenidyl (Artane) is the drug most commonly prescribed.

DRUGS WHOSE MODE OF ACTION IS UNCERTAIN. Amantadine (Symmetrel) is sometimes used as an early therapy before L-dopa is begun and as an add-on later in the disease. Its anti-Parkinsonian effects are mild and not seen in many patients. Clozapine (Clozaril) is effective especially against psychiatric symptoms of late PD, including psychosis and hallucinations.

Surgery

Two surgical procedures are used for treatment of PD that cannot be controlled adequately with drug therapy. In PD, a brain structure called the globus pallidus (GPi)

receives excess stimulation from the corpus striatum. In a pallidotomy, the GPi is destroyed by heat delivered by long, thin needles inserted under anesthesia. Electrical stimulation of the GPi is another way to reduce its action. Fine electrodes are inserted to deliver the stimulation, which may be adjusted or turned off as the response dictates. Other regions of the brain may also be stimulated by electrodes inserted elsewhere. In most patients, these procedures lead to significant improvement for some motor symptoms, including peak-dose dyskinesias, which allows the patient to receive more L-dopa, since these dyskinesias are usually what cause an upper limit on the L-dopa dose.

Deep brain stimulation (DBS) can help manage symptoms of PD. It involves surgically implanting a device that delivers electrical stimulation to a part of the brain called the basal ganglia. This treatment can help



Light micrograph of a section through the brain of a patient with Parkinson's disease, showing a neuron (center) containing Lewy bodies (dark red). Lewy bodies, which are deposits of protein, are thought to cause the progressive degeneration of the neurons that leads to the symptoms of this disorder. (Pr. A.M. Vedrenne, CNRI/Science Source)

control motor symptoms like stiffness, slowness, and tremor. It works very well for some people but does not work for all people with PD. It is approved for people who have had PD for at least four years but still have motor problems. DBS is not recommended for people with dementia as it may worsen problems with thinking or memory. Most people can decrease the amount of PD drugs that they need after DBS.

Focused ultrasound can be used to destroy brain cells that cause movement problems in PD patients. The type of symptoms determine the brain cells that are targeted. Focused ultrasound usually immediately decreases symptoms, but the treatment is permanent. The procedure is usually only done on one side of the brain and therefore only affects symptoms on that side, because doing the procedure on both sides may cause speech, swallowing, or memory problems.

Transplant of fetal nigral cells is highly experimental. Its benefits to date have been modest, although improvements in technique and patient selection are likely to change that.

Alternative treatment

Currently, the best treatments for PD involve the use of conventional drugs such as levodopa. Alternative therapies, including acupuncture, massage, and yoga, can help relieve some symptoms of the disease and loosen tight muscles. Alternative practitioners have also applied herbal and dietary therapies, including amino acid supplementation, antioxidant (vitamins A, C, E, selenium, and zinc) therapy, B vitamin supplementation, and calcium and magnesium supplementation, to the treatment of PD. Anyone using these therapies in conjunction with conventional drugs should check with his or her doctor to avoid the possibility of adverse interactions. For example, vitamin B₆, either as a supplement or from foods such as whole grains, bananas, beef, fish, liver, and potatoes, can interfere with the action of L-dopa when the drug is taken without carbidopa.

Exercise, nutrition, and physical therapy

Regular, moderate exercise has been shown to improve motor function without an increase in medication for a person with PD. Exercise helps maintain range of motion in stiff muscles, improve circulation, and stimulate appetite. An exercise program designed by a physical therapist has the best chance of meeting the specific needs of the person with PD. A physical therapist may also suggest strategies for balance compensation and techniques to stimulate movement during slowdowns or freezes.

KEY TERMS

AADC inhibitors—Drugs that block the amino acid decarboxylase, one type of enzyme that breaks down dopamine. Also called DC inhibitors, they include carbidopa and benserazide.

Akinesia—A loss of the ability to move; freezing in place.

Bradykinesia—Extremely slow movement.

COMT inhibitors—Drugs that block catechol-O-methyltransferase, an enzyme that breaks down dopamine. COMT inhibitors include entacapone and tolcapone.

Dopamine—A neurochemical made in the brain that is involved in many brain activities, including movement and emotion.

Dyskinesia—Impairment or difficulty in performing voluntary movements, usually resulting in jerky or interrupted movements.

MAO-B inhibitors—Inhibitors of the enzyme monoamine oxidase B. MAO-B helps break down dopamine; inhibiting it prolongs the action of dopamine in the brain. Selegiline is an MAO-B inhibitor.

Orthostatic hypotension—A sudden decrease in blood pressure upon sitting up or standing. It may be a side effect of several types of drugs.

Substantia nigra—One of the movement control centers of the brain.

Good nutrition is important to maintenance of general health. A person with PD may lose some interest in food, especially if depressed, and may have nausea from the disease or from medications, especially those known as dopamine agonists. Slow movements may make it difficult to eat quickly, and delayed gastric emptying may lead to a feeling of fullness without having eaten much. Increasing fiber in the diet can improve constipation, soft foods can reduce the amount of needed chewing, and a prokinetic drug such as cisapride (Propulsid) can increase the movement of food through the digestive system.

People with PD may need to limit the amount of protein in their diets. The main drug used to treat PD, L-dopa, is an amino acid and is absorbed by the digestive system by the same transporters that pick up other amino acids broken down from proteins in the diet. Limiting protein, under the direction of a physician or a nutritionist, can improve the absorption of L-dopa.

QUESTIONS TO ASK YOUR DOCTOR

- What do scientists know about the causes of Parkinson's disease?
- How does a physician know that a person has Parkinson's disease rather than some other similar medical condition?
- What medications are available for the treatment of Parkinson's disease, and how effective are they?
- Are there herbs or other alternative medicines that can be used for the treatment of Parkinson's disease?

No evidence indicates that vitamin or mineral supplements can have any effect on the disease other than in the improvement of the patient's general health. No antioxidants used to date have shown promise as a treatment except for selegiline, monoamine oxidase B (MAO-B) inhibitor. A large, carefully controlled study demonstrated that vitamin E could not halt disease progression.

Prognosis

Despite medical treatment, the symptoms of PD worsen over time and become less responsive to drug therapy. Late-stage psychiatric symptoms are often the most troubling, including difficulty sleeping, nightmares, intellectual impairment (dementia), hallucinations, and loss of contact with reality (psychosis).

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ORGANIZATIONS

American Parkinson Disease Association, 135 Parkinson Ave., Staten Island, NY 10305, (800) 223-2732 or (718) 981-8001, (718) 981-4399, apda@apdaparkinson.org, <http://www.apdaparkinson.org>

The Michael J. Fox Foundation for Parkinson's Research, Grand Central Station, P.O. Box 4777, New York, NY 10163-4777, (800) 708-7644, <https://www.michaeljfox.org>

National Parkinson Foundation, 200 SE 1st Street, Suite 800, Miami, FL 33136, (800) 473-4636, (305) 537-9901, contact@parkinson.org, <http://www.parkinson.org>

Parkinson's Disease Foundation, 1359 Broadway, Suite 1509, New York, NY 10018, (212) 923-4700 or (800) 457-6676, (212) 923-4778, <http://www.pdf.org>

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Paroxysmal nocturnal hemoglobinuria

Definition

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired form of hemolytic anemia that is caused by an intrinsic defect of the cell membrane in red blood cells. Primary PNH is characterized by a deficiency in protective proteins called glycosphosphatidylinositols, and the lack of these proteins allows the innate immune system of the body to attack blood cells and destroy them. Secondary PNH is a bone marrow disorder characterized as aplastic anemia.

As the red blood cells are destroyed, the iron-rich hemoglobin is released and disposed of in the urine,

which can sometimes be red in color. Historically, the acidification of the blood that happens during sleep was thought to contribute to PNH, and this is why “nocturnal” is a component to the disorder’s name; however there is little evidence that sleep has a role in the disease.

Description

Also known as Marchiafava-Micheli syndrome, PNH was first identified in 1882. PNH is caused by a change (mutation) in the gene that encodes phosphatidylinositol glycan A (PIGA), an enzyme that is required for the synthesis of the glycolipid glycosylphosphatidylinositol (GPI). GPI anchors proteins to membranes and when it is missing proteins cannot present on membrane of the cells. Proteins that are anchored to the cell membrane by GPI are important for cell identity, which protects the cell from the body’s immune system. All blood cells develop from hematopoietic stem cells in the bone marrow; when PIGA is mutated in these stem cells, all the cells produced will lack GPI anchors.

Many of the proteins that protect blood cells from the innate immune system require GPI anchors to be expressed on the cell surface. The main proteins involved in this protection are decay-accelerating factor (DAF/CD55) and protectin (CD59/MIRL/MAC-IP), which keep the components of the complement system from binding to the cell membrane. Although all types of blood cells can be susceptible to complement system attack, the RBC are most sensitive to cell lysis. Without GPI anchors, these protective proteins cannot protect blood cells from the complement system.

The severity of PNH varies greatly from individual to individual. In some affected people blood in the urine is barely detectable; others lose so much blood that they require repeated transfusions. In severe cases, abnormal platelets may cause abnormal clotting and about one-third of people with PNH die from clots in the veins of the liver, stomach, or brain.

Genetic profile

PNH is caused by a somatic mutation in the *PIG-A* gene, located on the X chromosome. When this mutation occurs in the bone marrow cells responsible for the production of blood cells, the symptoms of PNH are presented as more defective blood cells outnumber the normal ones that were made prior to the mutation event.

Although females have two X chromosomes, in most cells only one chromosome is actively used for gene transcription while the other is compacted into an inactive form of DNA called heterochromatin. This process is called X-chromosome inactivation. This means that

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Bone marrow—A spongy tissue located in the hollow centers of large bones. Bone marrow is the site of blood cell generation.

Complement system—Part of the innate immune system that helps clear pathogens from an organism. It stimulates a cascade of enzyme activity that effectively lyses cells/pathogens open that are marked for destruction.

Glycosylphosphatidylinositol (GPI)—A molecule that attaches proteins to the membranes of cells.

Hemoglobin—Protein-iron compound in the blood that carries oxygen and carbon dioxide to and from tissues/cells, respectively.

Innate immune system—A population of cells and mechanisms that defends the body against invasive organisms. This protection is generic and not long lasting. The innate immune system is sometimes considered to be the first responder against infection.

Platelets—Small, disc-shaped cells that circulate in the bloodstream and participate in blood clotting.

Red blood cell (RBC)—Hemoglobin-containing blood cells that transport oxygen from the lungs to tissues. In the tissues, the red blood cells exchange their oxygen for carbon dioxide that is then brought back to the lungs.

Somatic mutation—Mutations that occur in only some cells during an individual’s lifetime. These mutations are acquired rather than inherited.

White blood cell (WBC)—A cell in the blood that helps fight infections.

X-chromosome inactivation—The molecular process that inactivates one of two X-chromosomes in most cells present in female mammals. This inactivation prevents females from having twice as many X-chromosome gene products as males of that species.

in most cells, if a somatic mutation occurs on the X-chromosome, the affected gene can have developmental or phenotypic consequences for that cell, tissue, organ, or organism. In this way, women as well as men can suffer from PNH.

Demographics

PNH is a rare disease. In a million people, only about two to six cases of PNH will be diagnosed. PNH can affect any age group but is most common in adults between the ages of 30 and 50. The disease affects both men and women but is slightly more common in women (the ratio is 1.2 to 1). PNH has been described in all ethnicities but may occur in greater numbers in those from Southeast Asia, as this group is more susceptible to aplastic anemia.

Signs and symptoms

Only about one-quarter of people with PNH have the telltale sign, reddish-brown urine, for which the disease is named and is more common in cases of primary PNH. Other symptoms can include those associated with anemia, such as shortness of breath, tiredness, and heart palpitations. More severe cases of PNH can present symptoms like abdominal pain and trouble swallowing, which might be caused by the effect the products of red blood cell damage has on smooth muscle cell function.

Blood clots can also be a serious risk to people with PNH, especially if they travel to the lungs or brain. Forty percent of PNH patients usually develop blood clots at some point in their illness. Clots that form in the major veins of the liver can cause severe pain and damage to the internal organs.

Contributing to anemia in people with PNH is the decreased production of red blood cells in the bone marrow. As the bone marrow fails to produce functioning red blood cells, white blood cells, and platelets, the numbers of these blood cells drop dangerously low and lead to a condition called bone marrow failure. Those affected with PNH may have frequent infections because their white blood cells are decreased in number and the cells that circulate in the blood are abnormal.

Diagnosis

Blood tests can be used in the diagnosis of PNH. The Ham test, developed in 1938, has long been a standard laboratory test for confirming PNH. The test determines whether an individual's red blood cells break down when introduced to a mild acidic environment. Blood cells that are abnormally fragile break down faster in this environment compared to normal cells. The Ham test is not very sensitive or specific to PNH but was historically used for testing blood disorders. A second laboratory test, the sugar water or sucrose lysis test, works on principles similar to the Ham test in that the amount and rate of hemolysis is observed for in a patient's red blood cells when they are placed in low-ionic-strength solution. These tests are

generally considered obsolete now that there are more specific and sensitive diagnostic tools.

The most current laboratory test for PNH is flow cytometry that can measure the levels of CD55 and CD59 in white and red blood cells. In cases of mild and severe PNH the levels of these proteins are very low compared to normal blood cells. Flow cytometry analysis is considered the gold standard for an accurate diagnosis of PNH.

Another marker used in flow cytometry to diagnose PNH is the fluorescein-labeled proaerolysin (FLAER). Proaerolysin is a bacterial protein that selectively binds to GPI proteins. The FLAER test takes advantage of this and uses it as a more accurate marker than CD59 or CD55 in demonstrating a deficit in GPI in cases of PNH.

Individuals who are young with unexplained thrombosis (blood clotting) and have thrombosis in an unusual site (e.g., intra-abdominal veins, cerebral veins, dermal veins), have any evidence of hemolysis (i.e. a raised LDH), or have a low red blood cell, white blood cell, or platelet counts should be screened for PNH. Those who have a diagnosis of aplastic anemia should also be screened annually.

Treatment and management

Treatment can depend on the severity of the case of PNH. For mild forms of PNH patients may only have to take supplements of folic acid and iron to increase red blood cell production. In more severe cases steroids may be used to slow down the destruction of blood cells and symptoms of anemia. Patients who suffer from thrombosis can take anticoagulants to prevent the occurrence of blood clots. Blood transfusions may also be used for the treatment of PNH to replace abnormal blood cells with functional cells.

Bone marrow transplants are perhaps the only way to cure PNH. Bone marrow from a close relative such as a sibling can be used to replace the defective marrow of a PNH patient. The procedure is quite risky, with a 15%–20% chance of death, and is available only in the most severe cases of PNH or when other treatments have failed to improve a patient's symptoms.

Prognosis

After an affected individual has been diagnosed with PNH they usually live for another 10 to 20 years. About 25% of people with PNH live more than 25 years after first being diagnosed. In a few people (about 15%), the disease disappears altogether and the person recovers spontaneously.

QUESTIONS TO ASK YOUR DOCTOR

- What treatments are suggested for my type of PNH?
- I have a mild form of PNH; is it possible for it to progress to a more severe form of the disease?
- What physical and mental characteristics are most commonly associated with paroxysmal nocturnal hemoglobinuria?
- What is the genetic basis for this disorder, and how likely is it that my children will inherit the disease from me?
- Are there support groups or organization that can provide additional information about this condition?

Most people who die from PNH do so because of abnormal clotting. About 10% of these individuals develop and eventually die from another disease involving red blood cells, aplastic anemia. About 5% of people with PNH develop a disease involving abnormal white blood cells, acute myelogenous leukemia.

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ORGANIZATIONS

- Aplastic Anemia & MDS International Foundation, 100 Park Ave., Suite 108, Rockville, MD 20850, (800) 747-2820, <http://www.aamds.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06813, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Partial 11q monosomy syndrome see
Jacobsen syndrome

Patent ductus arteriosus

Definition

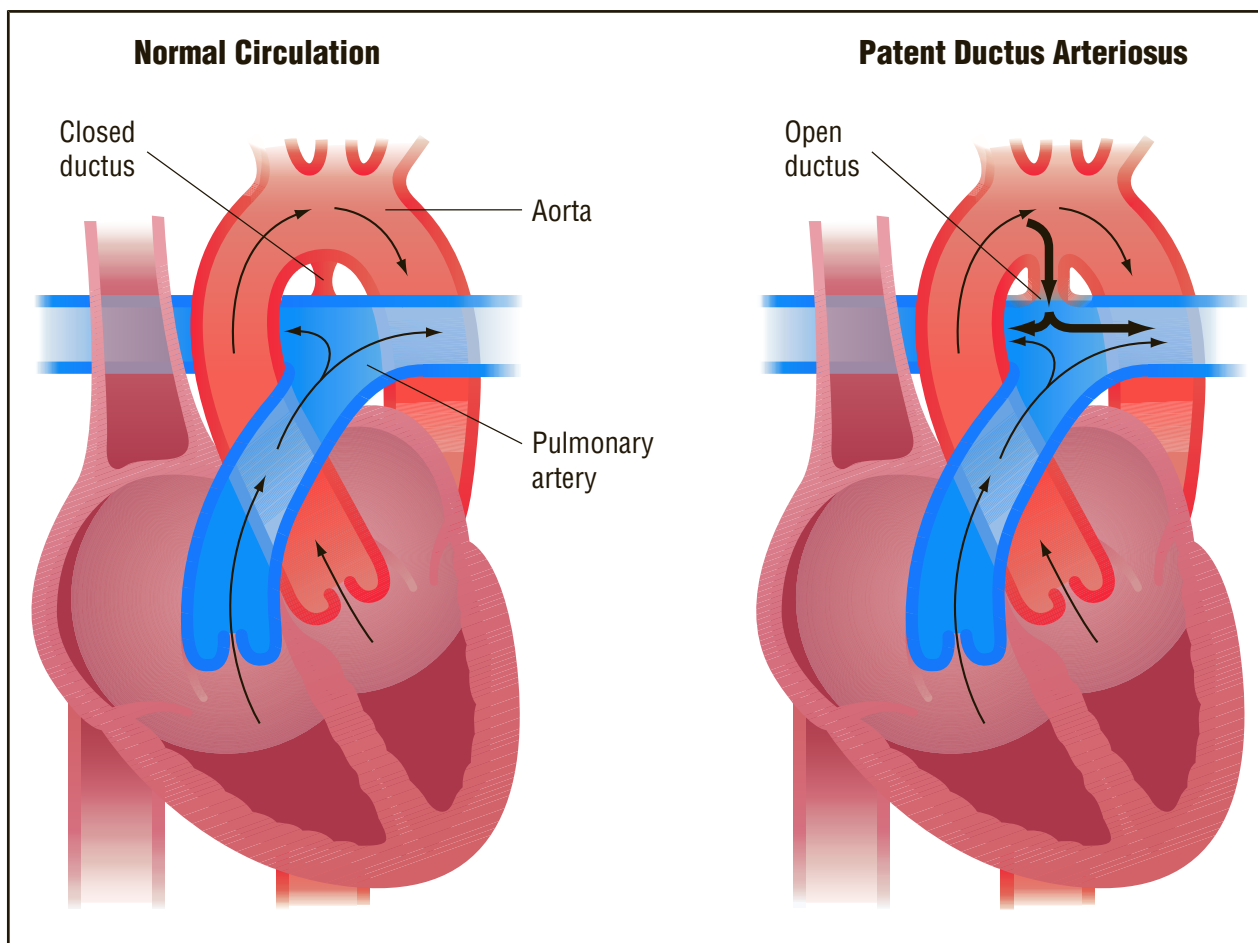
Patent ductus arteriosus (PDA) is a heart abnormality that occurs when the ductus arteriosus (the temporary fetal blood vessel that connects the aorta and the pulmonary artery) does not close at birth.

Description

The ductus arteriosus is a temporary fetal blood vessel that connects the aorta and the pulmonary artery before birth. The ductus arteriosus should be present and open before birth while the fetus is developing in the uterus. Since oxygen and nutrients are received from the placenta and the umbilical cord instead of the lungs, the ductus arteriosus acts as a "short cut" that allows blood to bypass the deflated lungs and go straight out to the body. After birth, when the lungs are needed to add oxygen to the blood, the ductus arteriosus normally closes. The closure of the ductus arteriosus ensures that blood goes to the lungs to pick up oxygen before going out to the body. Closure of the ductus arteriosus usually occurs at birth as levels of certain chemicals, called prostaglandins, change and the lungs fill with air. If the ductus arteriosus closes correctly, the blood pumped from the heart goes to the lungs, back into the heart, and then out to the body through the aorta. The blood returning from the lungs and moving out of the aorta carries oxygen to the cells of the body.

In some infants, the ductus arteriosus remains open (or patent), and the resulting heart defect is known as patent ductus arteriosus (PDA). In most cases, a small PDA does not result in physical symptoms. If the PDA is larger, health complications may occur.

In an average individual's body, the power of blood being pumped by the heart and other forces leads to a certain level of pressure between the heart and lungs. The



Failure of the temporary fetal blood vessel that connects the aorta and the pulmonary artery (ductus arteriosus) to close after birth results in patent ductus arteriosus. This open duct interferes with proper blood flow through the aorta. (Gale)

pressure between the heart and lungs of an individual affected by PDA causes some of the oxygenated blood that should go out to the body (through the aorta) to return back through the PDA into the pulmonary artery. The pulmonary artery takes the blood immediately back to the lungs. The recycling of the already oxygenated blood forces the heart to work harder as it tries to supply enough oxygenated blood to the body. In this case, the left side of the heart usually grows larger as it works harder and must contain all of the extra blood moving back into the heart. This is known as a left-to-right or aortic-pulmonary shunt.

The size of the PDA determines how much harder the heart has to work and how much bigger the heart becomes. If the PDA is large, the bottom-left side of the heart is forced to pump twice as much blood because it must supply enough blood to recycle back to the lungs and move out to the body. As the heart responds to the increased demands for more oxygenated blood by pumping harder, the pulmonary artery has to

change in size and shape in order to adapt to the increased amount and force of the blood. In some cases, the increase in size and shape changes the pressure in the pulmonary artery and lungs. If the pressure in the lungs is higher than that of the heart and body, blood returning to the heart will take the shortcut back into the aorta from the pulmonary artery through the PDA instead of going to the lungs. This backward flowing of blood does not carry much oxygen. If blood without much oxygen is being delivered to the body, the legs and toes turn blue or cyanotic. This is called a shunt reversal.

When a PDA results in a large amount of blood being cycled in the wrong order, either through a left-to-right shunt or shunt reversal, the overworked, enlarged heart may stop working (congestive heart failure) and the lungs can become filled with too much fluid (pulmonary edema). At this time, there is also an increased risk for a bacterial infection that can inflame the lining of the heart (endocarditis). These three complications are very serious.

Genetic profile

PDA can be a result of an environmental exposure before birth, inheriting a specific changed or mutated gene or genes, a symptom of a genetic syndrome, or be caused by a combination of genetic and environmental factors (multifactorial). Recent studies in mice and supporting human genomic data have shown that a critical region in chromosome 2 encoding eight genes, including genes for bone morphogenetic protein (BMP) 9 and BMP10, may be involved in PDA. These proteins are critical for the remodeling of newly formed microvascular beds.

Environmental exposures that can increase the chance for a baby to be affected by PDA include fetal exposure to rubella before birth, preterm delivery, and birth at a high-altitude location.

PDA can be an inherited condition running in families as isolated PDA or part of a genetic syndrome. In either case, there are specific gene changes or mutations that lead to an abnormality in the elastic tissue forming the walls of the ductus arteriosus. The genes causing isolated PDA have not been identified, but it is known that PDA can be inherited through a family in an autosomal dominant pattern or an autosomal recessive pattern.

Every person has approximately 30,000 genes, which tell our bodies how to grow and develop correctly. Each gene is present in pairs since one is inherited from the mother, and one is inherited from the father. In an autosomal dominant condition, only one changed or mutated copy of the gene for PDA is necessary for a person to have PDA. If a parent has an autosomal dominant form of PDA, there is a 50% chance for each child to have the same or similar condition.

PDA can also be inherited in an autosomal recessive manner. A recessive condition occurs when a child receives two changed or mutated copies of the gene for a particular condition, such as PDA (one copy from each parent). Individuals with a single changed or mutated copy of a gene for a recessive condition are known as carriers and have no health problems related to the condition. In fact, each individual carries between five and 10 genes for harmful, recessive conditions. However, when two people who each carry a changed or mutated copy of the same gene for a recessive condition meet, there is a chance, with each pregnancy, for the child to inherit the two changed or mutated copies from each parent. In this case, the child would have PDA. For two known carriers, there is a 25% risk with each child to have a child with PDA, a 50% chance to have a child who is a carrier, and a 25% chance to have a child who is neither affected nor a carrier.

KEY TERMS

Aorta—The main artery located above the heart that pumps oxygenated blood out into the body. Many congenital heart defects affect the aorta.

Catheterization—The process of inserting a hollow tube into a body cavity or blood vessel.

Ductus arteriosus—The temporary channel or blood vessel between the aorta and pulmonary artery in the fetus.

Echocardiograph—A record of the internal structures of the heart obtained from beams of ultrasonic waves directed through the wall of the chest.

Electrocardiogram (ECG, EKG)—A test used to measure electrical impulses coming from the heart in order to gain information about its structure or function.

Endocarditis—A dangerous infection of the heart valves caused by certain bacteria.

Oxygenated blood—Blood carrying oxygen through the body.

Pulmonary artery—An artery that carries blood from the heart to the lungs.

Pulmonary edema—A problem caused when fluid backs up into the veins of the lungs. Increased pressure in these veins forces fluid out of the vein and into the air spaces (alveoli). This interferes with the exchange of oxygen and carbon dioxide in the alveoli.

Most cases of PDA occur as the result of multifactorial inheritance, which is caused by the combination of genetic factors and environmental factors. The combined factors lead to isolated defects in the elastic tissue forming the walls of the ductus arteriosus. Family studies can provide different recurrence risks depending on the family member affected by multifactorial PDA. If an individual is affected by isolated, multifactorial PDA, they have a 2%–4% chance of having a child affected by PDA. If a couple has one child with isolated, multifactorial PDA, there is a 3% chance that another of their children could be affected by PDA. If a couple has two children affected by isolated, multifactorial PDA, there is a 10%–25% chance that they could have another child affected by PDA.

Unless a specific pattern of inheritance, preterm delivery, or known exposure is found through the examination of a detailed pregnancy and family history, the multifactorial family studies are used to estimate the possible risk of recurrence of PDA in a family.

Demographics

PDA is a very common heart disorder. The incidence of isolated PDA at live-term birth is 1 per 2,000. This accounts for 5%–10% of all congenital heart defects. PDA can occur in full-term infants, but is seen most frequently in preterm infants, infants born at a high altitude, and babies whose mothers were affected by German measles (rubella) during pregnancy. PDA is two to three times more common in females than in males. PDA occurs in individuals of every ethnic origin and does not occur more frequently in any one country or ethnic population.

Signs and symptoms

The main sign of PDA is a constant heart murmur that sounds like the hum of a refrigerator or other machinery. This murmur is usually heard by the doctor using a stethoscope. Otherwise, there are no specific symptoms of PDA, unless the ductus arteriosus size is large. Children and adults with a large ductus arteriosus can show difficulty in breathing during moderate physical exercise, an enlarged heart, and failure to gain weight. In some cases, heart failure and pulmonary congestion can indicate a PDA.

Diagnosis

Diagnosis is most often made by detecting the characteristic “machinery” heart murmur heard by a doctor through a stethoscope. Tests such as a chest x-ray, echocardiograph, and ECG are used to support the initial diagnosis. Other indications of PDA include failure to gain weight, frequent chest infections, heavy breathing during mild physical exertion, congestive heart failure, and pulmonary edema. Prenatal ultrasounds are unable to detect PDA because the heart defect does not occur until the time of birth.

Treatment and management

The treatment and management of PDA depends upon the size of the PDA and symptoms being experienced by the affected individual. In some cases, a PDA can correct itself in the first months of life. In preterm infants experiencing extreme symptoms, the first step in correcting a PDA is through treatment with Prostaglandin E1 until such time that the infant could survive corrective surgery. In less severe cases, treatment with medicine such as enteral paracetamol or intravenous Indomethacin is indicated. In preterm infants in which PDA is not closed through medication, full-term infants affected by PDA, and adults, surgery is an option for closing the ductus arteriosus. In 2000 and 2001, researchers developed and reviewed alternatives to surgical closure such as interventional cardiac catheterization and video-assisted

QUESTIONS TO ASK YOUR DOCTOR

- What is the “ductus arteriosus,” and what function does it have in the body?
- Why is patent ductus arteriosus classified as a genetic disease?
- How is patent ductus arteriosus diagnosed in a child?
- What treatments are available for this disorder?

thoroscopic surgical repair. A cardiologist can help individuals determine the best method for treatment based on their physical symptoms and medical history.

Prognosis

Adults and children can survive with a small opening remaining in the ductus arteriosus. Treatment, including surgery, of a larger PDA is usually successful and frequently occurs without complications. Proper treatment allows children and adults to lead normal lives.

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- “Patent Ductus Arteriosus.” MedlinePlus. October 22, 2019. <https://medlineplus.gov/ency/article/001560.htm> (accessed July 9, 2021).

ORGANIZATIONS

- American Heart Association, 7272 Greenville Ave., Dallas, TX 75231, (800) 242-8721, <http://www.heart.org>

Kids with Heart National Association for Children's Heart Disorders, 1578 Careful Dr., Green Bay, WI 54304, <http://kidswithheart.org>

National Heart, Lung, and Blood Institute, NHLBI Health Information Center, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbiinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov>

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PC deficiency see **Pyruvate carboxylase deficiency**

Pedigree analysis

Definition

A pedigree is a family tree or chart made of symbols and lines that represent a patient's genetic family history. The pedigree is a visual tool for documenting biological relationships in families and the presence of diseases. Pedigree analysis is an assessment made by a medical professional about genetic risk in a family.

Purpose

Pedigrees are most often constructed by medical geneticists or genetic counselors. People are referred to genetic professionals because of concern about the presence of a genetic condition in a family member. Pedigree analysis can help identify a genetic condition running through a family, aids in making a diagnosis, and aids in determining who in the family is at risk for genetic conditions. During pedigree construction, the family's beliefs about the cause for a genetic disease or emotional issues related to a diagnosis may be revealed. For instance, family members may experience guilt or shame about passing on a genetic trait. Thus, the communication process involved in taking the family history may allow the health care provider to identify areas in which the patient may need reassurance, education, or emotional support.

Creating a pedigree

Pedigree symbols

A standard set of symbols has been established for use in creating pedigrees. Some of the most commonly used symbols are shown in this entry. When a person is affected with a birth disorder, intellectual disability, or other health problems, the individual is shaded or marked. If more than one condition is present in a family, different identifying marks should be made. A key to decipher these

markings should also be included on the pedigree. The meaning of each horizontal and vertical line is also shown.

Information obtained

A typical pedigree is made of information about three generations of a family. The consultand is the person seeking genetic evaluation, counseling, or testing. The proband in a family is the person in a family affected with a genetic disease. Beginning with the consultand, questions should be asked about the health of first-, second-, and third-degree relatives. First-degree relatives are children, parents, and siblings. Second-degree relatives are half-siblings, nieces, nephews, aunts and uncles, grandparents, and grandchildren. Third-degree relatives are first cousins. Important information to obtain on both sides of the family includes:

- ages or dates of birth
- presence of any birth disorders, learning problems, chronic illnesses, surgeries, or medical treatments
- presence of specific features of a disease if the condition is suspected in the family
- genetic testing results if previously performed in the family
- cause of death for deceased family members
- pregnancy losses, stillbirths, or infant deaths and causes
- infertility in the family
- ethnic background of the families
- consanguinity

It is important to establish the accuracy of information given by patients. Therefore, medical records are often requested in order to provide accurate risk assessment.

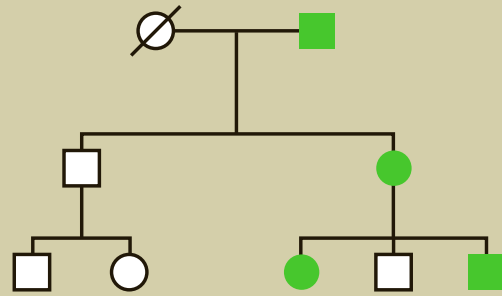
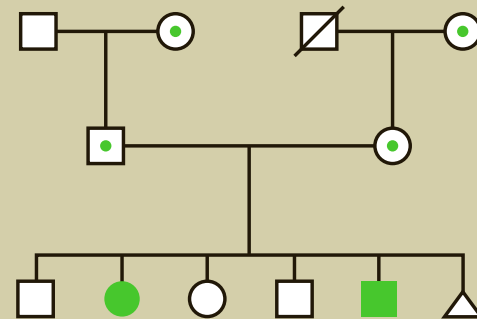
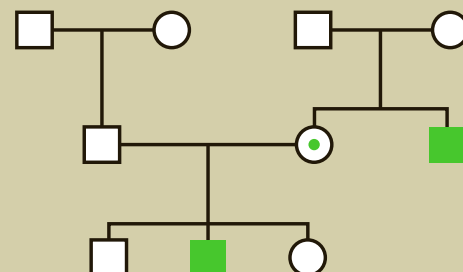
Pedigree patterns

Autosomal dominant inheritance

Pedigree 1 illustrates the occurrence of an autosomal dominant disorder called neurofibromatosis (NF). NF is characterized by growths under the skin called neurofibromas, dark spots on the skin called café au lait spots, and an eye finding called Lisch nodules. NF is caused by a single dominant gene on chromosome 17. Each person who is affected with NF has a 50% chance to pass the gene on to each child. The symptoms of NF are variable so that some family members are affected more seriously than others. The pedigree shows that in autosomal dominant inheritance, multiple generations of a family are affected. This is called vertical transmission of a trait through a family. Males and females are equally likely to be affected. In a particular sibship, about half of the siblings are affected.

Pedigree Symbols

-  Male
-  Female
-  Gender unknown
-  Miscarriage
-  Elective terminated of Pregnancy
-  Affected female
-  Affected male
-  Carrier female
-  Carrier male
-  Deceased

Pedigree 1: Neurofibromatosis
 Autosomal Dominant Inheritance

Pedigree 2: Cystic Fibrosis
 Autosomal Recessive Inheritance

Pedigree 3: Hemophilia
 X-Linked Recessive Inheritance


The illustration above identifies several common symbols used to represent individuals in a pedigree chart. The three pedigree charts on the right provide examples of different types of inheritance patterns and the transmission of abnormal genes through three generations in a family. (Gale)

Autosomal recessive inheritance

Pedigree 2 illustrates the occurrence of an autosomal recessive disorder called cystic fibrosis (CF) in a family. CF is a chronic respiratory disease characterized by digestive problems and a shortened lifespan. A person with CF has two genes for the condition on chromosome 7. Each parent is an obligate carrier of a gene for the condition. When both parents are carriers, there is a one in four or 25% chance that each child they have together will be affected. In autosomal recessive inheritance, siblings are most often affected rather than people in successive generations. Since siblings are affected, this is called horizontal transmission of a disease in the family. Males and females are equally likely to be affected in this type of inheritance, and others in the family have an increased chance to be unaffected carriers of the disease.

X-linked recessive inheritance

Pedigree 3 illustrates the occurrence of an X-linked disorder called hemophilia. Hemophilia is characterized by excessive bleeding and bruising. Depending on the type of hemophilia, a particular blood-clotting factor is deficient. In X-linked recessive inheritance, males are affected with the condition while females are unaffected carriers. In X-linked recessive inheritance, vertical transmission of the disease is seen, with skipping of generations. There is no male-to-male transmission of a disease in this type of inheritance. This is because males pass their Y chromosome to each son, instead of the X chromosome with the disease gene. Each daughter of an affected male is an obligate carrier of the disease, since she will always inherit his X chromosome. There is a 50% chance that each son of a carrier woman will be affected. There is a 50% chance that each daughter of a carrier female will be a carrier.

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- "Pedigree Analysis." Mendelian Genetics. <https://www.ndsu.edu/pubweb/~mcclean/plsc431/mendel/mendel9.htm> (accessed June 16, 2021).

ORGANIZATIONS

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Pelizaeus-Merzbacher disease

Definition

Pelizaeus-Merzbacher disease (PMD) is an X-linked recessive neurological condition that is associated with abnormalities in myelin, the insulation surrounding the nerves in the brain and spinal cord. It is associated with poor muscle control, involuntary repetitive movements of the eyes (nystagmus), floppy muscles (hypotonia), problems with controlling movement, stiff movements of the legs, developmental delays, and progressive deterioration of intellectual function. It primarily affects males.

Description

PMD was named for two German doctors, F. Pelizaeus and L. Merzbacher, who first described the condition in the late 1800s. The severity of characteristics in PMD can range from mild to severe. PMD primarily affects males, but occasionally females have mild or moderate symptoms. PMD is also called a leukodystrophy, meaning that it affects the myelin, sometimes called the white matter, in the brain and spinal cord. The brain and the spinal cord together are called the central nervous system.

Genetic profile

PMD is caused by a pathogenic variant (mutation) in the proteolipid protein gene (*PLP*). The *PLP* gene has the instructions to make proteolipid protein, one of the proteins that make up myelin in the central nervous system. When there is a pathogenic variant in the *PLP* gene, the myelin is not formed properly or is not made at all, resulting in PMD.

Genes are organized on structures called chromosomes. There are hundreds to thousands of genes on each chromosome. There are 46 chromosomes in each cell of the body. They are grouped into 23 pairs. The first 22 pairs are the same in both males and females. The 23rd pair are called the sex chromosomes; having one X chromosome and one Y chromosome causes a person to be male; having two X chromosomes causes a person to be female. A fetus acquires one member of each pair from

the mother's egg and one member from the father's sperm.

The *PLP* gene is located on the X chromosome. Since males have only one X chromosome, they have only one copy of the *PLP* gene. Thus, a male with a variant in his *PLP* gene will have PMD. Females have two X chromosomes and, therefore, have two copies of the *PLP* gene. If they have a variant in one copy of their *PLP* genes, they may only have mild symptoms of PMD or no symptoms at all, because their normal copy of the *PLP* gene makes normal myelin. Females who have one copy of the *PLP* gene with a variant and one normal copy are called carriers.

Inheritance

PMD is passed on through families by X-linked recessive inheritance, which means that affected males are related through females in the family. A male does not pass PMD on to his sons. Females pass one of their X chromosomes on to their sons or daughters. If the normal X chromosome is passed on, her son or daughter will be unaffected and cannot pass PMD onto their children. However, if the X chromosome with the *PLP* variant is passed on, a daughter will be a carrier, while the son will have PMD. Therefore, a female *PLP* variant carrier has a 50%, or one in two, chance of having a normal child (son or daughter), a 25%, or one in four, chance of having a carrier daughter, and a 25%, or one in four, chance of having an affected son. Males with PMD usually do not reproduce and therefore do not pass PMD on. Males with a milder form of PMD called SPG2 can reproduce, and all of their daughters are carriers of the *PLP* gene variant, and none of their sons inherit it. There have been some rare cases where the *PLP* variant was *de novo*, meaning that it originated in the person affected with PMD and was not inherited.

Pathogenic Variants

Different types of pathogenic variants in the *PLP* gene cause PMD. Everyone in a single family who has the condition, or is a carrier, has exactly the same *PLP* variant. The most common type of variant is a duplication (doubling) of the *PLP* gene, which means that two copies of the *PLP* gene are present on one X chromosome. Having this extra copy causes the myelin to be abnormal and leads to PMD. About 50%–75% of people with PMD have a *PLP* duplication. The duplication usually causes a severe form of PMD. Another 15% to 20% of people with PMD have point variants within their *PLP* gene. A point variant is like a typo in the gene. It changes the message of the gene and also causes the myelin to be abnormal. A few patients with PMD have a deletion of the *PLP* gene, which means that they have no copies of the *PLP* gene if they are male, or one copy if they are a carrier female. Another 5%

to 20% of patients have characteristics of PMD, but no variant has been found in their *PLP* gene. It is possible that they have an unknown variant in the *PLP* gene or a variant in another gene.

Some people with symptoms of PMD who do not have a variant in the *PLP* gene may have what is called Pelizaeus-Merzbacher-like disease. This condition has similar symptoms to PLP but is autosomal recessive. An autosomal recessive condition results when someone has variants in both copies of a gene that is found on a chromosome other than the sex chromosomes. Two carriers of Pelizaeus-Merzbacher-like disease have a 25% chance of having a child with the condition. People with Pelizaeus-Merzbacher-like disease can have variants in the *GJC2* or the *NPC1* gene. It is possible that variants in other genes cause this condition.

Demographics

PMD has been described in people from all over the world and from many different ethnic backgrounds. The condition affects males far more frequently than females, with an estimated one in 200,000 to 500,000 males affected in the United States.

Signs and symptoms

There is a range in the severity of symptoms of PMD. Rough categories have been set up based on the age of onset and severity of symptoms. However, many patients do not fall neatly into one of these categories and instead fall somewhere in between. Patients with different severities have been seen in the same family.

In the most severe form of PMD, symptoms are first noticed shortly after birth or in infancy. This is called *connatal* PMD. One of the first signs usually noticed is *nystagmus*, a side-to-side jerking of the eyes. This symptom does not usually cause problems with vision. Patients can have significant intellectual disability and never learn to walk, talk, or care for themselves. They may have noisy breathing called *stridor* and difficulty sucking. Seizures may be present in these children. They often are small for their age and have trouble gaining weight. Early on, they have floppy muscles called *hypotonia*, but later develop *spasticity*, which is stiffness or tightness in the muscles and joints.

Those patients who have classical PMD, which is less severe than the *connatal* type, usually have *nystagmus*, which develops within the first few months of life. Other symptoms typically develop within the first few years. These children also have *hypotonia* that turns into *spasticity*. Sometimes these patients will learn to walk. However, they may need a wheelchair as their *spasticity* increases. Shaking of the head and neck, called *titubation*,

KEY TERMS

Central nervous system (CNS)—In humans, the central nervous system is composed of the brain, the cranial nerves, and the spinal cord. It is responsible for the coordination and control of all body activities.

Leukodystrophy—A disease that affects the white matter, called myelin, in the CNS.

Myelin—An insulation that is wrapped around the nerves in the body. In the central nervous system, it is also called the white matter.

Nystagmus—Involuntary, rhythmic movement of the eye.

Proteolipid protein gene (PLP)—A gene that makes a protein that is part of the myelin in the central nervous system. Variants in this gene cause PMD.

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

may occur. Although these children often have moderate intellectual disability, they often learn to talk and often understand more than is evident by their speech.

A less severe type of PMD is called the PLP null syndrome. Those who are affected do not usually have nystagmus, and their spasticity may be mild. Symptoms develop in early childhood. This group of patients may also have a peripheral neuropathy, which is a problem with the nerves that run from the spinal cord through the body. It can cause weakness and problems with sensation such as difficulties sensing whether something is hot or cold. These patients usually talk and walk. They may have mild to moderate intellectual disability.

There are some people who have *PLP* variants who are very mildly affected. They have spasticity and sometimes have other problems such as a frequent and sudden urge to urinate that may be difficult to control (spastic bladder). Intelligence is normal or mildly impaired. This mild form of PMD is also called spastic paraplegia 2 (SPG2).

Diagnosis

When problems are first noticed in an infant or a child, they will usually be referred to a pediatric neurologist who is specially trained in diseases of the nerves and muscles in children. At the initial evaluation, the neurologist will perform a clinical examination to evaluate the child's development and how well the nerves and muscles work. At that time, a thorough family history should

be taken to determine whether there are others in the family that are affected and, if so, how they are related.

One of the initial tests that may be ordered is magnetic resonance imaging (MRI). In this test, pictures of the brain are taken, and the amount of white matter (myelin) in the brain is measured. In people with PMD, the amount of white matter is usually significantly reduced, compared to normal. However, a decrease in white matter is seen in other neurological conditions and is not specific to PMD. An MRI can be helpful in diagnosing PMD, but if changes are seen on MRI, it does not confirm the diagnosis of PMD. Changes in the white matter may only be seen after one to two years of age, when the brain has matured.

If no one else in the family is known to be affected, testing may be performed to rule out conditions other than PMD. Often, PMD will not be initially suspected when no one else is affected in the family. It is not uncommon for people to be misdiagnosed initially. Sometimes, the diagnosis of PMD is made only after a second affected child is born into a family.

Genetic testing

Genetic testing is the only way to definitely diagnose someone with PMD. If PMD is suspected, then variants can be looked for in just the *PLP* gene or in a number of genes, including the *PLP* gene. If testing is only done on the *PLP* gene, then the gene is often first evaluated for deletions or duplications of the gene. If this test is negative, additional testing can be done to look for other variants in the gene. In 80% of people who have clear symptoms of PMD, a variant can be found in the *PLP* gene. If a variant in the *PLP* gene has been identified, then testing is recommended in family members who might be carriers or affected with PMD.

Prenatal testing

Testing during pregnancy to determine whether an unborn child is affected is possible if genetic testing in a family has identified a specific *PLP* variant. This can be done at 10 to 12 weeks of gestation by a procedure called chorionic villus sampling (CVS), which involves removing a tiny piece of the placenta and examining the cells. It can also be done by amniocentesis after 16 weeks of gestation by removing a small amount of the amniotic fluid surrounding the baby and analyzing the cells in the fluid. Each of these procedures has a small risk of miscarriage associated with it. Couples who are interested in these options should have genetic counseling to carefully explore all of the benefits and limitations of these procedures.

Treatment and management

There is no treatment or cure for PMD. Medical management is aimed at making life as full as possible and keeping people free from illness. Different types of therapy might be suggested. An occupational therapist can suggest adaptive devices to make it easier for an affected person to get around his or her home and perform everyday activities such as eating and using the bathroom. For example, they may suggest installing bars to use in the bathroom or shower or special utensils for eating. Physical therapy can be helpful for reducing spasticity. Some patients with PMD require a feeding tube to help take in more calories. There are also medications that can assist in treating spasticity and seizures.

Treatments Under Investigation

Treatments for people who have duplications of the *PLP* gene or who have variants that increase the production of PLP protein are under investigation. Pharmacologic agents that lower expression of PLP1 are being researched. Researchers are also investigating the use of synthetic mRNA to decrease the production of the PLP protein. mRNA is created from DNA and contains the instructions for the production of proteins. Decreasing the production of the PLP protein seems to regenerate myelin and reduce the symptoms of PMD in mice. This therapy needs to be tested in human patients.

Research is also being done on a drug that may help treat PMD in some people. Researchers have found that cells from a mouse with PMD appeared to be damaged by excess iron. They injected a drug into the mice with PMD that binds to and removes iron. This drug appeared to stimulate the formation of new myelin. They plan to test this in children in Europe.

Prognosis

The prognosis for patients with PMD varies in part due to the severity of the symptoms. The quality of care that patients receive also makes a difference in their quality of life. Boys with congenital PMD may die in infancy or early childhood, although some have survived into their 30s. Those with classic PMD or the PLP null syndrome usually reach adulthood, and some have survived into their 70s. Males with SPG2 usually have a normal lifespan. The symptoms of PMD usually progress very slowly, and some people have a plateau of their symptoms over time. Some people's condition may seem to worsen over time, but that is likely to be due to factors such as growth spurts, poor nutrition, or frequent illness and not progression of the disease. Most patients with PMD die from pulmonary or breathing difficulties.

QUESTIONS TO ASK YOUR DOCTOR

- What are the usual signs and symptoms associated with Pelizaeus-Merzbacher disease?
- What is known about the genetic basis of this disorder?
- At what age can Pelizaeus-Merzbacher disease be diagnosed, and how is that diagnosis made?
- What factors affect the prognosis for a child diagnosed with Pelizaeus-Merzbacher disease?

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ORGANIZATIONS

- National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, <http://www.rarediseases.org>

PMD Foundation, 1 Greentree Center, 1000 Lincoln Drive East,
Suite 201, Marlton, NJ 08053, (609) 443-9623,
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United Leukodystrophy Foundation, 224 North 2nd Street, Suite
2, DeKalb, IL 60115, (800) 728-5483, office@ulf.org,
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Pendred syndrome

Definition

Pendred syndrome is an inherited condition that causes hearing loss typically beginning at birth and usually leads to the development of an enlarged thyroid, called a goiter. The thyroid is a gland responsible for normal body growth and metabolism. People with Pendred syndrome often have altered development of certain bones in the inner ear and/or balance problems. Vaughan Pendred first described the presence of hearing loss and goiter in two sisters in 1896, and the condition became known as Pendred syndrome. Genetic research has identified a gene on chromosome 7 that is usually altered in people with Pendred syndrome.

Description

Pendred syndrome is sometimes called goiter-sensorineural deafness, due to the common existence of both goiter and a form of hearing loss called sensorineural hearing loss in affected individuals. In order to understand how goiter occurs, it is helpful to first understand how the thyroid gland normally works. The thyroid is located underneath the larynx (voice box), in the front of the neck. The main role of the thyroid is to trap iodine, an essential nutrient found in various foods as well as salt, and to use it to make two important hormones: T3 and T4. These thyroid hormones allow the body to grow normally and to increase the speed of metabolism (breakdown) of nutrients. The thyroid is able to create these hormones because of a series of chemical reactions. A portion of the brain called the hypothalamus is responsible for controlling many body functions. One of its functions is to make a chemical called thyroid-releasing hormone (TRH). This hormone travels to another gland, called the anterior pituitary gland, which is located underneath the brain. The TRH stimulates the anterior pituitary gland, which makes a chemical called thyroid-stimulating hormone (TSH). This hormone travels to the thyroid and activates the release of T3 and T4 into the body.

The word “goiter” is used to describe an enlargement of the thyroid gland. People with goiter may have hypothyroidism (they make too little T3/T4), hyperthyroidism (they make too much T3/T4), or they may have thyroid glands that work normally. Approximately 44%–50% of people with Pendred syndrome have hypothyroidism, while the remaining 50%–56% have thyroid glands that create a normal amount of thyroid hormones. However, approximately 75% develop goiter at some point in time, although it is rarely present at birth. Thirty to 40% of individuals develop an enlarged thyroid in late childhood or during their early teenage years. The remaining 60%–70% show symptoms during their early adult years. The enlargement of the thyroid gland happens because the mechanisms that control iodine transfer within the cells of the thyroid do not work well. This transfer is necessary to allow the iodine to bind to (and in doing so, help generate) thyroid hormones stored inside the thyroid. Since the iodine is not moved to the correct area of the thyroid, it becomes “pooled,” rather than attaching itself to thyroid hormones. This faulty processing of iodine among people with Pendred syndrome can often be confirmed by the use of a perchlorate discharge test. Perchlorate is a chemical that causes the pooled iodine to be pushed out of the thyroid into the bloodstream, where it can be measured. Since people with Pendred syndrome usually have more pooled iodine than normal, they will push out or discharge a larger amount of iodine when they are exposed to perchlorate. However, not all affected individuals show abnormal results, so the test is not perfect.

Pendred syndrome causes a specific type of hearing impairment called sensorineural hearing loss (SNHL). The ear can be divided into three main parts: the outer ear, the middle ear, and the inner ear. The parts of the outer ear include the pinna (the visible portion of the ear), the ear canal, and the eardrum. The pinna directs sound waves from the environment through the ear canal, toward the eardrum. The eardrum vibrates and causes tiny bones (called ossicles), which are located in the middle ear, to move. This movement causes pressure changes in fluids surrounding the parts that make up the inner ear.

The main structures of the inner ear are the cochlea and the vestibular system. These structures send information regarding hearing and balance to the brain. The cochlea is shaped like a snail shell, and it contains specialized sensory cells (called hair cells) that change the sound waves into electrical messages. These messages are then sent to the brain through a nerve (called the auditory nerve) that allows the brain to “hear” sounds from the environment. The vestibular system is a specialized organ that helps people maintain balance. The vestibular system contains three structures called semicircular canals, which send electrical messages to the brain about

KEY TERMS

Cochlea—A bony structure shaped like a snail shell located in the inner ear. It is responsible for changing sound waves from the environment into electrical messages that the brain can understand, so people can hear.

Cochlear implantation—A surgical procedure in which a small electronic device is placed under the skin behind the ear and is attached to a wire that stimulates the inner ear, allowing people who have hearing loss to hear useful sounds.

Enlarged vestibular aqueduct (EVA)—An enlargement of a structure inside the inner ear called the vestibular aqueduct, which is a narrow canal that allows fluid to move within the inner ear. EVA is seen in approximately 10% of people who have sensorineural hearing loss.

Goiter—An enlargement of the thyroid gland, causing tissue swelling that may be seen and/or felt in the front of the neck. It may occur in people who have overactive production of thyroid hormones (hyperthyroidism), decreased production of thyroid hormones (hypothyroidism), or normal production of thyroid hormones.

Metabolism—The total combination of all of the chemical processes that occur within cells and tissues of a living body.

Pendrin—A protein encoded by the *SLC26A4* gene located on chromosome 7q31. Pendrin protein is

believed to transport iodide and chloride within the thyroid and the inner ear.

Perchlorate discharge test—A test used to check for Pendred syndrome by measuring the amount of iodine stored inside the thyroid gland. Individuals with Pendred syndrome usually have more iodine stored than normal, and thus their thyroid will release a large amount of iodine into the bloodstream when they are exposed to a chemical called perchlorate.

Sensorineural hearing loss (SNHL)—Hearing loss that occurs when parts of the inner ear, such as the cochlea and/or auditory nerve, do not work correctly. It is often defined as mild, moderate, severe, or profound, depending upon how much sound can be heard by the affected individual.

Thyroid gland—A gland located in the front of the neck that is responsible for normal body growth and metabolism. The thyroid traps a nutrient called iodine and uses it to make thyroid hormones, which allow for the breakdown of nutrients needed for growth, development, and body maintenance.

Vestibular system—A complex organ located inside the inner ear that sends messages to the brain about movement and body position. It allows people to maintain their balance when moving by sensing changes in their direction and speed.

movement and body position. This allows people to maintain their balance when moving by sensing changes in their direction and speed.

Sensorineural hearing loss occurs when parts of the inner ear (including the cochlea and/or auditory nerve) do not work correctly. The amount (or degree) of hearing loss can be described by measuring the hearing threshold (the sound level that a person can just barely hear) in decibels (dB). The greater a person's dB hearing level, the louder the sound must be to just barely be heard.

Hearing loss is often defined as mild, moderate, severe, or profound. For people with mild hearing loss (26–45 dB), understanding conversations in a noisy environment, at a distance, or with a soft-spoken person is difficult. Moderate hearing loss (46–65 dB) causes people to have difficulty understanding conversations, even if the environment is quiet. People with severe hearing loss (66–85 dB) have difficulty hearing conversation unless

the speaker is standing nearby or is talking loudly. Profound hearing loss (85 dB) may prevent people from hearing sounds from their environment or even loud conversation. People with Pendred syndrome generally have severe to profound SNHL that is congenital (i.e., present at birth) in both ears. However, some affected individuals develop SNHL during childhood, after they have learned to speak.

People with SNHL often undergo specialized imaging tests, such as computed tomography (CT) and/or magnetic resonance imaging (MRI) scans, which create detailed images of the tissue and bone structures of the inner ear. Approximately 85% of people affected with Pendred syndrome have physical changes in the inner ear that can be seen with these tests. A common finding is a visible change in the snail-shaped cochlea called a Mondini malformation, in which the cochlea is underdeveloped and has too few coils compared to a normal cochlea. Another visible change sometimes seen in the

inner ear is called enlarged vestibular aqueduct. The vestibular aqueduct is a narrow canal that allows fluid to move within the inner ear. Enlarged vestibular aqueduct (EVA) is the most common form of inner ear abnormality that is seen with CT or MRI scans. As the name implies, the vestibular aqueduct (canal) is larger than normal in people with EVA. Although EVA is seen in approximately 10%–12% of people who are born with SNHL, some people with EVA can have SNHL that fluctuates (comes and goes) or is progressive (gradually worsening), as well as balance problems.

In spite of the fact that Pendred syndrome has typically been diagnosed among people with both SNHL and goiter/thyroid problems, research supports the finding that some people with EVA and SNHL have a form of Pendred syndrome, even if they do not have goiter or thyroid problems.

Pendred syndrome causes vestibular dysfunction in approximately 66% of affected individuals, which means they have abnormalities in their vestibular (balance) system. This may cause problems such as dizziness because they cannot sense changes in direction or speed when they are moving.

A closely related condition involving hearing loss is DFNB4 hearing loss. This type of hearing loss is considered a nonsyndromic hearing loss because there are generally no other related abnormalities in the individual. It is very difficult to differentiate this type of hearing loss from Pendred syndrome. Researchers have discovered that DFNB4 hearing loss is caused by mutations in the same gene that cause Pendred syndrome. Pendred syndrome and DFNB4 hearing loss fall on a spectrum of hearing impairment conditions that may also include other abnormalities.

Genetic profile

The majority of Pendred syndrome cases are caused by mutations in the *SLC26A4* gene. Located on chromosome 7q31, this gene tells the body how to make a specific protein called pendrin. The pendrin protein is responsible for transporting negatively charged elements (ions) such as iodide and chloride (forms of iodine and chlorine) within the thyroid and the inner ear as well. Changes within the *SLC26A4* gene create an altered form of pendrin protein that does not work properly and thus causes the symptoms of Pendred syndrome. Genetic researchers have identified at least 60 different types of alterations in the *SLC26A4* gene among different families. However, four of these are more common than the others, and it is estimated that approximately 75% of affected people have these common changes.

QUESTIONS TO ASK YOUR DOCTOR

- What is a goiter, and what causes the development of a goiter?
- Why is Pendred syndrome considered to be a genetic disorder?
- If someone in my family has had Pendred syndrome, what are the chances that my own children will also develop the condition?
- Are there tests that can be conducted, either before a child is born or while the child is still an infant, that will predict if the child will develop Pendred syndrome?

Pendred syndrome is inherited in an autosomal recessive manner. Autosomal means that males and females are equally likely to be affected. Recessive refers to a specific type of inheritance in which both copies of a person's gene pair (both alleles) need to be changed or altered in order for the condition to develop. In this situation, an affected individual receives an altered copy of the same gene from each parent. If the parents are not affected, they each have one working copy of the gene and one nonworking (altered) copy and are only carriers for Pendred syndrome. The chance that two carrier parents will have a child affected with Pendred syndrome is 25% for each pregnancy. They also have a 50% chance to have an unaffected child who is simply a carrier, and a 25% chance to have an unaffected child who is not a carrier, with each pregnancy.

Genetic research on the *SLC26A4* gene has revealed that different types of gene changes can lead to different symptoms. For example, changes that completely inactivate the pendrin protein have been seen among people with Pendred syndrome, whereas other types of alterations that only decrease the activity of pendrin have been found in people who have an inherited form of deafness called DFNB4. These individuals do have SNHL, but they do not develop goiter. Researchers suspect that the small amount of pendrin activity in these individuals likely prevented or delayed the symptoms of goiter. Greater than 80% of people with EVA and SNHL have one or more changes in the *SLC26A4* gene, even though they may not all have thyroid changes such as goiter or abnormal perchlorate discharge test results. Changes in the pendrin gene cause a number of overlapping conditions. These conditions range from Pendred syndrome (SNHL and thyroid changes) to SNHL with EVA.

Demographics

It is estimated that 10% of all hearing loss may be attributed to Pendred syndrome. It has been diagnosed in many different ethnic groups, including European, Japanese, East Indian, and other Caucasian groups, as well as among people of African descent. Inherited forms of congenital SNHL occur in approximately 1 of every 2,000 children. Males and females are both affected.

Signs and symptoms

Although the symptoms of Pendred syndrome can vary among different individuals, the findings may include the following:

- sensorineural hearing loss that is usually congenital
- thyroid changes such as goiter, abnormal perchlorate discharge test results, and/or hypothyroidism
- inner ear changes, such as enlarged vestibular aqueduct (EVA) or Mondini malformation
- altered vestibular function that leads to balance problems

Diagnosis

The diagnosis of Pendred syndrome is typically based upon the results from a variety of tests that measure hearing, thyroid appearance/function, inner ear structure, and balance. Sometimes the diagnosis is not made until a person with SNHL reaches adolescence or adulthood and develops thyroid problems such as goiter or hypothyroidism. These problems are usually detected by physical examination and blood tests, and thus help diagnose Pendred syndrome. Children who are born with SNHL often undergo special imaging tests such as CT or MRI scans. These may show inner ear changes that raise the question of possible changes in the *SLC26A4* gene, even if the children do not have thyroid problems. In each of these situations, genetic testing may provide useful information that can confirm the diagnosis of Pendred syndrome.

Genetic research testing can be done for people with suspected or known Pendred syndrome by studying their DNA. The laboratory can check for mutations in the *SLC26A4* gene. If this testing identifies an affected person's specific genetic changes, other people in the same family who are not affected may have their DNA examined as well. This can determine whether an unaffected person is a carrier for Pendred syndrome or not. In addition, testing could be done during a pregnancy if both of a baby's parents are carriers and have each had specific changes diagnosed in their DNA.

If genetic testing is done for people with known or suspected Pendred syndrome and the laboratory finds only one changed gene or no changes in the *SLC26A4* gene, the diagnosis of Pendred syndrome cannot be

confirmed. However, this does not rule out the possibility of Pendred syndrome. Sometimes this happens simply because the affected person has a very unique change in the *SLC26A4* gene that the lab cannot clearly identify.

Treatment and management

There is no known cure for Pendred syndrome. However, there are several ways to treat some of the symptoms.

Treatment and management of SNHL

Regular visits with an audiologist (a hearing specialist) and an ENT (a physician specializing in the ear, nose, and throat) are important for people with Pendred syndrome. Hearing tests are necessary to check for changes in hearing ability, especially if people have milder forms of hearing loss and have some ability to hear. Among people with milder forms of hearing loss, hearing aids and speech therapy may be useful. However, people with profound SNHL and their families usually benefit from sign language training, which provides a good method of communication. Some people with severe to profound forms of hearing loss may also consider a procedure called cochlear implantation, in which a small electronic device is surgically placed behind the ear (underneath the skin) and is attached to a wire that stimulates the inner ear. This may allow people to hear useful sounds.

Treatment and management of thyroid problems

Regular examinations by an endocrinologist (a physician specializing in the treatment of hormone problems) who is familiar with Pendred syndrome is important. People who develop goiter and/or hypothyroidism are sometimes treated with a medication called thyroxine, which is basically the hormone called T4. Other people with goiter have most of their thyroid surgically removed. However, this form of treatment is not a cure, and the remaining thyroid tissue can grow and redevelop into goiter again. Among some people, the goiter does not require treatment or it simply disappears on its own.

There are a number of support groups available that provide education, support, and advice to help people cope with the symptoms of SNHL and thyroid problems that often occur among individuals with Pendred syndrome.

Prognosis

Pendred syndrome does not cause a shortened lifespan for affected individuals. Those who develop hypothyroidism and do not seek treatment may experience a

variety of health problems including low energy level, weight gain, constipation, and dry skin. However, hypothyroidism and goiter can usually be well managed with medication or surgery. The degree of hearing loss that occurs is typically severe to profound from an early age and usually changes very little over the years. Among affected people who develop SNHL during childhood (after learning to speak), the degree of hearing loss can worsen over time. Sign language training (and sometimes cochlear implants) allow alternative methods of communication and thus help people reach their full potential. Support groups for people with hearing loss often help individuals with SNHL (whether due to Pendred syndrome or other causes) maintain and/or improve their quality of life as well.

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"Pendred Syndrome." NIH. <https://www.nidcd.nih.gov/health/pendred-syndrome> (accessed June 16, 2021).

ORGANIZATIONS

American Society for Deaf Children, 800 Florida Ave. NE, No. 2047, Washington, DC 20002-3695, (800) 942-2732, (410) 795-0965, <http://www.deafchildren.org>

American Thyroid Association, 6066 Leesburg Pike, Suite 550, Falls Church, VA 22041, (703) 998-8890, (703) 998-8893, thyroid@thyroid.org, <http://www.thyroid.org>

National Association of the Deaf, 8630 Fenton St., No. 820, Silver Spring, MD 20910, (301) 328-1443, (301) 587-6380, nadinfo@nad.org, <http://www.nad.org>

National Institute on Deafness and Other Communication Disorders, 31 Center Dr., MSC 2320, Bethesda, MD 20892-2320, nidcdinfo@nidcd.nih.gov, <http://www.nidcd.nih.gov>

Vestibular Disorders Association, 5018 NE 15th Ave., Portland, OR 97211, (800) 837-8428, (503) 229-8064, info@vestibular.org, <http://www.vestibular.org>

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Pepper syndrome see **Cohen syndrome**

Perinatal sudanophilic leukodystrophy see **Pelizaeus-Merzbacher disease**

Peroutka sneeze see **ACHOO syndrome**

Pervasive developmental disorders

Definition

The pervasive developmental disorders, or PDDs, are a group of childhood disorders that manifest during the first years of a child's life. They are marked by severe weaknesses in several areas of development, including social interaction and communication, and the appearance of stereotyped behavior patterns and interests. The PDDs are also known as autistic spectrum disorders (ASDs). As the phrase "spectrum disorder" suggests, persons with these disorders fall at different points along a fairly wide continuum of disabilities and associated disorders. As defined by the *Diagnostic and Statistical Manual of Mental Disorders*, also referred to as *DSM-5*, the pervasive developmental disorders include the following:

- autistic disorder
- Rett syndrome
- childhood disintegrative disorder (CDD)
- Asperger syndrome
- pervasive developmental disorder not otherwise specified (PDD-NOS)

Description

The PDDs form a diagnostic category intended to identify children with delays in or deviant forms of social, linguistic, cognitive, and motor (muscular movement) development. The category covers children with a wide variety of developmental delays of differing severity in these four broad areas. The precise cause(s) of the PDDs are still obscure, but are assumed to be abnormalities of the central nervous system.

Autistic disorder

Autistic disorder, or autism, was first described in 1943. Autistic children are characterized by severe impairment in their interactions with others and delayed or abnormal patterns of communication; about 50% of autistic children do not speak at all. These abnormalities begin in the first weeks of life; it is not unusual for the parents of an autistic child to say that they "knew something was wrong" quite early in the child's development. Another characteristic symptom has

been termed “insistence on sameness”; that is, these children may become extremely upset by trivial changes in their environment or daily routine—such as a new picture on the wall or taking a different route to the grocery store. Autistic children often make repetitive or stereotyped gestures or movements with their hands or bodies. Their behavioral symptoms may also include impulsivity, aggressiveness, temper tantrums, and self-biting or other forms of self-injury.

About 75% of children diagnosed with autism are also diagnosed with moderate intellectual disability (IQ between 35 and 50). Their cognitive skills frequently develop unevenly, regardless of their general intelligence level. A minority of autistic children have IQs above 70; their condition is sometimes called high-functioning autism, or HFA. In addition to intellectual disability, autism is frequently associated with other neurological or medical conditions, including encephalitis, phenylketonuria, tuberous sclerosis, fragile X syndrome, and underdeveloped reflexes. About 25% of autistic children develop seizure disorders, most often in adolescence.

Rett syndrome

Unlike autism, Rett syndrome has a very distinctive onset and course. The child develops normally during the first five months of life; after the fifth month, head growth slows down and the child loses whatever purposeful hand movements she had developed during the first five months. After 30 months, the child frequently develops repetitive hand-washing or hand-wringing gestures; over 50% of children with the disorder will develop seizure disorders. Rett syndrome is also associated with severe or profound intellectual disability. This disorder is diagnosed only in females.

Childhood disintegrative disorder (Heller’s syndrome)

Childhood disintegrative disorder, or CDD, was first described by an educator named Theodore Heller in 1908. He referred to it as dementia infantilis. Children with CDD have apparently normal development during the first two years of life. Between two and ten years of age, the child loses two or more previously acquired skills, including language skills, social skills, toileting, self-help skills, or motor skills. The child may also lose interest in his or her surroundings and often comes to “look autistic.” CDD has several different patterns of onset and development; it may develop rapidly (within weeks) or more slowly (over a period of months).

CDD is frequently associated with severe intellectual disability. In addition, children with CDD have a higher risk of seizures. CDD is occasionally associated with general medical conditions (metachromatic leukodystrophy or Schilder’s disease) that could account for the

KEY TERMS

Atypical personality development—Another term for pervasive development disorder (PDD-NOS). Other synonyms for this diagnostic category are atypical autism and atypical PDD.

Autistic psychopathy—Hans Asperger’s original name for Asperger syndrome. It is still used occasionally as a synonym for the disorder.

Autistic spectrum disorders—Another term for the pervasive developmental disorders.

GABAergic system—The system by which gamma-aminobutyric acid (GABA), the main neuro-inhibitory transmitter and its receptor, function within the brain during pre- and post-synaptic events to modulate ion channels.

Heller’s syndrome—Another name for Childhood Disintegrative Disorder (CDD). It is also sometimes called dementia infantilis.

Kanner’s syndrome—Another name for autism.

developmental losses, but in most cases there is no known medical cause of the child’s symptoms.

Asperger syndrome

Asperger syndrome (AS) was first identified in 1944 by a Viennese psychiatrist. It is sometimes called autistic psychopathy. AS is distinguished from autism by later onset of symptoms. These children usually develop normally for the first few years of life and retain relatively strong verbal and self-help skills. They are often physically clumsy or awkward, however, and this symptom may be noticed before the child starts school. AS is diagnosed most frequently when the child is between five and nine years of age. One of the distinctive features of Asperger syndrome is an abnormal degree of fascination or preoccupation with a limited or restricted subject of interest, such as railroad timetables, the weather, astronomical data, French verb forms, etc. In addition, the child’s knowledge of the topic reflects rote memorization of facts rather than deep understanding.

Unlike autism, AS does not appear to be associated with a higher risk of seizure disorders or such general conditions as fragile X syndrome.

Pervasive developmental disorder not otherwise specified

PDD-NOS is regarded as a “subthreshold” category, which means that it covers cases in which the child has

some impairment of social interaction and communication or has some stereotyped patterns of behavior but does not meet the full criteria for another PDD. PDD-NOS is sometimes referred to as atypical personality development, atypical autism, or atypical PDD. No diagnostic criteria specific to this category are provided in *DSM-5*. Little research has been done on children diagnosed with PDD-NOS because the condition has no clear definition. The available data indicate that children placed in this category are diagnosed at later ages than children with autism and are less likely to have mental impairment.

Genetic profile

Of the PDDs, autism has the best-documented genetic component, although more research is required. It is known that the degree of similarity in a pair of twins with respect to autism is significantly higher in identical than in fraternal twins. The likelihood of the biological parents of an autistic child having another child with the disorder is thought to be about 1:20. It is possible that the actual rate is higher, since many parents of one autistic child decide against having more children.

The genetic profile of Asperger syndrome is less well known, although the disorder appears to run in families—most commonly families with histories of depression or bipolar disorder. Rett syndrome is known only from case studies, so data about its genetic profile is not available. The same lack of information is true also of CDD—partly because the disorder was first reported in 1966 and has only been officially recognized since 1994, and partly because the condition has been frequently misdiagnosed.

Demographics

ASD is thought to affect 1 in 68 U.S. children. CDD is much less frequent, perhaps only a tenth as common as ASD. Rett syndrome is also very rare and is known only from case series reported in the medical literature. The incidence of Asperger syndrome is not definitely known, but some estimates put it between 0.36% and 0.71% of the general population.

Some of the PDDs are considerably more common in boys than in girls. The male-to-female sex ratio in autism is variously given as 4:1 or 5:1. Less is known about the incidence of Asperger syndrome, but one study reported a male/female ratio of 4:1. Initial studies of CDD suggested an equal sex ratio, but more recent data indicate that the disorder is more common among males. Rett syndrome, on the other hand, has been reported only in females.

Signs and symptoms

The signs and symptoms of each PDD are included in its description.

Diagnosis

The differential diagnosis of ASD is complicated by several factors. One is the wide variation in normal rates of children's development. In addition, because some of the symptoms of autism are present in intellectual disability, it can be difficult to determine which condition is present in a specific child, or whether both conditions are present. A definitive diagnosis of autism is rarely given to children under the age of three years. Delays or abnormal patterns in cognitive and social development can be more accurately assessed in children age three or four; children with AS or PDD-NOS may not be diagnosed until age five or later. A third factor is the tangled history of differential diagnosis of childhood disorders. Autism was first described by a physician named Leo Kanner in 1943. For several decades after Kanner's initial observations, researchers assumed that there was an association or continuity between autism in children and schizophrenia in adults. In fact, the term "autism" was first used to describe the self-focused thinking that characterizes schizophrenia; it was only later that the word was applied to the severe impairment of social behaviors that is a major symptom of autistic disorder. It took years of further research to establish clear diagnostic distinctions between autism and schizophrenia. Furthermore, the early assumption of a connection between autism and schizophrenia led to the hypothesis that autism was caused by painful experiences in early childhood. It is now known that autism and the other PDDs are essentially neurological disturbances.

Medical or laboratory testing

There are no brain imaging studies or laboratory tests that can be performed to diagnose a pervasive developmental disorder. The examiner may recommend a hearing test to rule out deafness as a possible cause of a child's failure to respond to the environment or a brain scan to rule out other physical conditions.

Diagnostic interviews

A PDD may be diagnosed by a pediatrician, pediatric neurologist, psychologist, or specialist in child psychiatry. The diagnosis is usually based on a combination of the child's medical and developmental history and clinical interviews or observations of the child. Children who cannot talk can be evaluated for their patterns of nonverbal communication with familiar as well as unfamiliar people. The parents may be asked to describe the child's use of eye contact, gestures, facial expressions, and body language. A clinical psychologist can administer special tests designed to evaluate the child's problem-solving abilities without the use of language.

Diagnostic questionnaires and other tools

The examiner may use a diagnostic checklist or screener such as the Childhood Autism Rating Scale, or CARS, which was developed in 1993. In addition, the Autism Research Institute (ARI) distributes a Form E-2 questionnaire that can be completed by the parents of a child with a PDD and returned to ARI. Form E-2 is not a diagnostic instrument as such but a checklist that assists ARI in the compilation of a database of symptoms and behaviors associated with autistic spectrum disorders. Parents who complete the form will receive a brief report about their child. Researchers expect that the database will help to improve the accuracy of differential diagnosis as well as contribute to more effective treatments for children with PDDs.

Treatment and management

The treatment and management of children with PDDs varies considerably according to the severity of the child's impairment and the specific areas of impairment. It is known that the GABAergic system is disrupted in many of these neurological disorders, and recent research findings in animal models of many of the aforementioned disorders have shown that drugs that target and modulate the GABAergic system have had encouraging outcomes and should be tested in clinical trials.

Medications

There are no medications that can cure any of the PDDs, and no single medication that is recommended for the symptoms of all children with PDDs. In addition, there are few comparative medication studies of children with ASD. The five sites (UCLA, University of Indiana, Ohio State, Yale, and the Kennedy-Krieger Institute) involved in the Research Units in Pediatric Psychopharmacology (RUPP) Program are currently conducting a study of risperidone in PDD children with behavioral problems. The RUPP sites are also testing medications approved for use in adults with self-injuring behaviors, anxiety, aggressive behavior, and obsessive-compulsive disorder on children with PDDs. This research is expected to improve the available treatments for children with these disorders.

Psychotherapy

The only PDD patients who benefit from individual psychotherapy are persons with AS or with HFA who are intelligent enough to have some insight into their condition. Typically, they become depressed in adolescence or adult life when they recognize the nature and extent of their social disabilities.

Educational considerations

Most children with AS and some children with high-functioning autism are educable. Many people with AS, in

QUESTIONS TO ASK YOUR DOCTOR

- What does the phrase "pervasive developmental disorders" mean?
- At what stage of a person's life do pervasive developmental disorders typically manifest?
- Are there medications or other types of treatments that can be used with pervasive developmental disorders?
- Are there organizations that can provide parents with additional information about any one or more of the most common pervasive developmental disorders?
- Have any therapies been found to be useful in treating autism or AS?

fact, successfully complete graduate or professional school. Only a small percentage of autistic children, however, complete enough schooling to be able to live independently as adults. Children with CDD must be placed in schools for the severely disabled.

Employment

Most children with AS can finish school and enter the job market. They do best in occupations that have regular routines or allow them to work in isolation. Only a few high-functioning autistic children are potentially employable.

Prognosis

The PDDs as a group are lifelong disorders, but the prognoses vary according to the child's degree of impairment. As a general rule, language skills and the child's overall IQ are the most important factors in the prognosis. Children with AS have the most favorable educational prognosis but usually retain some degree of social impairment even as adults. Of autistic children, only about one-third achieve partial or complete independence in adult life. The prognoses for Rett syndrome and CDD are worse than that for autism, as the skill levels of these children often continue to deteriorate. Some, however, make very modest developmental gains in adolescence. Lastly, current information about the prognoses of children with PDDs is derived from treatments given to patients in the 1970s or 1980s. As knowledge of effective treatments for PDDs continues to accumulate, children with these disorders will receive treatment earlier than they did two decades ago. It is likely that future prognoses for the PDDs will reflect these improvements.

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ORGANIZATIONS

- Asperger/Autism Network, 51 Water St., Suite 206, Watertown, MA 02472, (617) 393-3824, info@aane.org, <http://www.aane.org>
- Asperger Autism Spectrum Education Network (ASPEN), 9 Aspen Circle, Edison, NJ 08820, (732) 321-0880, <http://aspennj.org>
- Autism Research Institute, 4182 Adams Ave., San Diego, CA 92116, (866) 366-3661, <http://www.autism.com>
- Autism Speaks, 1 E. 33rd St., 4th Floor, New York, NY 10016, (888) 288-4762, familyservices@autismspeaks.org, <https://www.autismspeaks.org>
- International Rett Syndrome Foundation, 4600 Devitt Dr., Cincinnati, OH 45246, (800) 818-7388, admin@rettsyndrome.org, <http://www.rettsyndrome.org>

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Peutz-Jeghers syndrome

Definition

Peutz-Jeghers syndrome (PJS) is named after two doctors who first studied and described it in 1921. It is an association of three very specific conditions in any one person. The first condition is the appearance of

freckles on parts of the body where freckles are not normally found. The second condition is the presence of multiple gastrointestinal polyps. The third condition is a risk, greater than the risk seen in the general population, of developing certain kinds of cancers.

Description

The freckles associated with PJS are dark brown, dark blue, or greenish black. In almost all people with PJS, these freckles are present at birth on the lining of the cheeks inside the mouth. By the time most children reach one or two years old, freckles develop around the lips, nostrils, eyes, anus, and genitals. This is in contrast to ordinary freckles, which are absent at birth and rarely develop in these locations. The freckles seen in PJS are sometimes called macules (discolored spot or patch on the skin of various colors, sizes, and shapes) or areas of hyperpigmentation (increased pigmentation of the skin).

Some people with PJS also have these freckles on the palms of their hands or feet or on their fingertips. Freckles may merge together. The freckles on the skin often fade or disappear by adolescence, but the freckles inside the mouth generally remain throughout the person's life.

Gastrointestinal polyps can develop in children as young as one or two years old. The age at which polyps appear and the number of polyps vary widely from patient to patient. Polyps can occur in infants and cause spasms and pain in the abdomen. On average, polyps appear by the time a child with PJS is ten years old. There may be anywhere from dozens to hundreds of polyps throughout the gastrointestinal tract. For this reason, PJS is sometimes called polyposis, which means "too many polyps." Most PJS polyps occur in the small intestine, but they can also develop in the esophagus, stomach, and colon. In some people with PJS, polyps have been found in the mouth or nose.

The polyps seen in PJS have a unique structure. They consist of overgrowths of normal tissue that smooth muscle bands of the stomach and intestines run through. This kind of overgrowth is called a hamartoma. Consequently, PJS is sometimes called hamartomatous intestinal polyposis. A hamartoma is a noncancerous tumor, and hamartomatous polyps are not cancerous. However, they can take up too much space, causing obstruction, pain, and even bleeding. They can also become cancerous, or malignant, if a genetic change results in uncontrolled cell growth.

It is this potential for malignant change that increases cancer risk in people with PJS. As might be expected, the gastrointestinal tract is the most common site for cancer in people with PJS. The small intestine,

stomach, gallbladder, pancreas, colon, and rectum are all susceptible. However, cancer can also occur outside the gastrointestinal tract. When this happens, the sites most likely to be involved are the breasts, ovaries, uterus, cervix, or testicles.

PJS does not affect intelligence or behavior.

Genetic profile

Researchers have identified the gene responsible for about seven out of ten PJS cases. The gene is named *STK11*, and it is located at the 19p13 site on chromosome 19. In some older studies, the same gene is referred to as *LKB1*. Researchers have connected more than 50 different *STK11* mutations to cases of PJS.

However, some cases do not appear to be connected to *STK11*. As a result, PJS qualifies as a genetically heterogeneous condition; this means that it has more than one known genetic cause. Research continues in order to locate the genes involved in the three out of ten cases not related to *STK11*.

When linked to *STK11*, PJS is an autosomal dominant disorder. This means that the condition occurs even when an individual inherits only one abnormal copy of *STK11* from either parent. In some people with PJS, the condition is limited to freckles on the lining of the cheeks inside the mouth. Many of these people also have gastrointestinal polyps. One abnormal copy of *STK11* also increases a person's risk of developing the kinds of cancer associated with PJS.

Since only one abnormal copy of *STK11* is needed to cause PJS, most people with the condition still have one normal copy of the gene. One normal copy is usually enough to protect against the kinds of cancer associated with PJS. This is because *STK11* is a tumor suppressor gene. A properly working tumor suppressor gene makes a product that controls cell growth. Since cancer is the result of uncontrolled cell growth, tumor suppressors prevent cancer. Even one working copy of *STK11* protects against cancer.

The reason people with PJS have an increased risk of developing cancer is that one *STK11* gene is already abnormal at birth. If damage to the normal *STK11* gene occurs later, the ability to control cell growth is lost, leading to the kinds of cancers associated with PJS.

Damage to normal genes can occur in anyone. However, it generally takes less time to damage one gene than two genes. Therefore, people with PJS are likely to develop cancer at earlier ages than are people born with two normal *STK11* genes.

About half of all PJS cases occur because a child inherits a changed gene from a parent with PJS. The other

KEY TERMS

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Colon—The large intestine.

Colonoscopy—Procedure for viewing the large intestine (colon) by inserting an illuminated tube into the rectum and guiding it up the large intestine.

Endoscopy—A slender, tubular optical instrument used as a viewing system for examining an inner part of the body and, with an attached instrument, for biopsy or surgery.

Enteroscopy—A procedure used to examine the small intestine.

Esophagus—The part of the digestive tract that connects the mouth and stomach; the food pipe.

Gastrointestinal—Concerning the stomach and intestine.

Hamartoma—An overgrowth of normal tissue.

Hyperpigmentation—An abnormal condition characterized by an excess of melanin in localized areas of the skin, which produces areas that are much darker than the surrounding unaffected skin.

Laparoscopy—A diagnostic procedure in which a small incision is made in the abdomen and a slender, hollow, lighted instrument is passed through it. The doctor can view the ovaries more closely through the laparoscope and, if necessary, obtain tissue samples for biopsy.

Macule—A flat, discolored spot or patch on the skin.

Mammogram—A procedure in which both breasts are compressed/flattened and exposed to low doses of x-rays, in an attempt to visualize the inner breast tissue.

Polyp—A mass of tissue bulging out from the normal surface of a mucous membrane.

Polypectomy—Surgical removal of polyps.

Tumor suppressor gene—Genes involved in controlling normal cell growth and preventing cancer.

half are due to a mutation in the cell from which the child develops. A person born with one abnormal gene can pass that gene on to the next generation. One out of two of this person's children will inherit the gene. In addition, if PJS is inherited, each parent or sibling of the affected person has a one out of two chance of carrying the gene.

Demographics

PJS occurs in about 1 out of 25,000 to 300,000 people. It affects males and females of all races and ethnic groups. The particular genetic mutation may differ among groups and even among families within a group.

Signs and symptoms

The first sign of PJS, freckling inside the mouth or in unusual places, generally appears in infants. Polyps usually begin causing symptoms by age ten. Polyps make themselves known in a variety of ways. They can cause abdominal pain or intestinal bleeding. Sometimes the blood loss leads to anemia (a condition where there is a reduction in circulating red blood cells, the amount of hemoglobin, or the volume of packed red cells). Polyps sometimes protrude outside the rectum or obstruct the gastrointestinal tract. Untreated obstructions can be fatal.

Tumors may appear in childhood. Children as young as six may develop a particular kind of ovarian or testicular tumor that causes early puberty. Affected boys sometimes begin to develop breasts. These tumors can be noncancerous, but they have the potential to become malignant.

A few patients develop malignant tumors in the first decade of life. Other patients have stomach, breast, or cervical cancer before age 30. The specific form of cervical cancer is extremely rare in the general population.

Diagnosis

Because the peculiar freckling seen in PJS is present so early, doctors familiar with the condition may suspect PJS even before other symptoms occur. This is ideal, since early diagnosis greatly improves the prognosis.

Many children or young adults come to medical attention due to the pain, bleeding, or anemia caused by polyps. Doctors can confirm the presence of multiple polyps using a variety of methods. Noninvasive methods include ultrasound and x-ray techniques. Invasive methods use a tube and an optical system to conduct an internal inspection of the gastrointestinal tract. These methods include endoscopy, enteroscopy, and colonoscopy, all of which involve entry to the gastrointestinal tract through an existing body orifice. Laparoscopy is another invasive method; it involves entering the gastrointestinal tract through an incision in the abdomen. All invasive methods allow for removal of polyps found during the exam. Once the polyps are removed and examined, their unique structure and large number lead to diagnosis of PJS. The average age at PJS diagnosis is 17.

Freckles and polyps occur in more than 95% of people with PJS. Sometimes, though, the freckles fade before

symptoms of polyps appear. It is important to take a medical history in order to determine if freckles were present on the skin earlier in life. The doctor should also examine the lining of the cheeks inside the mouth, where freckles are likely to remain throughout life.

The number and intensity of the freckles do not predict the severity of gastrointestinal symptoms or the risk of developing cancer. Any patient diagnosed with PJS needs regular cancer screening.

The presence of the rare cervical cancer, ovarian tumor, or testicular tumor associated with PJS leads to diagnosis in some patients.

A family history of PJS is suspicious but not required for diagnosis, since PJS can occur as a new mutation. Once PJS has occurred in a family, parents, siblings, and children of the affected person should seek medical attention.

Genetic testing is available to confirm clinical diagnosis or to determine if a person carries an abnormal *STK11* gene. Using a swab, cells are removed from the lining of the cheeks inside the mouth. DNA is extracted and analyzed. The test confirms PJS if analysis reveals an *STK11* mutation. However, the test cannot rule out PJS if an *STK11* mutation is not found, since some cases are due to other genetic causes.

Prenatal diagnosis of PJS is possible only if the family's specific *STK11* mutation has previously been identified. Prenatal testing is done by amniocentesis or chorionic villus sampling. Amniocentesis involves removal of a small amount of amniotic fluid from the uterus. Chorionic villus sampling involves removal of a small sample of placental tissue. In either case, DNA is extracted from sample cells and analyzed.

Even without genetic testing, diagnosis of PJS is fairly straightforward. Although several other conditions cause multiple intestinal polyps or hyperpigmentation, the distinctive structure of PJS polyps and the unusual location of PJS freckles eliminate other conditions from consideration.

Treatment and management

For people with a family history of PJS, treatment and management of the condition may begin even before diagnosis. If PJS freckles do not appear at birth and if there are no symptoms of polyps, affected families may desire genetic testing for their children.

For most genetic conditions, testing is delayed until children are old enough to understand the disease, its consequences, and the advantages and disadvantages of genetic screening. However, since PJS can affect children under the age of ten, any delay could be risky. Therefore,

it is appropriate for families with PJS to consider genetic testing for their children. Children who do carry an *STK11* mutation can begin a preventive care program immediately, and children who do not carry an *STK11* mutation can avoid unnecessary intervention.

The decision to seek genetic testing requires careful consideration. A positive test for PJS cannot predict the precise age of onset, symptoms, severity, or progress of the condition. A genetic counselor can assist interested family members as they confront the medical, social, personal, and economic issues involved in genetic testing.

Parents, siblings, and children of people with *STK11* mutations may not wish to undergo genetic testing. In this case, they should have a thorough clinical exam to confirm or rule out PJS. The exam includes a careful inspection for freckles. In addition, people age ten or older require gastrointestinal screening, abdominal ultrasound, and a blood test for anemia. Males over age ten should have a testicular exam. Females should have a pelvic exam and ultrasound, Pap smear, and breast exam annually, by age 20. Women age 35 or older should have a mammogram.

For people with no family history of PJS, treatment and management usually begin when PJS is diagnosed.

In past generations, polyp complications such as intestinal obstruction or hemorrhage were a frequent cause of death in PJS patients. However, treatment of polyps is now widely available. The doctor performs a polypectomy to remove the polyps. Polypectomy may be done at the same time as endoscopy, enteroscopy, colonoscopy, or laparoscopy. Anesthesia is used to make the patient more comfortable.

To manage polyps and screen for early signs of cancer, all people who have PJS and are age ten or older need preventive screening on a regular basis. Gastrointestinal screening is the first test, and polypectomy is performed at the same time. Also at age ten, the person begins an annual screening program that includes a blood test for anemia and a testicular exam for boys.

After age ten, gastrointestinal screening with polypectomy is performed every two years.

By age 20, annual screening is expanded to include an abdominal ultrasound for both males and females, as well as a pelvic exam and ultrasound, Pap smear, and breast exam for females.

By age 35, a woman with PJS should have her first mammogram; mammograms should be repeated every two years until the woman is 50. At that time, a mammogram should be added to the annual screening program.

Polyps found during preventive screening are immediately treated by polypectomy. Preventive screening

QUESTIONS TO ASK YOUR DOCTOR

- Are there other names by which Peutz-Jeghers syndrome is known?
- What are the characteristic signs and symptoms of Peutz-Jeghers syndrome?
- What are the most serious medical conditions associated with Peutz-Jeghers syndrome?
- What is the long-term prognosis for a child diagnosed with this genetic disorder?

may also reveal suspicious growths in the gastrointestinal tract or outside of it. These growths require urgent medical attention, since they may be precancerous or cancerous. Diagnosis may require additional tests or biopsy. Treatment is determined on an individual basis, depending on the patient's medical condition and the nature of the growth.

Some people with PJS do not care for the appearance of their freckles. Removal of freckles using laser therapy is an available treatment option.

Many people with PJS find the preventive screening program psychologically exhausting, and young children can find it frightening. These individuals often need the ongoing support and understanding of friends, family, and community. Several organizations composed of people with PJS, their family members, and medical professionals offer additional support and information. There is also an online support group dedicated to PJS.

People with PJS may find it helpful to consult a genetic counselor. Genetic counselors can provide up-to-date information about PJS research, therapy, and management.

Prognosis

Early detection of PJS is the key to its prognosis. Polyps cause less pain and fewer complications when found and removed early. In addition, the patient can begin a preventive screening program at an early age. This increases the likelihood of finding suspicious growths before they become malignant.

Unless they undergo regular screening, people with PJS have a one in two chance of dying from cancer before the age of 60. Moreover, the average age of cancer death in unscreened people with PJS is 39.

Researchers are actively investigating cancer screening, prevention, and treatment methods. In the meantime,

regular preventive screening may reduce the illness and premature death associated with PJS.

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ORGANIZATIONS

Genetic Alliance, 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008, (202) 966-5557, info@geneticalliance.org, <http://www.geneticalliance.org>
IMPACC (Intestinal Multiple Polyposis and Colorectal Cancer), PO Box 11, Conyngham, PA 18219, (570) 788-3712, impacc@epix.net

Avis L. Gibons

Pfeiffer syndrome

Definition

Pfeiffer syndrome is one of a group of disorders defined by premature closure of the sutures of the skull, resulting in an abnormal skull shape. People affected with these conditions, known as craniosynostosis syndromes, may also have differences in facial structure and hand and foot abnormalities. The defining features of Pfeiffer syndrome are abnormalities of the hands, feet, and shape of the skull.

Description

Pfeiffer syndrome is a complex disorder. Three subtypes of Pfeiffer have been defined based on symptoms. The syndrome is caused by a mutation (alteration) in either of two different genes. As the genes that cause craniosynostosis syndromes were discovered throughout the 1990s, scientists realized that these syndromes have overlapping underlying causes. Crouzon, Apert, Jackson-Weiss, and other syndromes are related to Pfeiffer

syndrome by genetic causation as well as associated symptoms. Noack syndrome, once thought to be a separate condition, is now known to be the same as Pfeiffer syndrome. Acrocephalosyndactyly, type V (ACS5) and Noack syndrome both refer to Pfeiffer syndrome.

Genetic profile

Pfeiffer syndrome is an autosomal dominant condition. Every person has two copies of every gene, one maternally inherited and one paternally inherited. Autosomal dominant conditions occur if a person has a change in one member of a gene pair. The chance for an affected individual to have an affected child is 50% with each pregnancy.

A person who has an autosomal dominant condition may have it because he or she inherited the altered gene from an affected parent or because of a new mutation. A new mutation occurs when the gene is altered for the first time in that individual. A person with an autosomal dominant condition due to a new mutation is the first person in his or her family to be affected.

Nearly all individuals with Pfeiffer syndrome types 2 and 3 described in the medical literature have new mutations. When a person has a new mutation, his or her parents are usually not at risk to have another child with the condition. The milder form, Pfeiffer syndrome type 1, is more likely to be inherited. When the mutation is inherited, the child's symptoms are often similar to those of the affected parent. Pfeiffer syndrome is fully penetrant. This means that all of the individuals who have the mutated gene associated with the condition are expected to have symptoms. In other words, the mutant gene is always expressed.

The two genes that cause Pfeiffer syndrome are called *FGFR1* and *FGFR2*. *FGFR1* is on chromosome 8, at the location 8p11.23-p11.22. *FGFR2* is on chromosome 10 at the location 10q26. These genes are members of a group of genes called the fibroblast growth factor receptors.

Fibroblasts play an important role in the development of connective tissue (e.g., skin and bone). Fibroblast growth factors (FGFs) stimulate certain cells to divide, differentiate (specialize to perform a specific function different than the function of the original cell), and migrate. FGFs are important in limb development, wound healing and repair, and other biological processes. FGFs communicate with targeted cells through the action of the fibroblast growth factor receptors. Fibroblast growth factor receptors (FGFRs) on the targeted cells bind the FGFs and relay their message within the cell.

In 2012, over 100 conditions were known to be caused by mutations in the four *FGFR* genes. Mutations

KEY TERMS

Craniosynostosis—Premature, delayed, or otherwise abnormal closure of the sutures of the skull.

Fibroblast growth factor—A type of gene that codes for a cell membrane receptor involved in normal bone growth and development.

Fibroblast growth factor receptor gene—Proteins that are important in such functions as the growth of new blood vessels (angiogenesis), in wound healing, and embryonic growth.

Gene—A building block of inheritance that contains the instructions for the production of a particular protein and is made up of a molecular sequence found on a section of DNA. Each gene is found at a precise location on a chromosome.

Suture—A “seam” that joins two surfaces together.

in *FGFR2* may cause Pfeiffer syndrome as well as Apert, Jackson-Weiss, and Crouzon syndromes. Nonetheless, a parent with Pfeiffer syndrome is at risk to have a child with Pfeiffer but is not at risk to have a child with Apert, Crouzon, or Jackson-Weiss syndromes. Because family members in multiple generations all have the same condition, the condition is said to “breed true” within families. A few exceptions—families with more than one *FGFR*-associated condition—are reported in the medical literature.

A given genetic condition may be associated with mutations in one particular gene, and mutations in a given gene may cause only one genetic condition. Alternatively, mutations in a gene may be associated with more than one genetic condition, and a particular genetic condition may be caused by any mutation in a number of multiple genes. *FGFR2* causing both Pfeiffer and Apert syndromes is an example of the former; *FGFR1* and *FGFR2* causing Pfeiffer syndrome is an example of the latter. Various mutations of a particular gene are called alleles. Sometimes a gene causes different genetic conditions because each allele leads to a specific set of symptoms.

The exact same mutation in the *FGFR2* gene may cause Pfeiffer syndrome in one family and cause a different craniosynostosis syndrome in another family. However, each family continues to have the same symptoms (the conditions breed true in each family). Differing effects of genes are sometimes explained by differing environmental influences and by differing interactions with other genes. However, the diverse effects of the

FGFR2 gene probably have a more specific explanation/mechanism. The underlying reasons for these phenomena may be explained when fibroblast growth factors and their receptors are better understood. At that time, criteria defining various craniosynostosis syndromes (e.g., Pfeiffer, Crouzon, and Jackson-Weiss) may be reexamined and revised.

Demographics

The incidence of Pfeiffer syndrome is approximately 1 in 100,000. The incidence of craniosynostosis is 1 in 2,000 to 1 in 2,500, which includes syndromic and nonsyndromic cases. In nonsyndromic cases, the craniosynostosis is an isolated finding; no other abnormalities are present. Nonsyndromic craniosynostosis is much more common than syndromic craniosynostosis. Usually, isolated craniosynostosis is sporadic (not familial). Mutations in ten different genes are associated with the development of some form of craniosynostosis.

Signs and symptoms

Individuals with Pfeiffer syndrome have a high forehead, a tower-shaped skull, and broad, deviated thumbs and great toes. The symptoms of type 1 are milder than those of types 2 and 3. Undergrowth of the midface leads to down-slanting, low-placed, widely spaced eyes; a small upper jaw bone; and a low nasal bridge. The larynx (voice organ below the base of the tongue) and the pharynx (tube that connects the larynx to the lungs) may be abnormal. Additional symptoms include a projecting chin, divergent visual axes, abnormalities of the passage between the nose and the pharynx, and hearing loss. Fingers and toes may be short and/or partially grown together. The palate may be especially high, and teeth may be crowded. In type 2, the elbow joint is frozen in place.

The skull is composed of many bones that fuse when the brain has finished growing. If the bones of the skull fuse prematurely (craniosynostosis), the skull continues to grow in an abnormal pattern. The places where the bones of the skull fuse are called sutures.

The suture that fuses prematurely in Pfeiffer syndrome is the coronal suture. This suture separates the frontal bone of the skull from the two middle bones (called the parietal bones). When the coronal suture closes prematurely, upward growth of the skull is increased, and growth toward the front and back is decreased. Sometimes the sagittal suture will also be fused prematurely in individuals with Pfeiffer syndrome. This suture separates the right and left sides of the middle of the skull. If both the coronal and sagittal sutures fuse prematurely, the skull develops a somewhat cloverleaf

shape. Individuals with Pfeiffer type 2 have cloverleaf skulls more often than individuals with types 1 and 3.

The coronal suture is also fused prematurely in Crouzon, Jackson-Weiss, Apert, and Beare-Stevenson syndromes. The thumbs and big toes are normal in Beare-Stevenson and Crouzon syndromes. Additional associated abnormalities distinguish Apert and Jackson-Weiss syndromes.

Serious complications of Pfeiffer syndrome include respiratory problems and hydrocephalus. Hydrocephalus is excessive fluid in the brain, which leads to mental impairment if untreated. Breathing problems may be caused by trachea abnormalities or be related to undergrowth of the midface. Some individuals may require an incision in the trachea (tracheostomy). Serious complications are more common in Pfeiffer types 2 and 3. Individuals with types 2 and 3 are severely affected and often do not survive past infancy. Death may result from severe brain abnormalities, breathing problems, prematurity, and surgical complications. Even without accompanying hydrocephalus, developmental delays and intellectual disability are common (in types 2 and 3). Lower displacement of the eyes may be so severe that the infant is unable to close his or her eyelids. Individuals with types 2 and 3 may also have seizures. Intellect is usually normal in Pfeiffer type 1.

Diagnosis

The diagnosis of Pfeiffer syndrome is initially based on clinical findings (symptoms) and is confirmed by genetic testing.

Often the doctor can determine which cranial suture closed prematurely by physical examination. For confirmation, an x-ray or computerized tomography (CT) scan of the head may be performed. Determining which suture is involved is crucial in making the correct craniosynostosis diagnosis.

Craniosynostosis may be caused by an underlying genetic abnormality, or it may be due to other, nongenetic factors. In Pfeiffer syndrome, the tissue itself is abnormal and causes the suture to fuse prematurely. The doctor will consider nongenetic causes of craniosynostosis. These secondary causes include external forces such as abnormal head positioning (in the uterus or in infancy) and a small brain.

Genetic testing may be useful for prenatal diagnosis, for confirmation of the diagnosis, and to provide information to other family members. Mutations are not detected in all individuals with Pfeiffer syndrome. People with Pfeiffer syndrome due to a mutation in the *FGFR1* gene may have less severe abnormalities than people who have Pfeiffer due to mutations in the *FGFR2* gene.

QUESTIONS TO ASK YOUR DOCTOR

- Please describe the process that occurs during craniosynostosis.
- Why is Pfeiffer syndrome considered a genetic disorder?
- How are the major symptoms of Pfeiffer syndrome treated?
- What are the most current therapies in use to treat the symptoms of Pfeiffer syndrome?

Prenatal diagnosis is available by chorionic villus sampling (CVS) or amniocentesis if a mutation has been identified in the affected parent. Amniocentesis is performed after the 15th week of pregnancy, and CVS is usually performed in the 10th and 12th weeks of pregnancy. A parent with Pfeiffer syndrome has a 50% chance of passing it to his or her offspring.

Craniosynostosis may be visible by fetal ultrasound. Conditions caused by mutations in the *FGFR* genes account for only a small portion of craniosynostosis. Assuming that the fetus does not have a family history of one of these conditions, genetic testing for the *FGFR* genes is unlikely to provide useful additional information.

Treatment and management

Children with Pfeiffer syndrome usually see a team of medical specialists at regular intervals. This team typically includes plastic surgeons; neurosurgeons; orthopedists; ear, nose, and throat doctors (otolaryngologists); dentists; and other specialists. The affected person may see the specialists all at once in a craniofacial clinic at a hospital. Many physical problems must be addressed. Developmental, psychosocial, and financial issues are additional concerns. Treatment is aimed at the symptoms, not the underlying cause. Even if craniosynostosis is discovered prenatally, only the symptoms can be treated.

Multiple surgeries are usually performed to progressively correct the craniosynostosis and to normalize facial appearance. A team of surgeons is often involved, including a neurosurgeon and a specialized plastic surgeon. The timing and order of surgeries vary. Patients with syndromic craniosynostosis often require surgery earlier than patients with nonsyndromic craniosynostosis. The first surgery is usually performed early in the first year of life, even in the first few months.

Additional surgeries may be performed for other physical problems. Limb abnormalities often are not

correctable. If the limb malformations do not lead to a loss of function, surgery is usually not required. Fixation of the elbow joints may be partially corrected, or at least altered to enable better functioning.

Hydrocephalus, airway obstruction, hearing loss, incomplete eyelid closure, and spine abnormalities require immediate medical attention.

Prognosis

The prognosis for an individual is based on the symptoms he or she has. Individuals with Pfeiffer syndrome type 1 have a better prognosis than individuals with types 2 or 3. But the designation of type is based on that person's symptoms.

Although people with Pfeiffer syndrome may not obtain a completely normal appearance, significant improvement is possible. Timing the surgeries correctly is an important factor in whether they are successful and whether repeat surgeries are required.

Although Pfeiffer syndrome is rare, craniosynostosis is relatively common. Multiple agencies and organizations exist to help families face the challenges of having a child with craniosynostosis and facial differences. The identification of the *FGFR* genes that cause Pfeiffer (and other) craniosynostosis syndromes has promoted research into the underlying process that causes Pfeiffer syndrome. It will be another enormous challenge to go from understanding the process to treating the process. When the process that causes Pfeiffer and related conditions is better understood, a much clearer knowledge of human development in general will also be established.

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AboutFace, 1057 Steeles Ave. W, PO Box 702, The Concourse, North York, ON, Canada M2R 3X1, (416) 597-2229 or (800) 665-3223, (416) 597-8494, info@aboutface.ca, <http://www.aboutface.ca>

Children's Craniofacial Association, 13140 Coit Rd., Suite 517, Dallas, TX 75240, (214) 570-9099 or (800) 535-3643, (214) 570-8811, contactcca@ccakids.com, <http://www.ccakids.com>

Cleft Palate Foundation, 1504 E. Franklin St., Suite 102, Chapel Hill, NC 27514-2820, (919) 993-9044 or (800) 242-5338, (919) 933-9604, <http://www.cleftline.org>

FACES: The National Craniofacial Association, PO Box 11082, Chattanooga, TN 37401, (423) 266-1632 or (800) 332-2373, faces@faces-cranio.org, <http://www.faces-cranio.org>

World Craniofacial Foundation, PO Box 515838, Dallas, TX 75251-5838, (972) 566-6669 or (800) 533-3315, info@worldcf.org, <http://www.worldcf.org>

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Pharmacogenetics

Definition

Pharmacogenetics is one of the newest subspecialties of genetics. It deals with the relationship between inherited genes and the ability of the body to metabolize drugs. The study of pharmacogenetics investigates how genetic factors affect the function of drugs or how the body reacts to drugs.

Description

Medicine today relies on the use of therapeutic drugs to treat disease, but one of the longstanding problems has been the documented variation in patient response to drug therapy. The "recommended" dosage is usually established at a level shown to be effective in 50% of a test population, and based on the patient's initial response the dosage may be increased, decreased, or discontinued. In rare situations the patient may experience an adverse reaction to the drug and be shown to have a pharmacogenetic disorder. The unique feature of this group of diseases is that the problem does not occur until after the drug is given, so a person may have a pharmacogenetic defect and never know it if the specific drug required to trigger the reaction is never administered.

Adverse reactions

Consider the case of a 35-year-old male who is scheduled for surgical repair of a hernia. The patient is otherwise in excellent health and has no family history of any serious medical problems. After entering the operating theater, an inhalation anesthetic and/or muscle relaxant is administered to render the patient unconscious. Unexpectedly, there is a significant increase in body temperature, and the patient experiences sustained muscle contraction. If this condition is not reversed promptly it can lead to death. Anesthesiologists are now very familiar with this type of reaction, but it occurs only rarely and uniquely identifies the patient as having malignant hyperthermia, a rare autosomal dominant disorder that affects the body's ability to respond normally to anesthetics. Once diagnosed with malignant hyperthermia, it is quite easy to avoid future episodes by simply using a different type of anesthetic when surgery is necessary, but it often takes one negative and potentially life-threatening experience to know the condition exists.

An incident that occurred in the 1950s further shows the diversity of pharmacogenetic disorders. During the Korean War, service personnel were deployed in a region of the world where they were at increased risk for malaria. To reduce the likelihood of acquiring that disease the antimalarial drug primaquine was administered prophylactically. Shortly thereafter, approximately 10% of the African-American servicemen were diagnosed with acute anemia, and a smaller percentage of soldiers of Mediterranean ancestry showed a more severe hemolytic anemia. Investigation revealed that the affected individuals had a mutation in the glucose 6-phosphate dehydrogenase (*G6PD*) gene. Functional *G6PD* is important in the maintenance of a balance between oxidized and reduced molecules in the cells, and under normal circumstances a mutation that eliminates the normal enzyme function can be compensated for by other cellular processes. However, mutation carriers are compromised when their cells are stressed, such as when the primaquine is administered. The system becomes overloaded and results in oxidative damage to red blood cells and anemia. Clearly, both the medics who administered the primaquine and the men who took the drug were unaware of the potential consequences. Fortunately, once the drug treatment was discontinued the individuals recovered.

Research efforts

Drugs are essential to modern medical practice, but as in the cases of malignant hyperthermia and *G6PD* deficiency, it has become clear that not all individuals respond equally to each drug. Reactions can vary from positive improvement in the quality of life to life-threatening episodes. Annually in the United States, there are over two

KEY TERMS

Drug metabolism—Chemical modification or breakdown of drugs. This usually occurs through the activity of specialized enzymatic pathways.

Metabolic pathways—A series of chemical reactions that happen in a cell that modify an initial substrate in sequential steps through the activity of specialized proteins called enzymes.

million reported cases of adverse drug reactions and a further 100,000 deaths per year as a result of drug treatments. The Human Genome Project and other research endeavors are now providing information that is allowing a better understanding of the underlying causes of pharmacogenetic anomalies with the hope that eventually the number of negative episodes can be reduced.

Research on one enzyme family is beginning to revolutionize the concepts of drug therapy. The cytochrome P450 system is a group of related enzymes that are key components in the metabolic conversion of over 50% of all currently used drugs. Studies involving one member of this family, CYP2D6, have revealed the presence of several polymorphic genetic variations that result in different clinical phenotypes with respect to drug metabolism. These variations are termed poor, intermediate, extensive, and ultra with respect to how they metabolize certain drugs. For example, a poor metabolizer has difficulty converting the therapeutic drug into a useable form, so the unmodified chemical will accumulate in the body and may cause a toxic overdose. To prevent this from happening the prescribed dosage of the drug must be reduced.

An ultra metabolizer, on the other hand, shows exceedingly rapid breakdown of the drug to the point that the substance may be destroyed so quickly that therapeutic levels may not be reached and the patient may never show any benefit from treatment. In these cases switching to another type of drug that is not associated with CYP2D6 metabolism may prove more beneficial.

The third phenotypic class, the extensive metabolizers, is less extreme than the ultra metabolism category but nevertheless presents a relatively rapid turnover of drug that may require a higher than normal dosage to maintain a proper level within the cells. The intermediate phenotype falls between the poor and extensive categories and gives reasonable metabolism and turnover of the drug. This is the group for whom most “recommended” drug dosages appear to be appropriate.

The elucidation of the four different metabolic classes has clearly shown that the usual “one size fits all” recommended drug dose is not appropriate for all individuals. In the future it will become increasingly necessary to know the patient’s metabolic phenotype with respect to the drug being given to determine the most appropriate regimen of therapy for that individual.

Future applications

Based on current studies it is possible to envision many different applications of pharmacogenetics. In addition to providing patient-specific drug therapies, pharmacogenetics will aid in the clinician’s ability to predict adverse reactions before they occur and identify the potential for drug addiction or overdose. New tests will be developed to monitor the effects of drugs and new medications will be found that specifically target a particular genetic abnormality. Increased knowledge in this field should provide a better understanding of the metabolic effects of food additives, work-related chemicals, and industrial by-products. In time, these advances will improve the practice of medicine and become the standard of care.

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Pharmacogenomics

Definition

Within the emerging field of precision medicine, pharmacogenomics (also called pharmacogenetics) studies how individual genetic variation affects

drug-treatment outcomes. Pharmacogenomics research helps physicians select the most effective treatments for some patients by studying how certain gene variants affect the safety of medications and how well they will work. A pharmacogenomic test looks for variations (mutations) in a person’s genes that can influence how their body reacts to certain medications. For example, it can test to see how much of a certain medication they might need, if any medications might be dangerous, and which medications might work better than others.

Description

People respond differently to certain medications partially because of our unique genetic makeup. Advances in this field, have led to genetic tests that can help doctors health providers the optimal medication and best dose for a patient.

Pharmacogenomics looks at gene variants that affect how the body breaks down and uses a drug (pharmacokinetics) and how well the body responds to the drug (pharmacodynamics). Pharmacokinetics includes: absorption, distribution, metabolism, and excretion (ADME). Absorption is how the drug enters the bloodstream. Distribution describe where the drug goes in the body after it is absorbed and how much reaches different parts of the body. Metabolism is how the body breaks down a drug and what products the drug is broken down into. Some of these products can have a particular action on the body. Drugs are mainly metabolized in the liver but some drugs are metabolized by other organs like the kidneys, lungs and intestines. Excretion describes how the drug leaves the body.

Gene variants can affect active drugs and prodrugs in different ways. An active drug is already active in the form that it is taken. The active drug usually becomes inactivated when it is converted into one or more compounds (metabolized). A prodrug is a medication that the body needs to metabolize in order for it to work. Prodrugs need to be metabolized to form a compound that can be used by the body.

Plavix, which is used to prevent heart problems, is an example of a prodrug. Normally it is converted to a compound that the body can use. About 30% of people have a variant in the CYP2C19 gene that prevents their body from properly breaking down Plavix into an active drug. Since Plavix does not work very well for people with this variant, other medications might be recommended.

Categories of drug response

Pharmacogenomic tests typically classify people into certain categories for each drug analyzed based on the type of variant that they have and the expected effect.

KEY TERMS

Cell—Building block that provides structure to the body and performs all the functions of the body. Cells contain genetic information and can copy themselves. The four main types of cells are: skin, nerve, muscle and connective tissue.

DNA (deoxyribonucleic acid)—The genetic material that contains the instructions for creating proteins.

DNA base—One unit in a DNA sequence. The four DNA bases are adenine (A), guanine (G), thymine (T) and cytosine (C). The sequence of these bases is the genetic code which contains the instructions for creating proteins.

DNA sequence—The sequence of DNA bases that contains the instructions for creating proteins. A three-base sequence in the DNA contains the instructions for making a particular amino acid. For example, CGC codes for the amino acid alanine. Proteins are made up of one or more amino acids strung together. The instructions for a particular protein are made up of a number of three-base sequences. Because DNA is double stranded it has two complementary sequences where the bases pair up together. C always pairs with G and A always pairs with T. An example double stranded DNA sequence for alanine is GCG/CGC.

Gene—A sequence of bases in a DNA sequence that contains the instructions for a protein.

Genome—The complete set of genetic instructions of an organism.

Metabolized—When a drug is converted into one or more compounds.

Pathogenic variant—Any change in the sequence of a genome that causes disease.

Pharmacodynamics—Study of how a drug affects the body.

Pharmacokinetics—Study of how the body breaks down and uses a drug.

Ribonucleic acid (RNA)—The genetic material that is involved in creating proteins. The DNA sequence that contains a gene needs to be transcribed into a single stranded molecule called messenger RNA (mRNA). In the RNA sequence, a base called uracil (U) replaces thymine (T) when it is found in the DNA sequence.

Single nucleotide polymorphism (SNP)—A variation in a single base pair in a genetic sequence.

Tissue—Made up of cells that have a common function. The four types of tissue are: connective, epithelial (skin), muscle and nervous tissue.

To sequence (verb)—Figure out the sequence of bases in genetic material like DNA or RNA.

Variant—Change in the sequence of a genome.

The expected effect will differ if it is a prodrug or active drug. These categories include:

- **Poor metabolizers.** People who break down a medication very slowly. If the medication is a prodrug then the drug may not work very well. If the medication is an active drug then there could be an accumulation of the active drug and a higher risk of side effects. A lower dosage of the medication may be required in poor metabolizers of an active drug.
- **Intermediate metabolizers.** People who break down a medication more slowly than normal, but not as slowly as a poor metabolizer. They will likely have similar effects as poor metabolizers but not as pronounced.
- **Extensive metabolizers.** People who metabolize medications normally.
- **Ultra-rapid metabolizers.** People who metabolize medications more quickly than average. In the case of active drugs they may metabolize the drug too quickly for it to work. They may need a higher dosage or a different

medication. In the case of prodrugs, they may produce too much of the active drug which can cause side effects or overdose.

Pharmacogenomic variants

The most common type of variant in a gene that affects our response to drugs is a single nucleotide polymorphism (SNP). A SNP involves a variation in a single base pair in a genetic sequence. Other types of genetic variants that can affect our response to different medications are:

- **Copy number variant (CNV).** Duplication of a piece of DNA sequence. This section can be duplicated many times. This often involves the duplication of a particular gene.
- **Insertions.** An additional piece of DNA inserted into a DNA sequence.
- **Deletions.** A piece missing from the DNA sequence.

Common pharmacogenomic genes

There are many genes which influence how our body metabolizes drugs and how they affect us. In 2021 there were about 100 variants in more than 900 genes that were known to affect response to medications. A number of these genes affect the metabolism of more than one drug. The three most common gene types included in pharmacogenomic tests are:

1. cytochrome P450s
2. VKORC1
3. TPMT

Cytochrome P450 (CYP)

Cytochrome P450 (CYP) gene variants are the most common variants associated with drug response. Variants in five of these genes: CYP2D6, CYP2C19, CYP2C9, CYP3A4 and CYP3A5 affect the drug response for approximately 70%–90% of currently available prescription drugs.

CYP2D6 is the most well known pharmacogenomic variant. More than 100 variants in this gene are known. Several of these variants result in inactive or absent protein. We each have two copies of each gene. People with a variant that decreases the activity of the CYP2D6 gene in both copies of their CYP2D6 gene, are poor metabolizers. About 5%–10% of white people are poor metabolizers. People with a variant in only one copy of this gene are normal metabolizers (extensive metabolizers). People with more than two copies of the CYP2D6 gene metabolize drugs more quickly and are called ultra-rapid metabolizers. Ultra-rapid metabolizers (UMs) have extremely high enzyme activity.

CYP2D6 gene variants affect most antidepressants, opioids, epilepsy drugs, and some heart medications. Commonly affected drugs are: tramadol, venlafaxine, morphine, mirtazapine, and metoprolol.

For example, ultra-rapid metabolizers with variations in the CYP2D6 turn codeine into morphine at a more rapid rate and make greater amounts of morphine. They are at greater risk for having an overdose if they use codeine or other opioids and having serious problems as a result. Breastfeeding mothers with this variation who use codeine, are at increased risk for providing excessive amounts of morphine to their baby. This can result in serious breathing problems in the infant and even death. Codeine does not work very well for poor metabolizers and they may need to use an alternative pain reliever.

The antidepressant drug amitriptyline is metabolized mainly by CYP2D6 and CYP2C19. People who are CYP2D6 ultra-rapid metabolizers have multiple copies of the gene. CYP2C19 ultra-rapid metabolizers possess

QUESTIONS TO ASK YOUR DOCTOR

- Is pharmacogenomic testing available for the drugs that I am taking?
- What are the limitations of pharmacogenomic testing?
- What pharmacogenomic test would you recommend?

variants in both copies of the gene that increase the function of this gene. People who are poor metabolizers have variants that produce non-functioning CYP2D6 or CYP2C19 proteins.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that CYP2D6 and CYP2C19 ultra-rapid metabolizers do not take amitriptyline because it does not work very well for them. If this drug must be used in an CYP2D6 ultra-rapid metabolizer then a higher dose is recommended. CYP2D6 intermediate metabolizers should start with a 25% lower dose of amitriptyline. Poor CYP2D6 and CYP2C19 metabolizers should avoid the drug because of potential side effects. If a CYP2D6 or CYP2C19 poor metabolizer must take amitriptyline then a 50% reduced starting dose is recommended.

VKORC1

The vitamin K epoxide reductase complex subunit 1 gene (VKORC1) is the main gene which affects response to warfarin. Warfarin is the most commonly prescribed drug used to decrease blood clots in patients with strokes, blood clots and irregular heart beat etc. The VKORC1 gene is responsible for production of the VKOR protein. Warfarin works by inhibiting VKOR which reduces the conversion of vitamin K epoxide into vitamin K and decreases the formation of clotting factors.

Variants in CYP2C9 also affect warfarin metabolism. A dose reduction is recommended for individuals who are CYP2C9 poor and intermediate metabolizers or those who carry 2 copies of the variant VKORC1 A allele.

TPMT

Thiopurine methyltransferase (TPMT) is a protein that is involved in metabolizing a class of drugs called thiopurines. Thiopurines are used to treat leukemia, and autoimmune disorders like rheumatoid arthritis. Up to 14% of people have decreased activity of TPMT resulting from one of four TPMT gene variants. High levels of drug metabolites can accumulate in poor metabolizers. If they are treated with

standard doses of thiopurines they are at increased risk for serious side effects that can be fatal like decreased production of blood cells, gastrointestinal intolerance, inflammation of the pancreas and immune reactions. It is recommended that poor metabolizers start with a drastically reduced dose and then increase their dose gradually.

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Phenotype see **Genotype and phenotype**

Phenylketonuria (PKU)

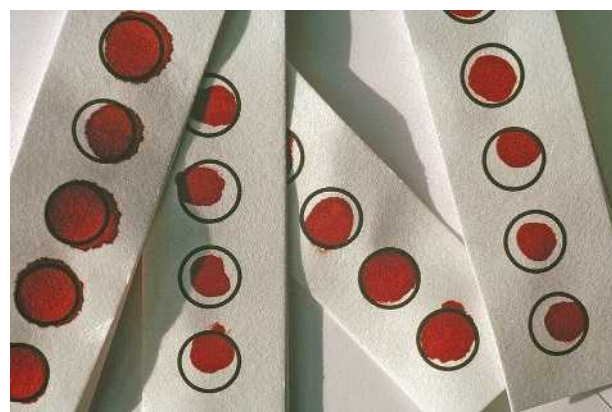
Definition

Phenylketonuria (PKU) is a rare metabolic disorder caused by a deficiency in the production of the hepatic (liver) enzyme phenylalanine hydroxylase (PAH). Phenylalanine hydroxylase deficiency describes a group of disorders that includes PKU. Other conditions described in this group are known as non-PKU hyperphenylalaninemia (non-PKU HPA) and variant PKU. PKU is the most serious form of the three diseases, all of which involve above-normal (elevated) levels of phenylalanine in the blood. The primary symptom of untreated PKU, intellectual disability, is the result of consuming foods that contain the amino acid phenylalanine, which is toxic to brain tissue.

PKU is an inherited, autosomal recessive disorder. It is the most common genetic disease involving amino acid metabolism. PKU is incurable, but early, effective treatment can prevent the development of serious mental incapacity.

Description

PKU is a disease caused by the liver's inability to produce the protein phenylalanine hydroxylase (PAH). This enzyme converts (metabolizes) the amino acid called phenylalanine into another amino acid, tyrosine. This is the only role of PAH in the body. A lack of PAH results in the build-up of abnormally high phenylalanine concentrations (or levels) in the blood and brain. Above-normal levels of phenylalanine are toxic to the cells that make up the nervous system and causes irreversible abnormalities in brain structure and function in PKU patients. Phenylalanine is a type of teratogen. Teratogens are any



Test strips used to screen for PKU. (Philippe Garo/Science Source)

substance or organism that can cause birth defects in a developing fetus.

PKU and the human nervous system

The extensive network of nerves in the brain and the rest of the nervous system are made up of nerve cells. Nerve cells have specialized extensions called dendrites and axons. Stimulating a nerve cell triggers nerve impulses, or signals, that slow down the axon. These nerve impulses then stimulate the end of an axon to release chemicals called neurotransmitters that spread out and communicate with the dendrites of neighboring nerve cells.

Many nerve cells have long, wire-like axons that are covered by an insulating layer called the myelin sheath. This covering helps speed nerve impulses along the axon. In untreated PKU patients, abnormally high phenylalanine levels in the blood and brain can produce nerve cells with abnormal axons and dendrites and cause imperfections in the myelin sheath referred to as hypomyelination and demyelination. This loss of myelin can “short circuit” nerve impulses (messages) and interrupt cell communication. A number of brain scan studies also indicate a degeneration of the white matter in the brains of older patients who have not maintained adequate dietary control.

PKU can also affect the production of one of the major neurotransmitters in the brain, called dopamine. The brain makes dopamine from the amino acid tyrosine. PKU patients who do not consume enough tyrosine cannot produce sufficient amounts of dopamine. Low dopamine levels in the brain disrupt normal communication between nerve cells, which results in impaired cognitive (mental) function.

Some preliminary research suggests that nerve cells of PKU patients also have difficulty absorbing tyrosine. This abnormality may explain why many PKU patients who receive sufficient dietary tyrosine still experience some form of learning disability.

Genetic profile

PKU symptoms are caused by alterations or mutations in the *PAH* gene, which is responsible for producing the enzyme phenylalanine hydroxylase. Mutations in the *PAH* gene prevent the liver from producing adequate levels of the PAH enzyme needed to break down phenylalanine. The *PAH* gene is found on chromosome 12 in the human genome. As of 2015, more than 500 different mutations had been identified in the *PAH* gene.

PKU is an autosomal recessive disorder. The term “autosomal” means that the gene for PKU is not located on either the X or Y sex chromosome, but rather on one of the numbered chromosomes. Everyone carries 46

chromosomes within their cells. Chromosomes contain genes, the blueprints for who we are and what we look like. Every person inherits 23 chromosomes from his or her mother and 23 from his or her father. The first 22 chromosomes are autosomes because they contain genes that are found in both males and females. The gender-specific chromosomes are XX for female and XY for male.

A person with one normal and one PKU gene mutation is called a carrier. A carrier does not display any symptoms of the disease because the liver produces normal quantities of the PAH enzyme. However, PKU carriers can pass the PKU genetic mutation on to their children. Two carrier parents have a 25% chance of producing a baby with PKU symptoms and a 50% chance of having a baby that is a carrier for the disease. Although PKU conforms to these basic genetic patterns of inheritance, the actual expression, or phenotype, of the disease is not strictly an “either/or” situation. This is because there are at least 500 different types of PKU mutations. Although some PKU mutations cause rather mild forms of the disease, others can initiate much more severe symptoms in untreated individuals. The more severe the PKU mutation, the greater the effect on cognitive development and performance (mental ability).

Also, it must be remembered that human cells contain two copies of each type of gene. Different combinations of any two PKU mutations tend to produce a wide spectrum of physiological and psychological symptoms. For example, patients who receive two “severe” PKU mutations from their parents can potentially develop more serious symptoms than people who possess a combination of one severe type and one milder form of mutation. To further complicate the genetic picture of PKU, other types of genes have been identified that seem to be responsible for the abnormal processing of phenylalanine in brain tissue. These abnormalities add to the severity of PKU symptoms experienced by patients who inherit these genes. In more detail, the association of multiple types of genes with a single condition, such as PKU, is referred to as molecular heterogeneity.

Demographics

One in 50 individuals of northern European origin are carriers for a PKU mutation. About 1 in 10,000 babies tests positive for PKU in the United States, but only one in a million babies is symptomatic with PKU due to the small number of infants who are not detected through carrier screening. Studies indicate that the incidence of this disease in northern European populations is higher than in African American, Eastern European, and Finnish populations.

KEY TERMS

Amino acids—Organic compounds that form the building blocks of protein. There are 20 types of amino acids (eight are “essential amino acids” that the body cannot make and that must be obtained from food).

Axon—Skinny, wire-like extension of nerve cells.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Gene—A building block of inheritance that contains the instructions for the production of a particular protein and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Genetic disease—A disease that is (partly or completely) the result of the abnormal function or expression of a gene; a disease caused by the inheritance and expression of a genetic mutation.

IQ—Abbreviation for Intelligence Quotient. Compares an individual’s mental age to his or her true or chronological age and multiplies that ratio by 100.

Metabolism—The total combination of all of the chemical processes that occur within the cells and tissues of a living body.

Mutation—An inherited or *de novo* change in the DNA sequence of the genome.

Myelin—A fatty sheath surrounding nerves in the peripheral nervous system that helps them conduct impulses more quickly.

Nervous system—The complete network of nerves, sense organs, and brain in the body.

Phenylalanine—An essential amino acid that must be obtained from food since the human body cannot manufacture it.

Protein—Important building blocks of the body, composed of amino acids, that are involved in the formation of body structures and control the basic functions of the human body.

Recessive—Refers to a genetic trait that is expressed only when present on both members of a pair of genes, one inherited from each parent.

Signs and symptoms

Untreated PKU patients develop a broad range of symptoms related to severely impaired cognitive function, sometimes referred to as intellectual disability.

Other symptoms can include extreme patterns of behavior, delayed speech development, seizures, a characteristic body odor, and light body pigmentation. The light pigmentation is due to a lack of melanin, which normally colors the hair, skin, and eyes. Melanin is made from the amino acid tyrosine, which is lacking in untreated cases of PKU. Physiologically, PKU patients show high levels of phenylalanine and low levels of tyrosine in the blood. Babies do not show any visible symptoms of the disease for the first few months of life. However, typical PKU symptoms usually do show up by a baby’s first birthday.

Diagnosis

The primary diagnostic test for PKU is the measurement of phenylalanine levels in a drop of blood taken from the heel of a newborn baby’s foot. PKU testing was introduced in the early 1960s and is the largest genetic screening program in the United States. It is required by law in all 50 states. Early diagnosis is critical. It ensures the early treatment PKU babies need to develop normally and avoid the complications of PKU.

The American Academy of Pediatrics recommends that this test be performed on infants between 24 hours and seven days after birth. The preferred time for testing is after the baby’s first feeding. Tandem mass spectrometry is terminology used to describe how newborn screening was performed as of 2015. This is a more accurate and fully automated analysis when compared to earlier newborn screening techniques. If the initial PKU test produces a positive result, then follow-up tests are performed to confirm the diagnosis and to determine if the elevated phenylalanine levels may be caused by some medical condition other than PKU. Treatment for PKU is recommended for babies who show a blood phenylalanine level of 7–10 mg/dL or higher for more than a few consecutive days. Another, more accurate test procedure for PKU measures the ratio (comparison) of the amount of phenylalanine to the amount of tyrosine in the blood.

To confirm a suspected diagnosis of PKU based on the newborn screening analysis, molecular genetic testing can be performed. Knowing the type of *PAH* mutation can help physicians with treatment decisions. For example, certain mutations will allow physicians to predict which infants will benefit from BH4 (tetrahydrobiopterin) supplementation.

Treatment and management

The severity of the PKU symptoms experienced by people with this disease is determined by both lifestyle and genetic factors. In the early 1950s, researchers first demonstrated that phenylalanine-restricted diets could eliminate most of the typical PKU symptoms—except

for intellectual disability. Dietary therapy (also called nutrition therapy) is the most common form of treatment for PKU patients. PKU patients who receive early and consistent dietary therapy can develop fairly normal mental capacity to within about five IQ points of their healthy peers. By comparison, untreated PKU patients generally have IQ scores below 50.

Infants with PKU should be put on a specialized diet as soon as they are diagnosed to avoid progressive brain damage and other problems caused by an accumulation of phenylalanine in the body. A PKU diet helps patients maintain very low blood levels of phenylalanine by restricting the intake of natural foods that contain this amino acid. Even breast milk is a problem for PKU babies. Special PKU dietary mixtures or formulas are usually obtained from medical clinics or pharmacies.

Phenylalanine is actually an essential amino acid. This means that it has to be obtained from food because the body cannot produce this substance on its own. Typical diets prescribed for PKU patients provide very small amounts of phenylalanine and higher quantities of other amino acids, including tyrosine. The amount of allowable phenylalanine can be increased slightly as a child becomes older.

In addition, PKU diets include all the nutrients normally required for good health and normal growth, such as carbohydrates, fats, vitamins, and minerals. High-protein foods like meat, fish, chicken, eggs, nuts, beans, milk, and other dairy products are banned from PKU diets. Small amounts of moderate-protein foods (such as grains and potatoes) and low-protein foods (some fruits and vegetables, low-protein breads and pastas) are allowed. Sugar-free foods, such as diet soda, which contain the artificial sweetener aspartame, are also prohibited foods for patients with PKU. This is because aspartame contains the amino acid phenylalanine.

Ideally, school-age children with PKU should be taught to assume responsibility for managing their diet, recording food intake, and performing simple blood tests to monitor their phenylalanine levels. Blood tests should be done in the early morning when phenylalanine levels are highest. Infants and young children require more frequent blood tests than older children and adults. The amount of natural foods allowed in a diet could be adjusted to ensure that the level of phenylalanine in the blood is kept within a safe range. Recommendations are for children under two to maintain their total phenylalanine intake to at least 3 g/kg/day and 25 mg of tyrosine/kg/day. For children older than two, the recommendation is to maintain their phenylalanine intake to 2 g/kg/day and 25 mg of tyrosine/kg/day.

A specialized PKU diet can cause abnormal fluctuations in tyrosine levels throughout the day. Thus, some health professionals recommend adding time-released tyrosine that can provide a more constant supply of this amino acid to the body. It should be noted that some PKU patients show signs of learning disabilities even with a special diet containing extra tyrosine. Research studies suggest that these patients may not be able to process tyrosine normally.

For PKU caregivers, providing a diet that is appealing as well as healthy and nutritious is a constant challenge. Many patients with PKU, especially teenagers, find it difficult to stick to the relatively bland PKU diet for extended periods of time. Some older patients decide to go off their diet plan simply because they feel healthy. However, many patients who abandon careful nutritional management develop cognitive problems, such as difficulties remembering, maintaining focus, and paying attention. Many PKU health professionals contend that all patients with PKU should adhere to a strictly controlled diet for life. The National Institutes of Health (NIH) recommends weekly monitoring of blood phenylalanine levels for the first year and then twice a week until age 13. After age 13, the NIH recommends monthly monitoring.

One promising line of PKU research involves the synthesis (manufacturing) of a new type of enzyme that can break down phenylalanine in food consumed by the patient. This medication would be taken orally and could prevent the absorption of digested phenylalanine into the patient's bloodstream.

In general, medical researchers express concern about the great variation in treatment programs currently available to PKU patients around the world. They have highlighted the urgent need for new, consistent international standards for proper management of PKU patients, which should emphasize comprehensive psychological as well as physiological monitoring and assessment.

PKU and pregnancy

Women with PKU must be especially careful with their diets if they want to have children. They should ensure that phenylalanine blood levels are under control before conception and throughout pregnancy. Mothers with elevated (higher than normal) phenylalanine levels are high risk for having babies with significant birth disorders, such as microencephaly (smaller than normal head size), congenital heart disease (abnormal heart structure and function), stunted growth, mental impairment, and psychomotor (coordination) difficulties. This condition is referred to as maternal PKU and can even affect babies who do not have the PKU disease.

QUESTIONS TO ASK YOUR DOCTOR

- How is phenylketonuria diagnosed?
- If I have phenylketonuria, what are the chances that any children I have will also contract the disorder?
- Are there any treatments other than diet control that I should consider to avoid complications associated with phenylketonuria?
- Can you recommend any books, pamphlets, brochures, or other material that provide further information about phenylketonuria?

Prognosis

Early newborn screening, careful monitoring, and life-long strict dietary management can help PKU patients to live normal, healthy, and long lives.

Resources

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ORGANIZATIONS

- Canadian PKU and Allied Disorders, 260 Adelaide St. E, No. 180, Toronto, ON, Canada M5A 1N1, (877) 226-7581, info@canpku.org, <http://www.canpku.org>
- Children's PKU Network, 3306 Bumann Rd., Encinitas, CA 92024, (858) 756-0079, (858) 756-1059, pkunetwork@aol.com, <http://www.pkunetwork.org>
- Cristine M. Trahms Program for Phenylketonuria, PKU Clinic, Box 357920, University of Washington, Seattle, WA 98195-7920, (206) 598-1800 or (877) 685-3015, pk@u.washington.edu, <http://depts.washington.edu/pku>

March of Dimes Birth Defects Foundation, 1275 Mamaroneck Ave., White Plains, NY 10605, (914) 997-4488, <http://www.marchofdimes.org>

National PKU Alliance, PO Box 501, Tomahawk, WI 54487, (715) 435-7670, <http://www.npkua.org>

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Phocomelia see **Roberts SC phocomelia**

Phytanic acid oxidase deficiency see **Refsum disease**

Pierre-Robin sequence

Definition

Pierre-Robin sequence consists of micrognathia (small lower jaw) or retrognathia (lower jaw displaced to the back), glossoptosis (displacement of the tongue into the throat), and obstruction of the airway. It is usually accompanied by a cleft palate (an opening in the roof of the mouth). The term "sequence" is used to describe the pattern of multiple anomalies derived from a single known prior anomaly or mechanical factor.

Description

Children who are born with Pierre-Robin sequence have small mandibles (lower jaws) or mandibles that are displaced back, tongues that are pushed back into the throat, and difficulty breathing of varying degrees. They also have difficulty feeding. Pierre-Robin sequence is usually accompanied by a cleft palate. Pierre-Robin sequence is more often associated with other types of hereditary disorders, most commonly Stickler syndrome and velocardiofacial syndrome. Pierre-Robin syndrome is also referred to as Robin sequence.

Genetic profile

Pierre-Robin sequence can occur in association with other syndromes, isolated (not associated with other malformations), or in association with other developmental disorders that do not represent a specific syndrome. Pierre-Robin sequence found in association with numerous syndromes may have a mode of inheritance that is related to the syndrome itself. The mode of inheritance includes single gene as well as chromosomal abnormalities.

Pierre-Robin sequence is usually not inherited, but when it is, it is inherited in an autosomal dominant pattern. This form of Pierre-Robin syndrome is due to a

genetic mutation of the *SOX9* gene, which is located on the long arm of chromosome 17. The *SOX9* gene codes for the development of the fetal skeleton and the fetal reproductive system and is also a transcription factor, regulating other genes.

Demographics

The incidence of Pierre-Robin sequence is reported to be one out of 8,500 to one out of 14,000 live births. This wide range is due to different diagnostic criteria and the presence or absence of associated syndromes. Less than 20%–40% of newborns born with Pierre-Robin sequence have the isolated type.

Signs and symptoms

In Pierre-Robin sequence, the lower jaw of the fetus displaces the tongue backward into the throat. The tongue located in this abnormal position blocks the embryonic structures from joining in the midline in order to form the palate, the roof of the mouth. The result is a cleft palate—an opening in the roof of the mouth. The size of the cleft palate varies, as does its position. It is not present in all patients.

Babies born with Pierre-Robin have difficulty feeding and breathing, because the tongue—pushed backward by the lower jaw—obstructs the throat. Feeding and breathing difficulties may be very mild or very severe.

Affected persons may also develop hearing problems due to fluid collecting in the ears.

Preconception Care

Maternal alcohol consumption is closely associated with alcohol-related birth defects and neurodevelopment. Hence, it is widely recommended for women to quit consuming alcohol before and during pregnancy. There is also evidence that paternal alcohol exposure biologically increases the risk of genetic and epigenetic sperm abnormalities. However, a recent study found that future fathers should be encouraged to modify their alcohol intake before conceiving, to reduce fetal risk, since a paternal drinking rate of 31% substantially elevated the risk of birth defects. This prospective, population-based study based was conducted in China and included couples who were planning a pregnancy within six months. Paternal alcohol consumption before conception was defined as at least one time drinking per week. Birth defects were reported by parents in the follow-up at 42 days after delivery. This study provided evidence for association of preconception paternal alcohol consumption with increased fetal birth defect risk and could have clinical implications for improving offspring life quality.

KEY TERMS

Endoscope—A slender, tubular optical instrument used as a viewing system for examining an inner part of the body. With an attached instrument, the endoscope can be used for biopsy or surgery.

Fibroid—A noncancerous tumor of connective tissue made of elongated, threadlike structures, or fibers, which usually grow slowly and are contained within an irregular shape. Fibroids are firm in consistency but may become painful if they start to break down or apply pressure to areas within the body. They frequently occur in the uterus and are generally left alone unless growing rapidly or causing other problems. Surgery is needed in order to remove fibroids.

Uterus—A muscular, hollow organ of the female reproductive tract. The uterus contains and nourishes the embryo and fetus from the time the fertilized egg is implanted until birth.

Diagnosis

Prenatal ultrasonic examination may show findings to indicate the possibility of Pierre-Robin sequence, alerting the physician to be prepared at birth for the possibility of the baby having breathing and feeding problems.

Treatment and management

The type of treatment varies according to the severity of the symptoms and their duration. Babies might not require any therapy if they have no symptoms of breathing difficulties and no feeding difficulties.

If breathing difficulties are mild, the easiest management is keeping the baby in the prone position, which causes the tongue to fall forward, relieving the obstruction. A thorough evaluation of these patients must be conducted, which includes endoscopy of the airways and upper digestive tract. Close monitoring must be maintained, because the prone position may obscure breathing difficulties.

If positioning the patient prone fails, a nasopharyngeal airway may be used, but only for a short time. The airway is a tube that the baby can breathe through, passed through the nose into the upper airway.

If the previously discussed methods fail or are required for a prolonged length of time, then some type of surgical intervention will be necessary. Surgical procedures include glossopepy, in which the tongue is sutured to the lower lip in order to prevent it from moving back

into the throat and causing obstruction. Subperiosteal release of the floor-of-the-mouth muscles on the lower jaw is an operation performed so that the tongue can no longer move back into the throat, because muscles are released from their insertions. Tracheotomy is performed by surgically cutting an opening in the trachea (wind-pipe). This opening bypasses the obstruction. The choice of surgical intervention varies according to the duration and severity of respiratory obstruction, other causes of respiratory obstruction that may be present, and the experience of the surgeon. Glossopexy and tracheotomy are temporary and reversed when the baby can breathe adequately on his or her own.

Another surgical procedure utilized for the treatment of Pierre-Robin sequence is known as Piezosurgery. This is a technique that uses ultrasound to cut bone, allowing for precise cutting and mandibular distraction to release the obstruction of the airway. It is the best technique currently available, due to its precision and low likelihood of damaging surrounding soft tissues of the head and neck.

The treatment of feeding difficulty varies according to its degree. It has been found that the severity of feeding difficulty is proportional to the severity of airway obstruction. Feeding is usually accomplished with a specialized cleft palate nipple and bottle or nasogastric tube (a feeding tube passed through the nose and into the stomach). Sometimes, a gastrostomy tube is needed for feeding. This is a tube passed through a surgical opening made in the abdominal wall and stomach.

Children with Pierre-Robin sequence are prone to hearing loss due to fluid collecting behind the tympanic membrane (eardrum); they may require drainage tubes placed into the ear.

If the child has a cleft palate, it is usually surgically repaired between the ages of nine and 18 months.

Prognosis

The prognosis for individuals with Pierre-Robin sequence varies with the severity of symptoms and depends on whether it is associated with other congenital abnormalities. The more severe the symptoms and associated congenital abnormalities, the greater the risk of complications. The mortality rate is about 30%.

The rate at which the lower jaw starts to catch up in growth depends on the cause of Pierre-Robin sequence. The majority of children with the isolated type will achieve near normal jaw size within a few years of birth. If Pierre-Robin sequence is part of a syndrome that has a small jaw, the jaw may remain small throughout life.

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ORGANIZATIONS

Foundation for Faces of Children, 258 Harvard Street, #367, Brookline, MA 02446-2904, (617) 355-8299, info@facesofchildren.org, <http://www.facesofchildren.org>

Bharati K. Hegde, BE, MS, PhD,
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and Taryn Terry, DC, MSACN, BA

Pierre-Robin syndrome see **Pierre-Robin sequence**

Pierre-Robin syndrome with fetal chondrodysplasia see **Weissenbacher-Zweymuller syndrome**

Poland anomaly

Definition

Poland anomaly (Poland syndrome) is a rare pattern of malformations present at birth that includes unilateral changes in the chest and shoulder girdle muscles, forearm bones, and fingers. Although there are other associated features, the most recognized characteristics are abnormalities of the major chest muscles (pectoralis) and the presence of syndactyly or webbing that joins the fingers of the hand. Treatment of this anomaly is mainly through reconstructive surgery.

Description

Poland anomaly (also known as Poland syndactyly, Poland syndrome, Poland sequence, or pectoral dysplasia-dysdactyly) was first described in 1841 by Alfred Poland, who was a medical student at Guy's Hospital in London when he noted malformations in the body of a deceased convict named George Elt. The diagnosis of Poland anomaly may encompass various combinations of the following abnormalities:

- absence of major chest muscles: pectoralis major, pectoralis minor
- hand anomalies: syndactyly (webbed or fused fingers), shortened fingers
- underdeveloped forearm bones: ulna, radius
- underdeveloped or absence of the nipple and, in females, the breast
- absence of groups of rib cartilage
- absence of shoulder girdle muscles: latissimus dorsi, serratus anterior
- underdeveloped skin and underlying tissue of the chest
- abnormal curvature of the spine
- patchy hair growth under the arm
- rare associations with abnormalities in the heart or kidney or development of certain cancers

In most cases, physical abnormalities are confined to one side of the body and tend to favor the right side by almost two to one. The manifestations of Poland anomaly are extremely variable, and rarely are all the features recognized in one individual. Involvement of the pectoralis muscle and fingers is the most consistent feature.

The exact cause of Poland anomaly is not known, but it may result from the interruption of fetal growth at about the forty-sixth day of pregnancy, when the fetal fingers and pectoralis muscle are developing. Several researchers have suggested that there may be too little blood flow through the fetal subclavian artery that goes to the chest and arm; the more severe the blood flow disruption, the more numerous and severe the resulting malformations. However, the final proof for this idea has not been found.

Genetic profile

Most occurrences of Poland anomaly appear to be sporadic (i.e., random and not associated with an inherited disorder) and are not passed from parent to child. However, there have been rare reports of Poland anomaly that appears in multiple members of the same family. In at least one case, this familial occurrence of Poland anomaly appears to be inherited in an autosomal dominant pattern. The fact that other organ systems (kidney, heart) and increased risks of certain cancers are associated with this condition supports

KEY TERMS

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a nonsex chromosome is required for a disease or inherited trait to develop in an individual.

Dextrocardia—Right-sided positioning of the heart.

Pectoralis muscles—Major muscles of the chest wall.

Renal agenesis—Complete absence of one or both kidneys.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

Syndactyly—Webbing or fusion between the fingers or toes.

the hypothesis that there may be some genetic abnormality. It has been noted that deletions of some tumor suppressor genes on chromosome 11, including *HRASLS5*, *RARRES3*, *HRASLS2* and *PLA2G16*, that are involved in cell growth and differentiation through the RAS-mediated signaling pathway are associated with Poland anomaly.

Demographics

Poland anomaly is not common. It affects 1 child in 30,000. Geographically, estimates of the frequency range from 1 in 17,213 in Japanese schoolchildren to an average of 1 in 32,000 live births in British Columbia, with a low incidence—1 in 52,530—in Hungary. For reasons that are unclear, Poland anomaly is two to three times more frequent in boys than in girls.

Signs and symptoms

The manifestations of Poland anomaly are most often limited to physical manifestations. The degree to which this condition is disabling depends on which manifestations are present and their individual severity, but it most often relates to disabilities in the affected arm and hand. Upon rare occasions, Poland anomaly is associated with dextrocardia (the position of the heart is the mirror image of its normal position), renal agenesis (maldevelopment of the kidney), or cancers such as leukemia, leiomyosarcoma, and non-Hodgkin lymphoma. Intelligence is not impaired by Poland anomaly.

Diagnosis

The diagnosis of Poland anomaly relies on physical exam and radiographic evaluation, such as the use of

QUESTIONS TO ASK YOUR DOCTOR

- What are the most common signs and symptoms associated with Poland anomaly?
- What kinds of treatment are available for this disorder, and what risks are associated with these treatments?
- What factors are involved in developing a prognosis for a child born with Poland anomaly?
- What is the direction of current research, if any, on Poland anomaly?

x-rays or other imaging techniques to define abnormal or missing structures that are consistent with the criteria for Poland anomaly. In 2015 there was a research group in Italy that performed molecular diagnostic testing for brachydactyly type E (*HOXD13* gene).

Treatment and management

During early development and progressing until young adulthood, children with Poland anomaly should be educated and trained in behavioral and mechanical methods to adapt to their disabilities. This program is usually initiated and overseen by a team of healthcare professionals, including a pediatrician, physical therapist, and occupational therapist. A counselor specially trained to deal with issues of disabilities in children is often helpful in assessing problem areas and encouraging healthy development of self-esteem. Support groups and community organizations for people with Poland anomaly or other disabilities often prove useful as well.

After growth development is advanced enough (usually late adolescence or early adulthood), reconstructive plastic surgery may be offered, primarily to correct cosmetic appearance. The goal of reconstruction is to restore the natural contour of the chest wall while stabilizing the chest wall defect. Chest wall reconstruction must be tailored to the requirements of each patient, but it often involves moving and grafting ribs and muscles from other parts of the body to reconstruct the chest wall and breast. In addition, bioengineered cartilage or breast implants can be used to help give the chest a more normal appearance. Hand abnormalities are treated according to the severity and require individual consultation with a reconstructive plastic surgeon.

Prognosis

The prognosis for people with Poland anomaly is excellent. Reconstructive surgery is safe, and the

cosmetic corrections achieved can be significant. Associated symptoms of heart and kidney defects as well as cancer association are rare, but they indicate that patients with Poland anomaly should be followed closely by a physician familiar with the condition.

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ORGANIZATIONS

Helping Hands Foundation, PO Box 332, Medfield, MA 02052, info@HelpingHandsGroup.org

National Institute of Arthritis and Musculoskeletal and Skin Diseases, 1 AMS Circle, Bethesda, MD 20892-3675, (301) 495-4484 or (877) 226-4267, (301) 718-6366, NIAMSinfo@mail.nih.gov, <http://www.niams.nih.gov>

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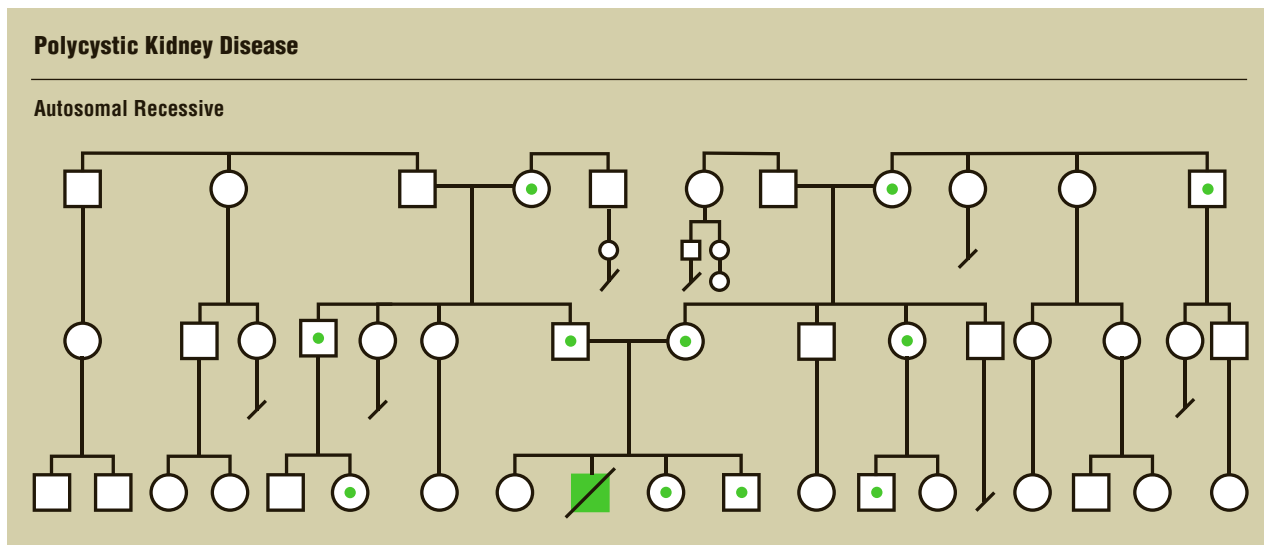
Poland syndactyly see **Poland anomaly**

Poland syndrome see **Poland anomaly**

Polycystic kidney disease

Definition

Polycystic kidney disease (PKD) is one of the most common of all life-threatening human genetic disorders. It is an incurable genetic disorder characterized by the formation of fluid-filled cysts in the kidneys of affected individuals. These cysts multiply over time. It was originally believed that the cysts eventually caused kidney failure by crowding out the healthy kidney tissue. It is now thought that the kidney damage seen in PKD is actually the result of the body's immune system. The immune system, in its attempts to rid the kidney of the cysts,



Polycystic kidney disease: pedigree analysis chart (Gale)

instead progressively destroys the formerly healthy kidney tissue.

Description

A healthy kidney is about the same size as a human fist. PKD cysts, which can be as small as the head of a pin or as large as a grapefruit, can expand the kidneys until each one is bigger than a football and weighs as much as 38 lb. (17 kg).

There are two types of PKD: infantile PKD, which generally shows symptoms prior to birth; and adult-onset PKD. Individuals affected with infantile PKD are often stillborn. Among the liveborn individuals affected with infantile PKD, very few of these children survive to the age of two. The adult-onset form of PKD is much more common. The time and degree of symptom onset in the adult form of PKD can vary widely, even within a single family with two or more affected individuals. Symptoms of this form of PKD usually start to appear between the ages of 20 and 50. Organ deterioration progresses more slowly in adult-onset PKD than it does in the infantile form; but, if left untreated, adult-onset PKD also eventually leads to kidney failure.

Genetic profile

Polycystic kidney disease is expressed as both a recessive and a dominant trait. A recessive genetic trait will not cause disease in a child unless it is inherited from both parents. A dominant genetic trait can be inherited from just one parent. Those people affected with autosomal dominant PKD (ADPKD) have the much more common adult-onset form. Those with autosomal recessive PKD (ARPKD) have the infantile form.

There are mutations on at least three genes that cause adult-onset PKD. Approximately 85% of these cases are known to arise from mutations in the *PKD1* gene that has been mapped to a region on the short arm of chromosome 16 (16p13.3-p13.12). Another 10%–15% of cases of adult-onset PKD are thought to be caused by mutations in the *PKD2* gene that has been mapped to a region on the long arm of chromosome 4 (4q21-q23). It is thought that the remainder of the cases of PKD are caused by mutations in the *PKD3* gene, which has not yet been mapped. This unidentified “*PKD3* gene” may, in fact, be more than one gene.

Adult-onset PKD is transmitted from parents to their offspring as a non-sex-linked (autosomal) dominant trait. This means that if either parent carries this genetic mutation, there is a 50% chance that their child will inherit this disease. In the case of two affected parents, there is a 75% probability that their children will be affected with adult-onset PKD.

Infantile PKD is caused by a non-sex-linked (autosomal) recessive genetic mutation that has been mapped to a region on the short arm of chromosome 6 (6p21). Both parents must be carriers of this mutation for their children to be affected with infantile PKD. In the case of two carrier parents, the probability is 25% that their child will be affected by infantile PKD.

Demographics

One of the most common of all life-threatening genetic diseases, PKD affects about 500,000 in the United States alone. Over 12.5 million people worldwide are affected with PKD. Approximately one in

every 500 to 1,000 people is affected with ADPKD. Another one in 20,000 to 40,000 is affected with ARPKD. PKD is observed in both males and females. PKD is also observed with equal probability among ethnic groups.

Signs and symptoms

A baby born with infantile PKD has floppy, low-set ears, a pointed nose, a small chin, and folds of skin surrounding the eyes (epicanthal folds). Large, rigid masses can be felt on the backs of both thighs (flanks), and the baby usually has trouble breathing.

In the early stages of adult-onset PKD, many people show no symptoms. Generally, the first symptoms to develop are high blood pressure (hypertension); general fatigue; pain in the lower back or the backs of the thighs; headaches; and/or urinary tract infections accompanied by frequent urination.

As PKD becomes more advanced, the kidneys' inability to function properly becomes more pronounced. The cysts on the kidney may begin to rupture, and the kidneys tend to be much larger than normal. Individuals affected with PKD have a much higher rate of kidney stones than the rest of the population at this, and later stages, of the disease. Approximately 60% of those individuals affected with PKD develop cysts in the liver, while 10% develop cysts in the pancreas.

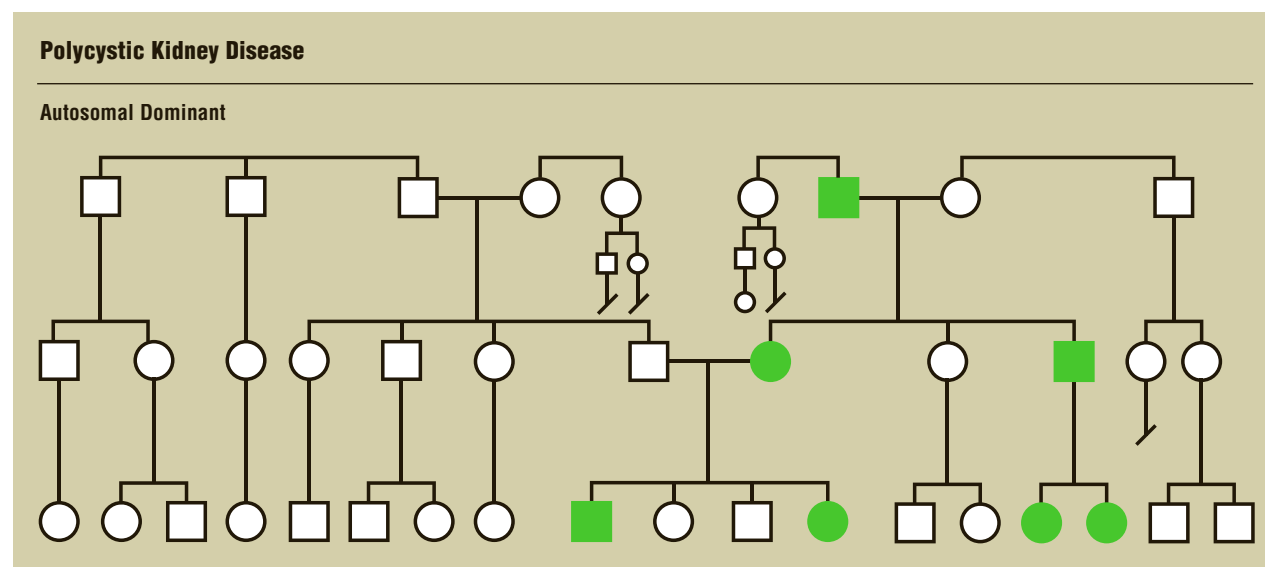
Because the kidneys are primarily responsible for cleaning the blood, individuals affected with PKD often have problems involving the circulatory system. These include an underproduction of red blood cells, which



PKD has made the kidney on the left substantially larger than the normal kidney on the right. (Jessica Wilson/Arthur Glauber/Science Source)

results in an insufficient supply of oxygen to the tissues and organs (anemia); an enlarged heart (cardiac hypertrophy), probably caused by long-term hypertension; and a leakage of the valve between the left chambers (auricle and ventricle) of the heart (mitral valve prolapse). Less common (affecting approximately 5% of PKD patients) are brain aneurysms. An aneurysm is an abnormal and localized bulging of the wall of a blood vessel. If an aneurysm within the brain leaks or bursts, it may cause a stroke or even death.

Other health problems associated with adult-onset PKD include chronic leg or back pain; frequent infections; and herniations of the groin and abdomen, including herniation of the colon (diverticular disease). A herniation, or hernia, is caused when a tissue,



Polycystic kidney disease: pedigree analysis chart (Gale)

KEY TERMS

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Cancer—A disease caused by uncontrolled growth of the body's cells.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Cyst—An abnormal sac or closed cavity filled with liquid or semisolid matter.

Diuretics—Medications that increase the excretion of urine.

Kidney—Either of two organs in the lumbar region that filter the blood, excreting the end products of the body's metabolism in the form of urine and regulating the concentrations of hydrogen, sodium, potassium, phosphate, and other ions in the body.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Ultrasonogram—A procedure where high-frequency sound waves that cannot be heard by human ears are bounced off internal organs and tissues. These sound waves produce a pattern of echoes, which are then used by the computer to create sonograms or pictures of areas inside the body.

Uremic poisoning—Accumulation of waste products in the body.

designed to hold the shape of an underlying tissue, becomes weakened at a particular spot. The underlying tissue pushes against this weakened area until the area is no longer able to hold back the underlying tissue and the area forms an abnormal bulge through which the underlying tissue projects. Diverticular disease is caused by a weakening of the muscles that hold the shape of the organs of the digestive tract. These muscles weaken, allowing these organs, particularly one section of the colon, to form sac-like projections that can trap feces and become infected, or rupture.

In the final stages of PKD, the major symptom is kidney (renal) failure. Renal failure is indicated by an increase of nitrogen (in the form of urea) in the blood (uremia, or uremic poisoning). Uremia is a rapidly fatal condition without treatment.

Diagnosis

Many patients who have PKD do not have any symptoms. Their condition may not be discovered unless tests that detect it are performed for other reasons.

When symptoms of PKD are present, the diagnostic procedure begins with a family medical history and physical examination of the patient. If several family members have PKD, there is a strong likelihood that the patient has it too. If the disease is advanced, the doctor will be able to feel the patient's enlarged kidneys. Heart murmur, high blood pressure, and other signs of cardiac impairment can also be detected.

Urinalysis and a blood test called creatinine clearance can indicate how effectively the kidneys are functioning. Scanning procedures using intravenous dye reveal kidney enlargement or deformity and scarring caused by cysts. Ultrasound and computed tomography (CT) scans can reveal kidney enlargement and the cysts that caused it. CT scans can highlight cyst-damaged areas of the kidneys. A sampling of the kidney cells (biopsy) may be performed to verify the diagnosis.

Treatment and management

There is no way to prevent cysts from forming or becoming enlarged or to prevent PKD from progressing to kidney failure. Treatment goals include preserving healthy kidney tissue; controlling symptoms; and preventing infection and other complications.

If adult PKD is diagnosed before symptoms become evident, urinalysis and other diagnostic tests are performed at six-week intervals to monitor the patient's health status. If results indicate the presence of infection or another PKD-related health problem, aggressive antibiotic therapy is initiated to prevent inflammation that can accelerate disease progression; iron supplements or infusion of red blood cells are used to treat anemia; and surgery may be needed to drain cysts that bleed, cause pain, have become infected, or interfere with normal kidney function.

Lowering high blood pressure can slow loss of kidney function. Blood-pressure control, which is the cornerstone of PKD treatment, is difficult to achieve. Therapy may include antihypertensive medications, diuretic medications, and/or a low-salt diet. As kidney function declines, some patients need dialysis and/or a kidney transplant.

There is no known way to prevent PKD, but certain lifestyle modifications can help control symptoms. People who have PKD should not drink heavily or smoke. They should not use aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), or other prescription or over-the-counter medications that can impair kidney function. Individuals affected with PKD should eat a

QUESTIONS TO ASK YOUR DOCTOR

- What is the process by which polycystic kidney disease damages the human body?
- What is the genetic basis for this disorder?
- Are there treatments available that will extend the lifespan of a child diagnosed with polycystic kidney disease?
- What is the prognosis for a child with this condition?

balanced diet, exercise regularly, and maintain a weight appropriate for their height, age, and body type. Regular medical monitoring is also recommended.

Prognosis

There is no known cure for PKD. Those affected with infantile PKD generally die before the age of two. In adults, untreated disease can be rapidly fatal or continue to progress slowly, even after symptoms of kidney failure appear. About half of all adults with PKD also develop kidney failure. Unless the patient undergoes dialysis or has a kidney transplant, they usually do not survive more than four years after diagnosis.

Although medical treatment can temporarily alleviate symptoms of PKD, the expanding cysts continue to increase pressure on the kidneys. Kidney failure and uremic poisoning (accumulation of waste products the body is unable to eliminate) generally cause death about ten years after symptoms first appear.

Medications used to fight cancer and reduce elevated cholesterol levels have slowed the advance of PKD in laboratory animals. They may soon be used to treat adults and children who have the disease. Researchers are also evaluating the potential benefits of anti-inflammatory drugs, which may prevent the scarring that destroys kidney function.

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ORGANIZATIONS

Polycystic Kidney Disease Foundation National Headquarters, 8330 Ward Pkwy., Suite 510, Kansas City, MO 64114, (800) 753-2873, pkdcure@pkdcure.org, <http://www.pkdcure.org>

Paul A. Johnson

Polycystic ovary syndrome

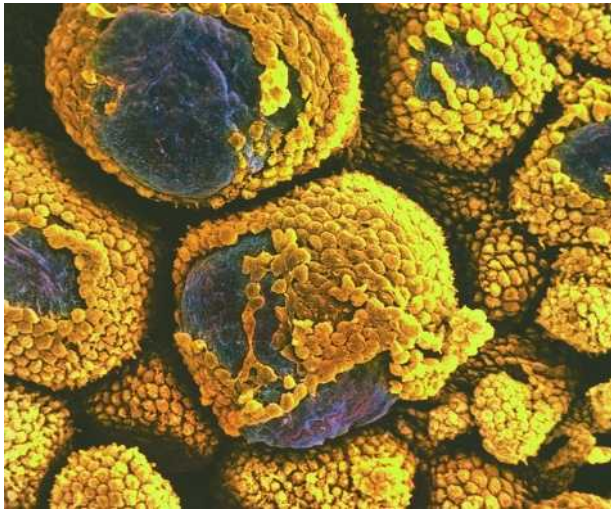
Definition

Polycystic ovary syndrome (PCOS), formerly Stein-Leventhal syndrome, is a disorder in which women do not experience normal release of eggs from the ovaries, they have an abnormal production of male hormones, and their body is resistant to the effects of the hormone insulin. The disorder results in infertility, abnormal masculinization, and increased risk of developing heart disease and certain cancers.

Description

The normal function of the female reproductive system is complex, requiring the interplay of different organ systems. One set of important organs are the ovaries. The ovaries are two small structures contained in the lower abdomen, on either side of the uterus, that contain small immature eggs called ova. Ova are stored within the ovaries in individual structures called follicles.

In a monthly cycle, a part of the brain called the pituitary gland secretes two substances into the bloodstream—luteinizing hormone (LH) and follicle-stimulating hormone (FSH). As certain levels of LH and FSH build in the bloodstream, the follicles of the eggs begin to swell and grow, creating a maturing follicle that eventually ejects an oocyte. Eventually, the changing levels of LH and FSH cause one of the ovarian follicles to burst open, releasing a mature egg. This process by which an egg is released from the ovary is called ovulation.



False-color scanning electron micrograph of a polycystic ovary, showing several cystic follicles protruding from the wall of the ovary. (Pietro M. Motta/Sayoko Makabe/Science Source)

Once a mature egg is released from the ovary, it passes into the fallopian tubes, tube-like structures that are passageways to the uterus. If sperm cells from the male are present within the fallopian tubes, they will join with the egg in a process called fertilization. The fertilized egg can then pass into the uterus and implant into the thickened wall of the uterus where it can develop into a fetus. If no sperm cells are present, the mature egg goes unfertilized and is lost, along with the thickened layer of the uterus, in a monthly process called menstruation.

Polycystic ovary syndrome (PCOS), first described by I. F. Stein and M. L. Leventhal in 1935, is a disorder in which normal ovulation does not occur. The term “polycystic” derives from the fact that the egg-containing cysts in the ovaries do not burst open, resulting in enlarged ovaries containing many swelled cysts. The reason for this problem in ovulation is unclear; however, several abnormalities have been characterized in women with PCOS. First, there is a disturbance in the production of LH and FSH by the pituitary, leading to altered levels of the substances in the bloodstream. There is also evidence that the ovaries do not respond appropriately to the FH and LSH that is present. Second, there is an abnormal overproduction of male hormones, called androgens, by the ovaries and the adrenal gland. Finally, women with PCOS are resistant to the effects of the hormone insulin. Insulin is a hormone made in the pancreas that is responsible for transport of sugar from the blood into the cells. While these abnormalities have been well characterized, it is unclear whether they cause PCOS or whether they are a result of the disease.

Genetic profile

Women diagnosed with PCOS frequently have relatives with symptoms similar to that seen in the disorder. As a result of these observations, many scientists have proposed that genetic factors play a role in the disease. Over the past few decades, researchers have identified families in which PCOS appears to be inherited with an autosomal dominant or an X-linked pattern. However, these cases are rare and do not hold true for the majority of people with PCOS.

Current theories suggest that different genetic changes may result in PCOS or that multiple genetic factors are needed for the full manifestation of the disease. Abnormalities in several genes have been associated with PCOS, including mutations in the genes for follistatin (locus 5p14), 17-beta-hydroxysteroid dehydrogenase (locus 9p22), and a cytochrome P450 enzyme (locus 15q23-q24). Each of these genes plays a different role in the response to LH and FSH, or in the conversion of male hormones to female hormones, although their relationship to PCOS is unclear. Ongoing research is likely to identify further genetic mutations that are associated with PCOS.

Demographics

Estimates of the prevalence of PCOS in the general population have ranged from 2%–20%, with recent studies suggesting that 5%–10% of women of reproductive age are affected by the disorder. This makes PCOS one of the most common hormone disorders in women of reproductive age. Thirty percent of women show some symptoms of PCOS. The overall prevalence rate of PCOS is about one in 40 women.

It is unclear whether this disease is distributed uniformly among different geographical areas and ethnic groups. However, studies performed in 1999 show the prevalence of this disorder in the United States is just over 3% in African-American females and almost 5% in Caucasian females. The prevalence of PCOS in Greek women was shown to be higher, at nearly 7%.

Signs and symptoms

The first signs of PCOS tend to manifest at puberty. As a result of the failure to ovulate normally, young women with PCOS may fail to menstruate or menstruate only erratically. A small percentage of women may have normal menstrual cycles. Women affected with PCOS often experience infertility, an inability to become pregnant. Additionally, women with PCOS tend to gain weight, and 70% eventually become obese.

KEY TERMS

Acanthosis nigricans—A skin condition characterized by darkly pigmented areas of velvety wart-like growths. Acanthosis nigricans usually affects the skin of the armpits, neck, and groin.

Androgens—A group of steroid hormones that stimulate the development of male sex organs and male secondary sexual characteristics.

Diabetes—An inability to control the levels of sugar in the blood due to an abnormality in the production of, or response to, the hormone insulin.

Fallopian tube—Either of a pair of tubes that conduct ova from the ovaries to the uterus.

Follicle—A pouch-like depression.

Follicle-stimulating hormone (FSH)—A hormone that stimulates estrogen in females and sperm production in males.

Hirsutism—The presence of coarse hair on the face, chest, upper back, or abdomen in a female as a result of excessive androgen production.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Infertility—Inability in a woman to become pregnant.

Insulin—A hormone produced by the pancreas that is secreted into the bloodstream and regulates blood sugar levels.

Luteinizing hormone (LH)—A hormone secreted by the pituitary gland that regulates the menstrual cycle

and triggers ovulation in females. In males it stimulates the testes to produce testosterone.

Masculinization—Development of excess body and facial hair, deepening of the voice, and increase in muscle bulk in a female due to a hormone disorder.

Menstruation—Discharge of blood and fragments of the uterine wall from the vagina in a monthly cycle in the absence of pregnancy.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Ova—Another name for the egg cells that are located in the ovaries.

Ovary—The female reproductive organ that produces the reproductive cell (ovum) and female hormones.

Ovulation—The monthly process by which an ovarian follicle or cyst ruptures, releasing a mature egg cell.

Pituitary gland—A small gland at the base of the brain responsible for releasing many hormones, including luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Uterus—A muscular, hollow organ of the female reproductive tract. The uterus contains and nourishes the embryo and fetus from the time the fertilized egg is implanted until birth.

The overproduction of androgens leads to changes in the body that are more typical of male development. For example, approximately 70% of women with PCOS will show hair growth on the face, chest, stomach, and thighs (hirsutism). Simultaneously, they show thinning of the hair more typical of male-pattern baldness. Other male characteristics, such as a deep voice, acne, and increased sex drive, may also be present, and affected women often have decreased breast size.

Women with PCOS do not respond appropriately to insulin. As a result, 15% of women with PCOS may develop high levels of sugar in the blood later in life, a condition known as diabetes. Resistance to insulin is also associated with dark, warty skin growths in the groin and armpits, known as acanthosis nigricans.

Untreated PCOS is a risk factor for the development of several dangerous conditions. The hormone abnormalities

in PCOS place women at considerable risk for endometrial cancer and possibly breast cancer. The risk of endometrial cancer is three times higher in women with PCOS than in normal women, and small studies suggest that the risk of breast cancer may be three to four times higher. PCOS also results in increased risk of high blood pressure, diabetes, and high cholesterol, all of which contribute to heart disease and stroke.

Diagnosis

A diagnostic search for PCOS is usually initiated when women experience an absence of menstrual periods for at least six months, an inability to become pregnant, and/or abnormal hair growth or acne. A comprehensive physical exam performed at that time may reveal excessive body hair, low voice, acanthosis nigricans, or

obesity. Enlarged ovaries are also identifiable on pelvic examination in about 50% of patients.

Blood tests can be performed that may yield results consistent with PCOS, including abnormal levels of LH and FSH (typically in a ratio of 3:1), abnormally high levels of androgens (testosterone, DHEA, DHEAS), abnormally high levels of insulin, and abnormally low levels of a substance called sex hormone-binding globulin. In addition, a physician may perform a diagnostic test called a progesterone challenge. In this test, a physician administers a hormone called progesterone to the patient to determine if it will provoke menstruation. If menstruation does occur in response to the progesterone, it is likely that a patient has PCOS.

Finally, an ultrasound examination of the ovaries may be performed to determine if large cystic follicles can be documented. With this approach, the diagnosis of PCOS is based on the finding of more than eight enlarged follicles in the ovary.

Treatment and management

There is no cure for PCOS, thus treatment focuses on several goals, including the restoration of the menstrual cycle, blocking the effect of androgens, reducing insulin resistance, lowering the risk of cancer and heart disease, and possibly restoring ovulation and fertility.

In patients who do not desire pregnancy, hormones can be administered in the form of birth control pills, which may result in normal menstrual cycles, decreased hair growth and acne, and a lower risk of developing endometrial cancer. Although women will note a decrease in hair growth after approximately six months of treatment with birth control pills, additional cosmetic hair removal therapy is often necessary. In women who do not respond appropriately to birth control pills, another medication known as leuprolide (Lupron) can be used, but with more long-term side effects (e.g., hot flashes, bone demineralization, atrophic vaginitis).

Other types of medication can be used to block the effects of androgens. When these medications are taken with birth control pills, 75% of women report decreased body hair growth. The most commonly used medications to block androgen effects are spironolactone (Aldactone), flutamide (Eulexin), and cyproterone (Cyprostat).

Treatment with medications that restore the body's normal response to insulin has been shown to decrease LH and androgen levels. Recent studies have demonstrated that such agents restore the menstrual cycle in 68%–95% of patients treated for as short a time as four to six months. One of the most commonly used medications to improve the effects of insulin is metformin (Glucophage).

QUESTIONS TO ASK YOUR DOCTOR

- How common is polycystic ovary syndrome in the general public?
- What medical conditions are associated with this disorder?
- How is polycystic ovary syndrome treated, and how effective are those treatments?
- Can you recommend an Internet site or two that will provide additional information on this condition?

In patients who are trying to become pregnant, a physician can administer medications that will cause ovulation. The main medication used to induce ovulation is clomiphene citrate (Clomid). Ovulation is successful in approximately 75% of women treated with clomiphene, but only 30%–40% of women will successfully become pregnant. Another medication, follitropin alpha (Gonal-F), has achieved pregnancy rates of 58%–82%, but may cause more side effects and frequently results in more than one baby per pregnancy.

Some women who do not respond to medications may undergo surgery to remove portions of the ovary. For reasons that are not completely understood, removal of a portion of the ovary may result in some degree of normal menstrual cycles.

While medications and surgery may provide a degree of symptomatic relief for some women, other simultaneous strategies can increase their benefits. Behavior modifications, including weight reduction, diet, and exercise, are recommended for all women with PCOS. As little as a 7% reduction in body weight can lead to a significant decrease in androgen levels and to the resumption of ovulation in obese women with PCOS. Cosmetic techniques, including electrolysis (destruction of the hair follicle using electricity) and laser therapy, may be used to decrease hair growth. Finally, women should be seen regularly for full physical examinations including pelvic exams to aid in the early detection of ovarian, breast, and uterine cancer and should be managed by an interdisciplinary health care team including a primary care physician, obstetrician/gynecologist, and reproductive endocrinologist.

Prognosis

While PCOS is one of the most common hormone disorders in young women, proper diagnosis and

treatment has greatly increased the quality of life in these individuals. Roughly half of women with PCOS will be able to achieve pregnancy, and about three-quarters will see reduction in masculine traits such as hair growth with proper medical treatment. Initiation of vigorous exercise and a restricted diet may result in even better outcomes. Patients with PCOS are at higher risk of developing diabetes, heart disease, and certain cancers and should be seen regularly by a physician. Barring these developments, lifespan in patients with PCOS is approximately the same as the general population.

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PCOS Foundation, 10901 Katy Freeway, Houston, TX 77079, (713) 487-7267, info@pcosfoundation.org, <http://www.pcosfoundation.org>

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Polydactyly

Definition

Polydactyly is the presence of extra fingers and toes (digits) at birth. Rather than having five fingers per hand or five toes per foot, an infant with polydactyly will have six or more digits on either the hands or feet that may or may not be fully formed.

Description

Polydactyly, also called supernumerary digits or extra digits, can occur on either the hands or feet, and the extent of the digit development is variable. Individuals with polydactyly can have one small extra rudimentary finger or toe on one of their hands or feet or they can



X-ray of a child's foot showing polydactyly; in this case, there are seven toes on the foot. (Zephyr/Science Source)

have fully formed extra digits on both their hands and feet. Extra digits can be fully formed or rudimentary and may contain no bones at all. Rudimentary digits may only be attached by a thin stalk of skin. Individuals are described as having isolated polydactyly if they only have extra digits and have no other obvious malformations. Most of the time, polydactyly occurs as an isolated condition, but it can occur as a symptom of different genetic syndromes. There are more than 100 different genetic syndromes that have polydactyly as one of their findings.

Different experts have different systems for describing polydactyly. The two most common systems describe the location and extent of the polydactyly. "Preaxial," "central," and "postaxial" are the terms used to describe the location of the extra digit. If the extra digit is located on the side of the hand by the thumb or on the side of the foot by the big toe, then a person is diagnosed with preaxial polydactyly. Postaxial polydactyly occurs when the extra digit is located on the side of the hand or foot by the fifth digit (the pinky or small toe), and central polydactyly occurs when the extra digit is located in between the thumb and pinky or between the big and little toes.

Type A and type B are used to describe the variable size of the digits in polydactyly. Extra digits can be fully formed with the right number of joints and bones, or they

KEY TERMS

Central polydactyly—Occurring between the thumb and little finger or between the big toe and the little toe.

Digit—A finger or a toe.

Dominant trait—A pattern of inheritance that involves genes that are located on autosomes (not sex chromosomes). In autosomal dominant inheritance, only one copy of a particular form of a gene is needed in order to show that trait.

Postaxial polydactyly—Occurring near the little finger (pinky) or the little toe.

Preaxial polydactyly—Occurring near the thumb or the big toe.

can be poorly formed with the wrong number of joints and no bones (rudimentary digits). Fully formed digits are type A polydactyly, and poorly formed or rudimentary digits are type B polydactyly. Thus, a person with a small rudimentary digit on the outside of the pinky is diagnosed with isolated postaxial polydactyly type B.

Genetic profile

Polydactyly is caused by errors that occur during the process of fetal development. There are a number of genes that determine the pattern of hands and feet. Some of these genes include *SHH*, *ZIC*, and *GLI3*, all of which have a direct connection to polydactyly when mutated, as seen in animal studies, as well as any disruption to the apical embryological ridge, which is important in the timing of growth and development. Many genes must be transcribed and translated correctly for growth and development to occur correctly, hence the incompleteness of the genetic model of polydactyly. Knockout studies in animals have been successful, however, in determining the role of many of these genes. There is strong evidence that the *GLI3* gene is the primary gene involved in polydactyly. This gene is located on the short arm of chromosome 7, and other genes involved in some manner are typically located on chromosome 13.

The three different types of polydactyly—postaxial, central, and preaxial—appear to have different patterns of inheritance. Postaxial polydactyly is inherited as an autosomal dominant that shows variable expressivity. The inheritance patterns for postaxial and central polydactyly are not well understood.

Genes are made of deoxyribonucleic acid (DNA) and located on chromosomes. DNA is composed of four units

(called bases) that are designated A, T, G, and C, named according to the nucleobase they represent. The sequence of the bases contains the instructions for making each of the body's structures. A change in one of the DNA letters making up a gene is a mutation. In some cases, mutations can alter the instructions and lead to malformations.

All individuals pass their chromosomes on to their children and, therefore, pass down their DNA instructions (genes). Genes always come in pairs: one pair each from the mother and one from the father. In an autosomal dominant disorder, only one gene needs to be altered for an individual to have the disorder or malformation. If an individual has the gene change (mutation) that causes postaxial polydactyly, there is a 50% chance that the disorder will be passed on to an offspring.

While the gene for polydactyly is passed unchanged from generation to generation, it often manifests itself very differently in different individuals. For example, a father may have the gene for polydactyly and have had a very small nubbin of soft skin on the outer edge of his hand. However, his child with the same gene may have extra fully formed digits on both hands and feet. This difference in how the gene manifests is called variable expression. The causes of variable expression are not well understood.

Most polydactyly occurs as an isolated condition. However, it can occur as one symptom of other more complicated genetic conditions. Some of the syndromes that polydactyly is a feature of are trisomy 13 syndrome, Meckel-Gruber syndrome, Bardet-Biedl syndrome, and Ellis-van Creveld syndrome.

Trisomy 13 is a rare, usually lethal, genetic syndrome caused by an extra number 13 chromosome. Infants with trisomy 13 have poor growth and multiple birth defects, including cleft lip, heart defects, and defects of the abdominal wall. This syndrome is usually diagnosed at birth.

Meckel-Gruber syndrome is an autosomal recessive syndrome characterized by poor growth, encephalocele (opening on the spine), postaxial polydactyly, and cystic kidneys. This syndrome is usually diagnosed at birth.

Bardet-Biedl is a rare autosomal recessive genetic syndrome characterized by obesity, postaxial polydactyly, retina (eye) abnormalities, and intellectual disability. Often, individuals with this syndrome are not diagnosed until childhood.

Ellis-van Creveld syndrome is a rare autosomal recessive genetic syndrome common in the Amish population. Infants with this syndrome have skeletal abnormalities, short arms and legs, and polydactyly. About half of these infants also have a heart defect. Most infants

with this syndrome are diagnosed shortly after birth or in infancy.

A 2015 study reported an extreme case of polydactyly that researchers named radial polydactyly. In this case study, duplication of many bones in the forearm, wrist, and hand were present on the radial side (thumb side). This study concluded that radial polydactyly should be included in the classification of types of polydactyly.

Demographics

Polydactyly is a relatively common birth defect that occurs in all ethnic groups. Postaxial polydactyly is the most common form of polydactyly and accounts for about 80% of cases. It occurs in about 1 in 2,000 Caucasian births and is about ten times more common in individuals with African ancestry. In about 30% of cases of polydactyly, there is a positive family history, and about 50% of polydactyly is bilateral (affects both sides of the body). Preaxial polydactyly is the most common form of polydactyly in individuals of Asian ancestry.

Signs and symptoms

The presence of polydactyly is most often noted at birth. While it can be shocking for some parents, the presence of isolated polydactyly poses no immediate health risks for the infant. It is a very common malformation that is easily treated by surgical removal.

Individuals with polydactyly can have one small extra rudimentary finger or toe on one of their hands or feet or they can have fully formed extra digits on both their hands and feet. Extra digits can be fully formed or rudimentary and may contain no bones at all. Rudimentary digits may only be attached by a thin stalk of skin.

Diagnosis

The diagnosis of polydactyly is usually made shortly after birth by physical examination. It can also be diagnosed prenatally or before a baby is born. Polydactyly can sometimes be seen on a prenatal ultrasound (sonogram) as early as 18 weeks gestation. If polydactyly is noticed on a sonogram, other medical tests may be suggested to make sure that the fetus does not have any of the problems associated with other genetic syndromes. A detailed sonogram should be done to measure the limbs and growth of the baby, while an amniocentesis may be offered to do a chromosomal analysis of the fetus. A fetal echocardiograph (heart ultrasound) may be performed to rule out heart abnormalities. In addition, other tests may be done to rule out other syndromes.

QUESTIONS TO ASK YOUR DOCTOR

- Is this the only genetic malformation my child has?
- Is surgery an option and, if so, how will it be performed?
- What is the best age for surgery to be performed on my child?
- What is the likelihood that my future children will have this type of growth abnormality?
- What will daily life be like if we do not perform surgery?

Treatment and management

When polydactyly is noted in an infant, a number of the following tests may be done.

- A very thorough medical examination to make sure that there are no other birth defects or abnormalities
- A medical family history to determine if anyone else in the family has had polydactyly or any other syndromes associated with polydactyly
- X-rays to determine the extent of the polydactyly (i.e., whether the digit contains bone or is just skin)
- Laboratory tests, such as chromosome analysis, enzyme assays, and further x-rays to determine that a suspected disorder is present.

While the initial diagnosis may be shocking to most parents, isolated polydactyly has no health consequences and is usually surgically corrected before the infant leaves the hospital.

Polydactyly is rarely a functional concern, and the removal of the extra digit is often for cosmetic purposes or to aid in the wearing of shoes. The age at which surgery is performed depends on the extent and degree of the polydactyly. A type B, or partially formed, digit that contains no bone may be removed before the infant leaves the hospital. A type A polydactyly is often corrected when the patient is one year of age.

Complex polydactyly (central polydactyly) may require multiple surgeries to improve function and cosmetic appearance.

Surgery is often successful, but in some cases the remaining digit may be smaller in size or slightly weaker in musculature, depending on the structure and placement of the additional digit. In this case, post-surgical physical

therapy and/or occupational therapy may be necessary during adolescence.

Prognosis

The prognosis for isolated polydactyly is excellent. When polydactyly is associated with another genetic syndrome, the prognosis is dependent on the presence of other features of that syndrome. Many of the genetic syndromes that have polydactyly as one of their symptoms are quite serious, and early death and significant disability are possibilities.

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ORGANIZATIONS

Helping Hands Foundation, PO Box 332, Medfield, MA 02052, info@HelpingHandsGroup.org, <http://helpinghandsgroup.org>

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Polygenic risk scoring

Definition

Polygenic risk scoring (PRS) is a recently devised technique for estimating the total effect of many DNA variants on an individual's observable characteristics (phenotype) in order to determine his or her genetic predisposition for a given trait—most often, the risk of developing a complex disease. Another way of defining PRS is that it collects or compiles data from an individual's germline genome into a single number

proportional to the risk for a given disease. PRS is also known as a polygenic score (PGS), genetic risk score, or genome-wide score.

Purpose

PRS is currently used to assess a person's risk of developing complex diseases that cannot be predicted in the same way as Mendelian or single-gene diseases. Complex diseases are also called polygenic because they are influenced by a number of different genes for a specific trait, or multifactorial because they result from interactions between a person's genes and environmental factors. Because complex diseases such as heart disorders, stroke, and Alzheimer's disease are much more common in the general population than single-gene disorders like Huntington's disease or hemophilia, the development of risk profiles that could be used to advise people before they begin to show symptoms of a complex disease would be a major advance in improving population health.

Description

PRS was made possible by the introduction and publication of genome-wide association studies, or GWAS, in the early 2000s for such complex diseases as diabetes, coronary artery disease (CAD), and breast cancer. GWAS, also known as whole-genome association study or WGAS, differs from previous methods of genetic research in that it does *not* begin with candidate genes that are tested to see whether they are associated with the disease in question. Instead, GWAS researchers scan the complete genomes of many different subjects looking for single nucleotide polymorphisms (SNPs) that may be genetic markers of the disease. SNPs are variations in a genome involving a single base pair (two complementary nucleotides bonded together by hydrogen to form a unit within the double-helix structure of DNA). Most SNPs do not have a significant effect on health; however, others are located in portions of the human genome where they influence a person's risk of developing a complex disease even though they do not lie on the same chromosome.

In order to carry out a GWAS, researchers select two large groups of human subjects: a group of people diagnosed with the disease under investigation, and a group of controls (people who do not have the disease). Samples of DNA are collected from each subject and analyzed using SNP microarrays. If one SNP variant (one allele) is more common in the subjects diagnosed with the disease than in the control subjects, the SNP is said to be associated with the disease. The researchers then assign a statistical weight to each SNP to estimate its effect on total disease risk. There are several different

methods of statistical analysis that are currently used to refine the accuracy of the estimate; some involve machine learning, which involves computer algorithms that improve with use and the addition of new data.

Between 2008 and 2010, scientists began to expand GWAS by compiling many genomic variants associated with a disease into what is termed a polygenic score. While these early polygenic scores did improve the accuracy of disease risk prediction, physicians in clinical practice did not find these scores useful in advising or treating patients. Three developments led to a major change in polygenic risk scoring: 1) larger GWAS sample sizes, which led to more precise estimates of the effects of SNPs taken as a group; 2) algorithms that allowed researchers to combine sets of variants from across the genome; and 3) the availability of large biobanks that allow scientists to test their findings in a population group different from the one from which they recruited their subjects and controls.

Biobanks are large collections of samples of human blood and other biological specimens stored for use by qualified researchers. The biobank that was first used in polygenic risk scoring is the UK Biobank in Manchester, England, with its participant resource center in Cardiff, Wales. The UK Biobank contains over 500,000 biosamples, most of them taken from healthy British citizens. The scientists at the Broad Institute in Massachusetts who published a groundbreaking paper on PRS in 2018 derived their initial risk scores from GWAS studies of American subjects, primarily of European background. The Broad Institute team then used UK Biobank samples to validate the American data and calculations.

The first complex diseases that were investigated in 2018 include CAD, atrial fibrillation (an abnormal heart rhythm), type 2 diabetes, breast cancer, and inflammatory bowel disease (IBD). Subsequent PRS studies have looked at obesity, type 1 diabetes, schizophrenia, Alzheimer's disease, prostate cancer, malignant melanoma, basal cell carcinoma, hypothyroidism, high blood cholesterol levels, high blood pressure, asthma, gallstones, and glaucoma. One advantage of polygenic risk scoring for these and other complex disorders is that PRS can be assessed at the time of a person's birth, long before the symptoms that physicians use to evaluate a person's risk of CAD or other diseases begin to appear. In theory, finding a person's risk score early in life would allow intensive long-term preventive measures.

Limitations

The Broad Institute researchers noted that one major limitation of most GWAS in recent years is the overrepresentation of data derived from subjects of European

heritage. According to the National Human Genome Research Institute (NHGRI), 78% of the data used in current polygenic risk scoring is derived from people with European ancestry; 10% of the data is derived from Asians, 2% from Africans, and 1% from Hispanics, while the ancestry of the subjects who supplied 8.5% of the data is unreported. This disproportion means that current polygenic risk scores are most accurate for people of European ancestry but may be much less useful in estimating disease risk for individuals from other ethnic or racial groups. This situation is changing, however. In early 2021, the American College of Cardiology and the American Heart Association announced the validation of an integrated risk tool for predicting the 10-year risk of cardiovascular disease in persons of African American, Black African, Black Caribbean, Pakistani, Bangladeshi, or Indian ethnicities.

Another limitation of the PRS studies published to date is inconsistency in score reporting, which results from differences in study populations; the scientists' reasons for choosing those populations; statistical methods for interpreting the data; and transparency of reporting. In order to speed up the application of polygenic risk scoring to clinical use by standardizing reports, the Clinical Genome Resource (ClinGen) Complex Disease Working Group (an international group of researchers and clinicians funded primarily by NHGRI) and the Polygenic Score (PGS) Catalog (a resource supported by British and Australian public health authorities) drew up a list of 22 items to improve consistency in publishing PRS studies. The new reporting framework was published in *Nature* on March 10, 2021.

Another limitation of PRS is that it provides information only about relative, rather than absolute, risks of developing a disease. A person could be placed at the upper end of a PRS score distribution and never develop the disease in question. Conversely, someone at the low-risk end of the bell-shaped curve could still develop the disease. In addition, PRS poses ethical questions about the psychological impact of a high risk score on the patient receiving it. The usefulness of the information and the possible harm to the recipient are real difficulties for adult-onset disorders like Alzheimer's disease that currently have no effective preventive measures and no cure. At the very least, the physician would have to carefully explain the difference between relative and absolute risk to the patient.

Future applications

Polygenic risk scoring is not yet ready for general clinical use. While researchers hope that PRS can be used at some point to identify those at highest risk of a complex disease, evaluate the benefits of various preventive

KEY TERMS

Algorithm—A set of rules for solving a problem in a finite number of steps.

Allele—One of two (or more) forms of the same gene at the same place on a chromosome.

Atrial fibrillation—An abnormal heart rhythm characterized by the rapid and irregular beating of the two upper chambers (atria) of the heart.

Base pair (bp)—Any of the complementary nucleotide bases (adenine-thymine and cytosine-guanine in DNA; adenine-uracil and cytosine-guanine in RNA) held together by weak hydrogen bonds. Base pairs form links between the two strands of DNA.

Biobank—A repository of biological samples (usually human samples) for use in research.

Genome—The total amount of genetic information within an organism's chromosomes, including its genes and DNA sequences.

Genome-wide association study (GWAS)—An approach that involves rapidly scanning markers across the complete sets of DNA (genomes) of many people to find genetic variations associated with a particular disease.

Genotype—The complete set of an organism's genetic material. The term is sometimes used to refer to the genes or set of genes for a single trait, such as height or eye color.

Machine learning—A subtype of artificial intelligence (AI) based on the concept that a computer can learn and adapt to new data inputs without human intervention. Applied to polygenic risk scoring, machine learning is said to improve the accuracy of PRS scores as the computer is given new population data without the need for a human operator to adjust the computer's algorithm.

Mendelian disease—A disease caused by a single mutated gene; also called a single-gene disease. These diseases are named for Gregor Mendel (1822–1884), an Austrian monk who discovered the basic principles of inheritance of single-gene traits through experimentation with plants in his garden.

Monogenic disease—Another term for a single-gene disorder.

Multifactorial disorders—A general term for polygenic disorders complicated by the effects of environmental factors. Multifactorial disorders do not have clear patterns of inheritance. They are sometimes called complex diseases or disorders.

Nucleotide—A building block of a nucleic acid (DNA or RNA), consisting of a sugar molecule, a phosphate group, and one of the nitrogen-containing bases (adenine, cytosine, guanine, and thymine in DNA; adenine, cytosine, guanine, and uracil in RNA).

Phenotype—The set of observable characteristics or traits of an organism. It includes physical form and structure, development, metabolic processes, movement, and behavior.

Polygenic—Referring to an inherited disorder or trait whose phenotype is influenced by more than one gene.

Single nucleotide polymorphism (SNP)—A germline substitution of a single nucleotide (any of a group of molecules that form the building blocks of DNA or RNA) at a specific position in a person's genome.

Trait—In genetics, a specific characteristic of an individual organism, such as height, weight, or blood type. Traits are determined both by genes and the interaction of the environment with genes.

strategies, and develop new treatments for these diseases, more work needs to be done to improve the accuracy of polygenic risk scoring. The growing number and size of biobanks, along with increases in population sampling size and standardized reporting guidelines, should add to the clinical applicability of PRS. In addition, some private health care companies, including Myriad and Ambry Genetics, are already offering polygenic risk scoring for hereditary cancers, and direct-to-consumer (DTC) genetic testing companies are beginning to make polygenic risk scores available to their customers; 23andMe calls them “health predisposition reports.”

Clinical trials of PRS

In 2021, there were 17 clinical trials of PRS registered with the National Institutes of Health (NIH). The most extensive was a trial of PRS for six complex diseases with established preventive strategies: CAD, atrial fibrillation, type 2 diabetes, colorectal cancer, prostate cancer, and breast cancer. The trial was conducted at a Department of Veterans Affairs (VA) hospital in order to test the clinical effectiveness of PRS as measured by changes in primary health care providers' management of their patients. Six other clinical trials were focused on PRS for breast cancer screening; two on the use of PRS

QUESTIONS TO ASK YOUR DOCTOR

- How do you think PRS could be helpful in your clinical practice?
- Have any of your patients used DTC genetic testing to estimate their risk of a complex disease?
- If PRS becomes widespread in clinical practice, how would you counsel a patient who is at high risk of an incurable disease like Huntington's or ALS (Lou Gehrig's disease)?
- Would you consider participating in a PRS study?

in screening for coronary artery disease; and one on PRS in children at risk of type 2 diabetes.

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- Broad Institute, 415 Main Street, Cambridge, MA 02142, (617) 714-7000, <https://www.broadinstitute.org/contact>, <https://www.broadinstitute.org/>
- National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, <https://www.genome.gov/about-nhgri/Contact>, <https://www.genome.gov/>
- Polygenic Score (PGS) Catalog, c/o European Molecular Biology Laboratory-Hinxton, Wellcome Genome Campus, Hinxton, Cambridgeshire, United Kingdom CB10 1SD, +44 (0)1223 494 444, info@ebi.ac.uk, <https://www.pgscatalog.org/>
- UK Biobank Participant Resource Centre, Division of Population Medicine, Cardiff University, 5th Floor, Neuadd Meirionnydd, Heath Park, Cardiff, United Kingdom CF14 4YS, 0800 0 276 276, ukbiobank@ukbiobank.ac.uk, <https://www.ukbiobank.ac.uk/>

Rebecca J. Frey, PhD

Polyps and spots syndrome see **Peutz-Jeghers syndrome**

Polysplenia syndrome see **Asplenia**

Pompe disease

Definition

Pompe disease, also called acid maltase deficiency, is a non-sex-linked recessive genetic disorder that is the most serious of the glycogen storage diseases affecting muscle tissue. It is one of several known congenital (present at birth) muscular diseases (myopathies), which are distinct from a muscular dystrophy, which is a family of muscle disorders arising from faulty nutrition. The Dutch pathologist J. C. Pompe first described this genetic disorder in 1932.

Description

Pompe disease is also known as glycogen storage disease type II (GSD II) because it is characterized by a buildup of glycogen in the muscle cells. Glycogen is the chemical substance muscles use to store sugars and starches for later use. Some of the sugars and starches from the diet that are not immediately put to use are converted into glycogen and then stored in the muscle cells. These stores of glycogen are then broken down into sugars as the muscles require them. Acid maltase is the chemical substance that regulates the amount of glycogen stored in muscle cells. When too much glycogen begins to accumulate in a muscle cell, acid maltase is released to break down this excess glycogen into products that will be either reabsorbed for later use in other cells or passed out of the body via the digestive system. Individuals affected with Pompe disease have either a complete inability or a severely limited ability to produce acid maltase. Since these individuals cannot produce the amounts of acid maltase required to process excess glycogen in the muscle cells, the muscle cells become overrun with glycogen. This excess glycogen in the muscle cells causes a progressive degeneration of the muscle tissues.

Acid maltase is an enzyme. An enzyme is a chemical that facilitates (catalyzes) the chemical reaction of another chemical or of other chemicals; it is neither a reactant nor a product in the chemical reaction that it catalyzes. As a result, enzymes are not used up in chemical reactions, but rather recycled. One molecule of an enzyme may be used to catalyze the same chemical reaction over and over again several hundreds of thousands of times. All the enzymes necessary for catalyzing the various reactions of human life are produced within the body by genes. Genetic enzyme deficiency disorders, such as Pompe disease, result from only one cause: the affected individual cannot produce enough of the necessary enzyme because the gene designed to make the enzyme is faulty. Enzymes are not used up in chemical reactions, but they do eventually wear out or accidentally get

expelled. Also, as an individual grows, he or she may require greater quantities of an enzyme. Therefore, most enzyme deficiency disorders will have a time component to them. Individuals with no ability to produce a particular enzyme may show effects of this deficiency at birth or shortly thereafter. Individuals with only a partial ability to produce a particular enzyme may not show the effects of this deficiency until their need for the enzyme, because of growth or maturation, has outpaced their ability to produce it.

The level of ability of individuals with Pompe disease to produce acid maltase, or their ability to sustain existing levels of acid maltase, are the sole determinants of the severity of the observed symptoms in individuals and the age of onset of these symptoms.

Pompe disease is categorized into three separate types based on the age of onset of symptoms in the affected individual. Type a, or infantile, Pompe disease usually begins to produce observable symptoms in affected individuals between the ages of two and five months. Type b, or childhood, Pompe disease usually begins to produce observable symptoms in affected individuals in early childhood. This type generally progresses much more slowly than infantile Pompe disease. Type c, or adult, Pompe disease generally begins to produce observable symptoms in affected individuals in the third or fourth decades of life. This type progresses even more slowly than childhood Pompe disease.

Genetic profile

The locus of the gene responsible for Pompe disease has been localized to 17q23. The severity of the associated symptoms and the age of onset in affected individuals have been closely tied to the particular mutation at this locus. Three specific mutations and one additional mutation type have been demonstrated to occur along the gene responsible for Pompe disease. Each of these is associated with varying symptoms.

A gene is a particular segment of a particular chromosome. However, within the segment containing a particular gene there are two types of areas: introns and exons. Introns are sections of the segment that do not actively participate in the functioning of the gene. Exons are those sections that do actively participate in gene function. A typical gene consists of several areas that are exons divided by several areas of introns.

One mutation on the gene responsible for the production of acid maltase is a deletion of exon 18. A second mutation on the gene responsible for the production of acid maltase is the deletion of a single base pair of exon 2. Both these mutations are associated with a complete inability of the affected individual to produce acid

maltase. Individuals with these mutations will invariably be affected with infantile (type a) Pompe disease.

The third mutation on the gene responsible for the production of acid maltase is a complicated mutation within intron 1 that causes the cutting-out of exon 2. This mutation is generally not complete in every copy of the gene within a given individual, so it is associated with a partial ability of the affected individual to produce acid maltase. Individuals with this mutation will be affected with either childhood (type b) or, more commonly, adult (type c) Pompe disease. In fact, greater than 70% of all individuals affected with adult Pompe disease possess this particular mutation.

The final mutation class known to occur on the gene responsible for the production of acid maltase is missense at various locations along the various exons. Missense is the alteration of a single coding sequence (codon) that codes for a single amino acid that will be used to build the protein that is the precursor to the acid maltase molecule. These missense mutations generally prevent the production of acid maltase and lead to infantile (type a) Pompe disease.

The exact mutations responsible for the other 30% of the adult (type c) and the remainder of the childhood (type b) Pompe disease cases have not yet been determined.

Demographics

Pompe disease is observed in approximately 1 in every 40,000 live births. It is observed in equal numbers of males and females and across all ethnic subpopulations.

Since Pompe disease is a recessive disorder, both parents must be carriers of the disorder for it to be passed to their children. In the case of carrier parents with one child affected by Pompe disease, there is a 25% likelihood that their next child will also be affected with the disorder. However, because type c (adult) Pompe disease generally does not show symptoms in the affected individual until that individual is past age 30, it is possible for an affected individual to parent children. In this case, the probability of a second child being affected with Pompe disease is 50%. Should two affected individuals bear offspring, the probability of their child being affected with Pompe disease is 100%.

In families with more than one affected child, the symptoms of the siblings will closely correspond. That is, if one child develops infantile Pompe disease, a second child, if affected with the disorder, will also develop the infantile form.

Signs and symptoms

The symptoms of Pompe disease vary depending on the severity of the deficiency of acid maltase in the affected individual. The most acid-maltase-deficient individuals will develop infantile Pompe disease and will exhibit the most severe symptoms. Likewise, the least acid-maltase-deficient individuals will develop adult Pompe disease and have less severe symptoms.

Infantile (type a) Pompe disease is characterized by the so-called “floppy baby” syndrome. This condition is caused by extreme weakness and lack of tone of the skeletal muscles. This observed weakness in the skeletal muscles is accompanied by the much more serious problems of overall weakness of the heart muscle (cardiomyopathy) and the muscles of the respiratory system, primarily the diaphragm. Enlargement of the heart (cardiomegaly), tongue, and liver are also observed. Glycogen accumulation is observed in most tissues of the body.

Childhood (type b) Pompe disease is characterized by weakness of the muscles of the trunk and large muscle mass with little muscle tone. This is due to a buildup of glycogen in the muscle cells. The heart and liver of those affected with childhood maltase deficiency are generally normal. However, there is a progressive weakening of the skeletal and respiratory muscles. The observed muscle weakness in childhood Pompe disease-affected individuals gradually progresses from the muscles of the trunk to the muscles of the arms and the legs. Glycogen accumulation is observed primarily in the muscle tissues.

Adult (type c) Pompe disease is characterized by fatigue in younger affected individuals and by weakness of the muscles of the trunk in older affected individuals. The observed muscle weakness in adult Pompe disease-affected individuals gradually progresses from the muscles of the trunk to the muscles of the arms and the legs. High blood pressure in the artery that delivers blood to the lungs (pulmonary hypertension) is also generally observed in affected adults. Glycogen accumulation is observed primarily in the muscle tissues.

Diagnosis

Infantile Pompe disease is generally diagnosed between the ages of two and five months when symptoms begin to appear. The first indicator of infantile Pompe disease is general weakness and lack of tone (hypotonia) of the skeletal muscles, particularly those of the trunk.

A blood test called a serum CK test is the most commonly used test to determine whether muscular degeneration is causing an observed muscular weakness. It is used to rule out other possible causes of muscle weakness, such as nerve problems. To determine the CK serum

KEY TERMS

Acid maltase—The enzyme that regulates the amount of glycogen stored in muscle cells. When too much glycogen is present, acid maltase is released to break it down into waste products.

Acidosis—A condition of decreased alkalinity resulting from abnormally high acid levels (low pH) in the blood and tissues. Usually indicated by sickly sweet breath, headaches, nausea, vomiting, and visual impairments.

Catalyze—Facilitate. A catalyst lowers the amount of energy required for a specific chemical reaction to occur. Catalysts are not used up in the chemical reactions they facilitate.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Exon—The expressed portion of a gene. The exons of genes are those portions that actually chemically code for the protein or polypeptide that the gene is responsible for producing.

Fibroblast—Cells that form connective tissue fibers like skin.

Glycogen—The chemical substance used by muscles to store sugars and starches for later use. It is composed of repeating units of glucose.

Hypoglycemia—An abnormally low glucose (blood sugar) concentration in the blood.

Intron—That portion of the DNA sequence of a gene that is not directly involved in the formation of the chemical that the gene codes for.

Myopathy—Any abnormal condition or disease of the muscle.

Serum CK test—A blood test that determines the amount of the enzyme creatine kinase (CK) in the blood serum. An elevated level of CK in the blood indicates that muscular degeneration has occurred and/or is occurring.

level, blood is drawn and separated into the part containing the cells and the liquid remaining (the serum). The serum is then tested for the amount of creatine kinase (CK) present. Creatine kinase is an enzyme found almost exclusively in the muscle cells and not typically in high amounts in the bloodstream. Higher than normal amounts of CK in the blood serum indicate that muscular degeneration is occurring—that the muscle cells are breaking open and spilling their contents, including the enzyme

creatine kinase into the bloodstream. Individuals affected with Pompe disease have extremely high serum CK levels. Those affected with infantile Pompe disease have much higher serum CK levels than those affected with the childhood or adult forms. The actual serum CK level, once observed to be higher than normal, can also be used to differentiate between various types of muscular degeneration.

Serum CK levels cannot be used to distinguish Pompe disease from other glycogen storage diseases. Pompe disease (type II glycogen storage disease) is differentially diagnosed from type I glycogen storage disease by blood tests for abnormally low levels of glucose (hypoglycemia) and a low pH, or high acidity (acidosis). Hypoglycemia and acidosis are both characteristic of type I glycogen storage disease, but neither is characteristic of Pompe disease.

It is sometimes possible to determine the abnormally low levels of the acid maltase enzyme in the white blood cells (leukocytes) removed during the blood serum tests. If these levels can be determined and they are abnormally low, a definitive diagnosis of Pompe disease can be made. When the results of this leukocyte test are not clear, Pompe disease types a and b may be positively diagnosed by testing muscle cells removed from the affected individual (muscle biopsy) for the actual absence or lack of sufficient acid maltase. This test is 100% accurate for type a and type b Pompe disease, but it may give improper results for type c Pompe disease. In these hard-to-identify cases of type c Pompe disease, an identical test to that performed on the leukocytes may be performed on cultured fibroblasts grown from a sample from the affected individual. This test is 100% accurate for type c Pompe disease.

Treatment and management

The only potential treatment for this deficiency is enzyme replacement therapy. This approach was initially undertaken in the 1970s for Pompe disease with no success. A new enzyme replacement therapy, which began in 1999, is, however, still being tested in human clinical trials. Animal studies have shown a positive response to enzyme replacement therapy and recombinant gene therapy, particularly for increasing cardiac and respiratory function.

Prognosis

Pompe disease of all three types is 100% fatal. Individuals affected with infantile Pompe disease generally die from heart or respiratory failure prior to age one. Individuals affected with childhood Pompe disease generally die from respiratory failure between the ages of three

QUESTIONS TO ASK YOUR DOCTOR

- What is the prognosis for my child?
- How can we improve my child's quality of life?
- How often should my child be assessed for cardiac and respiratory decline?
- What are the chances any future children will have Pompe disease, and what are the ways we can screen for it?
- Are there support groups for me and my child?
- How rapid or slow of a progression do you anticipate with this disease?
- What signs/symptoms that indicate a decline in function should we watch for?
- Is ERT or any other therapy a choice for us, and, if so, what are the chances of the therapy taking effect?
- Are we a candidate to be involved in current clinical trials?

and 24. Individuals affected with adult Pompe disease generally die from respiratory failure within ten to 20 years of the onset of symptoms.

Human clinical trials involving enzyme replacement therapy, in which a synthetic form of acid maltase is administered to affected individuals, were begun in 1999 at Duke University Medical Center in North Carolina and Erasmus University Rotterdam in the Netherlands. Genzyme Corporation and Pharming Group N. V. announced the first results of these trials in a joint press release on October 5, 2000. These two companies currently own the worldwide patent rights to the synthetic enzyme being studied. In 2015, these clinical trials were in phase II of the three-stage testing process for use in humans.

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ORGANIZATIONS

- Acid Maltase Deficiency Association (AMDA), PO Box 700248, San Antonio, TX 78270, (210) 494-6144, (210) 490-7161, <http://www.amda-pompe.org>
- Association for Glycogen Storage Disease, PO Box 896, Durant, IA 52747, (563) 514-4022, info@agsdus.org, <http://www.agsdus.org>

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Pontocerebellar hypoplasia (PCH)

Definition

CLP1 is a gene that produces the CLP1 protein that is essential for translating DNA into protein via RNA. In 2014, researchers discovered that mutations (changes) in the *CLP1* gene cause pontocerebellar hypoplasia type 10 (PCH10), an extremely rare disorder that is characterized by the degeneration of both the central nervous system (brain and spinal cord) and the peripheral nervous system located throughout the body.

Description

Pontocerebellar hypoplasia (PCH) encompasses at least ten different disorders that are characterized by the underdevelopment of the brain, especially the parts of the brain called the cerebellum and the pons. The cerebellum, located at the back of the brain, is responsible for coordinating movement. The pons, which is located in the brain stem at the base of the brain, is responsible for transmitting signals between the cerebellum and the rest of the brain. Although the signs and symptoms of different types of PCH vary, they are all characterized by delayed psychomotor development (voluntary movement directed by the brain), movement problems, and intellectual or cognitive defects. Because PCH impairs the growth of other parts of the brain in addition to the pons and cerebellum, it causes a small head and brain (microcephaly). Some types of PCH are caused by different mutations in the same gene, resulting in overlapping

symptoms. *PCH* type 1 (*PCH1*) and type 2 (*PCH2*) are the major forms of this disorder.

PCH10 is a severe, inherited neurodevelopmental and neurodegenerative disorder. It is a novel form of *PCH* that is extremely rare and affects both sensory and motor nerve cells (neurons). *PCH10* is characterized by much delayed motor development, failure of the head and brain to grow (progressive microcephaly), and brain abnormalities. In addition to a small cerebellum and pons, these abnormalities include delayed myelination (the formation of the protective myelin covering of nerve cell axons that form the white matter of the brain) and brain degeneration (atrophy). *PCH10* also causes overall delays in growth and development, severe intellectual disability, spasticity, and seizures that are resistant to treatment. Children with *PCH10* have characteristic facial features.

Mutations in the *CLP1* gene are responsible for *PCH10*. “*CLP1*” stands for “cleavage and polyadenylation factor I subunit 1.” The *CLP1* gene produces a *CLP1* protein called an RNA kinase. Kinases are enzymes that add phosphate groups to other proteins in a process called phosphorylation. *CLP1* was first identified in human cells in 2007, making it the first known RNA kinase in mammals.

CLP1 has several different functions. It is a component of the protein complexes that splice (cleave and rejoin) molecules called transfer RNAs (tRNAs) and messenger RNAs (mRNAs). tRNAs add amino acids to growing polypeptide chains during protein synthesis, according to the instructions contained in mRNAs that are copied (transcribed) from the DNA of genes. After tRNAs are transcribed from their corresponding genes, they must undergo a series of complicated alterations, including splicing, before they are functional. Some of these alterations require the *CLP1* protein. *CLP1* is also involved in the processing or maturation of mRNAs and small interfering RNAs (siRNAs). siRNAs are important for regulating the translation of mRNAs into proteins. Thus, *CLP1* has very important functions in cells throughout the body. Although the production and processing of tRNAs are essential to all cells of the body, mutations in the genes involved in these processes appear to particularly affect the functioning of neurons in the central and peripheral nervous systems. Disorders such as *PCH10*, which affect the production of tRNAs, represent a newly recognized class of neurological disorders.

In 2013, researchers showed that mice lacking the *CLP1* gene progressively lost their spinal motor neurons. The axons (projections that transmit nerve impulses) of their peripheral nerves also degenerated, as did the junctions where nerve cells stimulate muscle. These losses resulted in impaired movement and muscle weakness

KEY TERMS

Autosomal recessive—A gene located on a chromosome other than the X or Y sex chromosomes and carrying a trait or mutation that is not expressed unless the second copy of the same gene inherited from the other parent is also recessive or mutated.

Cerebellum—The part of the brain between the brain stem and back of the cerebrum, consisting of two lateral lobes and a median lobe and involved especially in muscle coordination and maintenance of equilibrium.

Consanguineous—People who are closely related, such as first cousins.

Microcephaly—An abnormally small head, often accompanied by a small, underdeveloped brain.

Pons—A mass of nerve fibers in the brain stem that relay nerve impulses between the cerebellum and the rest of the brain.

Pontocerebellar hypoplasia (PCH)—Underdevelopment of the pons and cerebellum of the brain; *PCH10* is caused by a mutation in the *CLP1* gene.

Transfer RNA (tRNA)—Relatively small RNA (ribonucleic acid) that is responsible for adding a specific amino acid to the growing polypeptide chain of a protein; specific tRNAs must be produced for each of the 20 or so amino acids in proteins.

and eventually led to paralysis and death from respiratory failure. Human *CLP1* gene mutations, and the resulting neurologic disorder *PCH10*, which also affects both the central and peripheral nervous systems, were first reported in 2014.

Genetic profile

The *CLP1* gene is located at position 12 on the long arm (q) of chromosome 11 (11q12). Mutated *CLP1* genes are inherited in an autosomal recessive pattern. This means that the development of *PCH10* requires inheriting two mutated *CLP1* genes, one from each parent, so that the cells of the body cannot make any functional *CLP1* protein. The inheritance of a mutated gene from each parent is more likely if the parents are closely related to each other (consanguineous). The parents, whose cells all have one normal *CLP1* gene and one mutated *CLP1* gene, do not usually have signs and symptoms of the disorder; however, each of their children has a 25% risk of inheriting two mutated *CLP1* genes and developing *PCH10*. Each of their children has an additional 50% risk of

inheriting one mutated *CLP1* gene that can be passed on to offspring.

In 2014, two groups of researchers independently identified the same missense mutation in both *CLP1* genes of multiple children with PCH10 from nine consanguineous Turkish families. Missense mutations change a single building block (nucleotide) in the DNA sequence of a gene so that the three-nucleotide sequence no longer codes for an amino acid in a protein; as a result, no protein is produced from that gene. Genetic analysis also revealed that all of the mutated *CLP1* genes in the affected children had originated from the same single original mutation in a common ancestor. This phenomenon is called a “founder effect.” The researchers further demonstrated that this absence of the CLP1 protein prevented the proper splicing of tRNAs.

Demographics

PCH10, as well as types of PCH other than PCH1 and PCH2, appear to be extremely rare. They have been reported in very few individuals.

Signs and symptoms

Brain abnormalities associated with PCH10 are present at birth, and signs and symptoms of the condition develop within the first months of life. Some signs and symptoms may also occur with other types of PCH, and include:

- Microcephaly that is usually not apparent at birth but becomes obvious during infancy and early childhood as brain growth slows
- Characteristic facial features that include highly arched eyebrows, prominent eyes, strabismus (lack of binocular vision due to imbalanced eyeball muscles), long palpebral fissures (the space between the margins of the eyelids), long eyelashes, and a broad nose
- Developmental delays, including failure to develop gross and fine motor skills and speech that is absent or delayed
- Lack of head control
- Inability to sit unsupported or walk
- Severe intellectual disabilities
- Seizures that do not respond to treatment
- Poor overall growth
- Progressively spastic limbs with excessive muscle tone and increased tendon reflexes
- Severe degeneration of the axons of both motor and sensory nerves

QUESTIONS TO ASK YOUR DOCTOR

- What are the signs and symptoms of pontocerebellar hypoplasia?
- Can pontocerebellar hypoplasia be detected prenatally?
- Should family members be tested for a mutated CLP1 gene?
- What is the risk that a couple will have a second child with pontocerebellar hypoplasia type 10?
- What is the prognosis for a child with pontocerebellar hypoplasia?

Diagnosis

The brain and other abnormalities associated with PCH can sometimes be detected by prenatal ultrasound. Brain imaging, such as magnetic resonance imaging (MRI), can reveal the underdevelopment and structural defects of the cerebellum and pons, as well as thinning of the brain stem and the corpus callosum (the fibers connecting the two hemispheres of the brain), enlarged ventricles (the cavities within the brain containing the cerebrospinal fluid), and possibly abnormalities of the white matter (myelinated nerve axons) of the brain. MRIs of the brain and spinal cord, computed axial tomography (CAT or CT) scans of the brain, ultrasound imaging, and metabolic analysis may be used to rule out other causes of the brain abnormalities. Electromyography and nerve conduction tests will show significant degeneration of sensory and motor neurons in the spinal cord and the peripheral nervous system. Electroencephalography (EEG)—tests of electrical activity in the brain—may also be performed. Ophthalmologic evaluation for vision problems is usually required. In 2015, identification of *CLP1* gene mutations required sequencing the entire region of the gene that codes for the CLP1 protein.

Treatment and management

Treatment of PCH10 is symptomatic and supportive. It is directed at ameliorating apparent symptoms.

Prognosis

Many children with PCH do not survive infancy or live only into childhood. Occasionally, individuals affected by some types of PCH have been known to survive into adulthood.

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National Institute of Neurological Disorders and Stroke, PO Box 5801, Bethesda, MD 20824, (301) 496-5751 or (800) 496-5751, <http://www.ninds.nih.gov>

Office of Rare Diseases Research, National Center for Advancing Translational Sciences, National Institutes of Health, 6701 Democracy Blvd., Suite 1001, MSC 4874, Bethesda, MD 20892x, (301) 402-4336, (301) 480-9655, ordr@nih.gov, <https://rarediseases.info.nih.gov>

Margaret Alic, PhD

Porphyrrias

Definition

The porphyrias comprise a group of eight metabolic disorders in which the body produces too much porphyrin and insufficient heme, the iron-containing molecule found, for example, in hemoglobin, the oxygen-carrier protein. Porphyrins are precursor molecules for heme and certain enzymes. Excess porphyrins are excreted as waste in the urine and stool. Overproduction and overexcretion of porphyrins cause low, unhealthy levels of heme and certain important enzymes, creating various physical symptoms.

Description

Biosynthesis of heme is a multistep process that begins with simple molecules and ends with a large, complex heme molecule. Each step of the chemical pathway is directed by its own task-specific protein, called an



Early symptoms of porphyrias including blistering on the hands, face, and arms following minor injuries or exposure to sunlight. (Zara/BSIP SA/Alamy)

enzyme. As a heme precursor molecule moves through each step, an enzyme modifies the precursor for the next step. If a precursor molecule is not modified, it cannot proceed further in the pathway, causing a build-up of that specific precursor.

The precursors prevented from proceeding further along the pathway accumulate at the stage of the enzyme defect, causing an array of physical symptoms in an affected person. Specific symptoms depend on the point at which heme biosynthesis is blocked and which precursors accumulate. In general, the porphyrias primarily affect the skin and the nervous system. Symptoms can be debilitating or life-threatening in some cases. Porphyria is most commonly an inherited condition. It can also, however, be acquired after exposure to poisonous substances.

Heme

Heme is produced in several tissues in the body, but its primary biosynthesis sites are the liver and bone marrow. Heme synthesis for immature red blood cells, namely the erythroblasts and the reticulocytes, occurs in the bone marrow.

Although production is concentrated in the liver and bone marrow, heme is utilized in various capacities in virtually every tissue in the body. In most cells, heme is a key building block in the construction of factors that oversee metabolism and transport of oxygen and energy. In the liver, heme is a component of several vital enzymes, particularly cytochrome P450. Cytochrome P450 is involved in the metabolism of chemicals, vitamins, fatty acids, and hormones; it is very important in transforming toxic substances into easily excretable materials. In immature red blood cells, heme is the crucial

component of hemoglobin, the biomolecule that carries oxygen in red blood cells.

Heme biosynthesis

The heme molecule consists of a cyclic porphyrin molecule containing a central iron atom. The heme biosynthesis pathway is a series of steps building the complete heme molecule, and the last step involves incorporation of the iron atom.

The production of heme may be compared to a factory assembly line. At the start of the line, raw materials are fed into the process. At specific points along the line, an addition or adjustment is made to further development. Once additions and adjustments are complete, the final product rolls off the end of the line.

Heme biosynthesis is an eight-step process, requiring eight different and properly functioning enzymes:

- delta-aminolevulinic acid synthase
- delta-aminolevulinic acid dehydratase
- uroporphobilinogen deaminase
- uroporphyrinogen III cosynthase
- uroporphyrinogen decarboxylase
- coproporphyrinogen oxidase
- protoporphyrinogen oxidase
- ferrochelatase

The control of heme biosynthesis is complex. Various chemical signals can trigger increased or decreased production. These signals can affect the enzymes themselves or the production of these enzymes, starting at the genetic level. For example, one point at which heme biosynthesis may be controlled is at the first step. When heme levels are low, greater quantities of delta-aminolevulinic acid (ALA) synthase are produced. As a result, larger quantities of heme precursors are fed into the biosynthesis pathway to step up heme production.

Types of porphyrias

Under normal circumstances, when heme concentrations are at an appropriate level, precursor production decreases. However, a defective enzyme can prevent heme biosynthesis from reaching completion. Because heme levels remain low, the synthesis pathway continues to churn out precursor molecules in an attempt to correct the heme deficit.

The net effect of this continued production is an abnormal accumulation of precursor molecules and development of some type of porphyria. Each type of porphyria corresponds to a specific enzyme defect and an accumulation of the associated precursor. Although there are eight steps in heme biosynthesis, there are only

seven types of porphyrias; a change in ALA synthase activity does not have a corresponding porphyria.

Enzymes involved in heme biosynthesis display subtle, tissue-specific variations; therefore, heme biosynthesis may be impaired in the liver, but normal in the immature red blood cells, or vice versa. Incidence of porphyria varies widely between types and occasionally by geographic location. Although certain porphyrias are more common than others, their greater frequency is only relative to other types. All porphyrias are considered to be rare disorders.

In the past, the porphyrias were divided into two general categories based on the location of the porphyrin production. Porphyrias affecting heme biosynthesis in the liver were referred to as hepatic porphyrias. Porphyrias affecting heme biosynthesis in immature red blood cells were referred to as erythropoietic porphyrias (erythropoiesis is the process through which red blood cells are produced). Porphyrias are usually grouped into acute and nonacute types. Acute porphyrias produce severe attacks of pain and neurological effects. Nonacute porphyrias present as chronic diseases.

The acute porphyrias, and the heme biosynthesis steps at which enzyme problems occur, are:

- ALA dehydratase deficiency porphyria (step 2): the enzyme aminolevulinic acid dehydratase is deficient.
- Acute intermittent porphyria, also known as Swedish porphyria, pyroloporphyria, and intermittent acute porphyria (step 3): the enzyme uroporphobilinogen deaminase is deficient.
- Hereditary coproporphyria (step 6): the enzyme coproporphyrinogen oxidase is deficient.
- Variegate porphyria (VP), also known as porphyria variegata, protocoproporphyria, South African genetic porphyria, and Royal malady (supposedly King George III of England and Mary, Queen of Scots, had VP) (step 7): the enzyme protoporphyrinogen oxidase is deficient.

The nonacute porphyrias, and the steps of heme biosynthesis at which they occur, are:

- Congenital erythropoietic porphyria (CEP), also called Gunther's disease, erythropoietic porphyria, congenital porphyria, congenital hematoporphyria, or erythropoietic uroporphyria, is a rare disease (step 4): the enzyme uroporphyrinogen III synthase is deficient.
- Porphyria cutanea tarda (PCT), also called symptomatic porphyria, porphyria cutanea symptomatica, or idiosyncratic porphyria (step 5): the enzyme uroporphyrinogen decarboxylase is deficient. PCT may be acquired, typically as a result of disease (especially hepatitis C), or inherited. Most people remain latent—that is, symptoms never develop.

- Hepatoerythropoietic porphyria (HEP) (also step 5). HEP affects heme biosynthesis in both the liver and the bone marrow. HEP also results from a defect in uroporphyrinogen decarboxylase activity. Disease symptoms, however, strongly resemble congenital erythropoietic porphyria.
- Erythropoietic protoporphyria (EPP), also known as protoporphyria and erythrohepatic protoporphyria (step 8): ferrochelatase is the deficient enzyme.

Genetic profile

The underlying cause of all porphyrias is a deficiency of one of the enzymes involved in the heme biosynthesis pathway. Porphyrias are inherited conditions, and in virtually all types, an inherited factor causes the enzyme deficiency. An environmental factor—such as diet, drugs, or sun exposure—may trigger symptoms, but in many cases, symptoms never develop.

Each of the seven porphyrias has a specific inheritance pattern and a gene mutation responsible for its occurrence:

- ALA dehydratase porphyria: autosomal recessive inheritance, due to a mutation of the *ALAD* gene in chromosome 9q34. This porphyria type is very rare. In autosomal recessively inherited disorders, a person must inherit two defective genes, one from each parent. A parent with only one gene for an autosomal recessive disorder does not display symptoms of the disease.
- Acute intermittent porphyria: autosomal dominant inheritance, due to a mutation of the *PBGD* gene in chromosome 11q23.3. An autosomal dominant pattern, which means that only one copy of the abnormal gene needs to be present for the disorder to occur. Simply inheriting this gene, however, does not necessarily mean that a person will develop the disease. Approximately 5 to 10 per 100,000 persons in the United States carry a gene for AIP, but only 10% of these people ever develop symptoms of the disease.
- Congenital erythropoietic porphyria: autosomal recessive inheritance, due to a mutation of the *UROS* gene in chromosome 10q25.2–q26.3.
- Porphyria cutanea tarda: autosomal dominant or sporadic inheritance, due to a mutation of the *UROD* gene in chromosome 1p34.
- Hereditary coproporphyria: autosomal dominant inheritance, due to a mutation of the *CPOX* gene in chromosome 3q12.
- Variegate porphyria: autosomal dominant inheritance, due to a mutation of the *PPOX* gene in chromosome 1q22.

- Erythropoietic protoporphyria: autosomal dominant inheritance, due to a mutation of the *FECH* gene in chromosome 18q21.3.

Demographics

Porphyrias are rare conditions and are often misdiagnosed because their symptoms are easily confused with other diseases. Congenital erythropoietic porphyria is typically seen in early childhood; erythropoietic protoporphyria in older childhood; acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, and delta-aminolevulinic acid dehydratase deficiency porphyria in teens and young adults; and porphyria cutanea tarda in adults older than 40 years of age. The most common form of porphyria worldwide is porphyria cutanea tarda. In 2012, the prevalence of PCT in the world was estimated at 10 cases in 100,000; the prevalence of acute intermittent porphyria, erythropoietic protoporphyria, and variegate porphyria at 1–10 of 100,000 people; and hereditary coproporphyria at less than 1 in 100,000 of the population. Delta-aminolevulinic acid dehydratase deficiency porphyria and congenital erythropoietic porphyria are both extremely rare.

Signs and symptoms

General characteristics

All of the hepatic porphyrias—except porphyria cutanea tarda—follow a pattern of acute attacks separated by periods in which no symptoms are present. For this reason, this group is often referred to as the acute porphyrias. The erythropoietic porphyrias and porphyria cutanea tarda do not follow this pattern and are considered to be chronic conditions.

The specific symptoms of each porphyria vary based on which enzyme is affected and whether that enzyme occurs in the liver or in the bone marrow. The severity of symptoms can vary widely, even within the same type of porphyria. If the porphyria becomes symptomatic, the common factor between all types is an abnormal accumulation of protoporphyrins or porphyrin.

ALA dehydratase porphyria (ADP)

ADP is characterized by a deficiency of ALA dehydratase. Of the few cases on record, the prominent symptoms were vomiting; pain in the abdomen, arms, and legs; and neuropathy. (Neuropathy refers to nerve damage that can cause pain, numbness, or paralysis.) The nerve damage associated with ADP could cause breathing impairment or lead to weakness or paralysis of the arms and legs.

Acute intermittent porphyria (AIP)

Symptoms of AIP usually do not occur unless a person with the deficiency encounters a trigger substance. Trigger substances can include hormones (for example, oral contraceptives, menstruation, pregnancy), drugs, and dietary factors. Most people with this deficiency never develop symptoms.

Attacks occur after puberty and commonly feature severe abdominal pain, nausea, vomiting, and constipation. Muscle weakness and pain in the back, arms, and legs are also typical symptoms. During an attack, the urine is a deep reddish color. The central nervous system may also be involved. Possible psychological symptoms include hallucinations, confusion, seizures, and mood changes.

Congenital erythropoietic porphyria (CEP)

Symptoms of CEP are often apparent in infancy and include reddish urine and possibly an enlarged spleen. The skin is unusually sensitive to light and blisters easily if exposed to sunlight. (Sunlight induces protoporphyrin changes in the plasma and skin. These altered protoporphyrin molecules can cause skin damage.) Increased hair growth is common. Damage from recurrent blistering and associated skin infections can be severe. In some cases facial features and fingers may be lost to recurrent damage and infection. Deposits of protoporphyrins can sometimes lead to red staining of the teeth and bones.

Porphyrria cutanea tarda (PCT)

PCT may occur as an acquired or an inherited condition. The acquired form usually does not appear until adulthood. The inherited form may appear in childhood, but often demonstrates no symptoms. Early symptoms include blistering on the hands, face, and arms following minor injuries or exposure to sunlight. Lightening or darkening of the skin may occur along with increased hair growth or loss of hair. Liver function is abnormal but the signs are mild.

Hepatoerythropoietic porphyria (HEP)

The symptoms of HEP are similar to those of CEP.

Hereditary coproporphyrria (HCP)

HCP is similar to AIP, but the symptoms are typically milder. The greatest difference between HCP and AIP is that people with HCP may have some skin sensitivity to sunlight. However, extensive damage to the skin is rarely seen.

Variegate porphyria (VP)

Like AIP, symptoms of VP occur only during attacks. Major symptoms of this type of porphyria include neurological problems and sensitivity to light. Areas of the skin that are exposed to sunlight are susceptible to burning, blistering, and scarring.

Erythropoietic protoporphyria (EPP)

Owing to deficient ferrochelatase, the last step in the heme biosynthesis pathway—the insertion of an iron atom into a porphyrin molecule—cannot be completed. The major symptoms of this disorder are related to sensitivity to light—including both artificial and natural light sources. Following exposure to light, a person with EPP experiences burning, itching, swelling, and reddening of the skin. Blistering and scarring may occur but are neither common nor severe. EPP is associated with increased risks for gallstones and liver complications. Symptoms can appear in childhood and tend to be more severe during the summer when exposure to sunlight is more likely.

Diagnosis

Depending on the array of symptoms an individual may exhibit, the possibility of porphyria may not immediately come to a physician's mind. In the absence of a family history of porphyria, nonspecific symptoms, such as abdominal pain and vomiting, may be attributed to other disorders. Neurological symptoms, including confusion and hallucinations, can lead to an initial suspicion of psychiatric disease. Diagnosis is more easily accomplished in cases in which nonspecific symptoms appear in combination with symptoms more specific to porphyria, like neuropathy, sensitivity to sunlight, or certain other manifestations. Certain symptoms, such as urine the color of port wine, are hallmark signs very specific to porphyria. As of 2015, DNA analysis was becoming more widely used for the diagnosis of a porphyria. After a urine analysis identifies a porphyria is present, mutation analysis can be performed. Identifying the genetic cause of the porphyria is extremely beneficial in the treatment and management of the case, proving DNA testing to be essential in the diagnosis of the syndrome.

A common initial test measures protoporphyrins in the urine. However, if skin sensitivity to light is a symptom, a blood plasma test is indicated. If these tests reveal abnormal levels of protoporphyrins, further tests are done to measure heme precursor levels in red blood cells and the stool. The presence and estimated quantity of porphyrin and protoporphyrins in biological samples are easily detected using spectrofluorometric testing. Spectrofluorometric testing uses a spectrofluorometer that directs light of a specific strength at a fluid sample. The porphyrins

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Biosynthesis—The manufacture of materials in a biological system.

Bone marrow—A spongy tissue located in the hollow centers of certain bones, such as the skull and hip bones. Bone marrow is the site of blood cell generation.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Erythropoiesis—The process through which new red blood cells are created; it begins in the bone marrow.

Erythropoietic—Referring to the creation of new red blood cells.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Hematin—A drug administered intravenously to halt an acute porphyria attack. It causes heme biosynthesis to decrease, preventing the further accumulation of heme precursors.

Heme—The iron-containing molecule in hemoglobin that serves as the site for oxygen binding.

Hemoglobin—Protein-iron compound in the blood that carries oxygen to the cells and carries carbon dioxide away from the cells.

Hepatic—Referring to the liver.

Neuropathy—A condition caused by nerve damage. Major symptoms include weakness, numbness, paralysis, or pain in the affected area.

Porphyrin—A large cyclic molecule shaped like a four-leaf clover. Combined with an iron atom, it forms a heme molecule.

Protoporphyrin—A precursor molecule to the porphyrin molecule.

Whether heme precursors occur in the blood, urine, or stool gives some indication of the type of porphyria, but more detailed biochemical testing is required to determine their exact identity. Making this determination yields a strong indicator of which enzyme in the heme biosynthesis pathway is defective; this, in turn, allows a diagnosis of the particular type of porphyria.

Biochemical tests rely on the color, chemical properties, and other unique features of each heme precursor. For example, a screening test for acute intermittent porphyria (AIP) is the Watson-Schwartz test. In this test, a special dye is added to a urine sample. If one of two heme precursors—porphobilinogen or urobilinogen—is present, the sample turns pink or red. Further testing is necessary to determine whether the precursor present is porphobilinogen or urobilinogen—only porphobilinogen is indicative of AIP.

Other biochemical tests rely on the fact that heme precursors become less soluble in water (able to be dissolved in water) as they progress further through the heme biosynthesis pathway. For example, to determine whether the Watson-Schwartz urine test is positive for porphobilinogen or urobilinogen, chloroform is added to the test tube. Chloroform is a water-insoluble substance. Even after vigorous mixing, the water and chloroform separate into two distinct layers. Urobilinogen is slightly insoluble in water, while porphobilinogen tends to be water-soluble. The porphobilinogen mixes more readily in water than chloroform, so if the water layer is pink (from the dye added to the urine sample), that indicates the presence of porphobilinogen, and a diagnosis of AIP is probable.

As a final test, measuring specific enzymes and their activities may be done for some types of porphyrias; however, such tests are not done as a screening method. Certain enzymes, such as porphobilinogen deaminase (the abnormal enzyme in AIP), can be easily extracted from red blood cells; other enzymes, however, are less readily collected or tested. Basically, an enzyme test involves adding a certain amount of the enzyme to a test tube that contains the precursor it is supposed to modify. Both the production of modified precursor and the rate at which it appears can be measured using laboratory equipment. If a modified precursor is produced, the test indicates that the enzyme is doing its job. The rate at which the modified precursor is produced can be compared to a standard to measure the efficiency of the enzyme.

Treatment and management

Treatment for porphyria revolves around avoiding acute attacks, limiting potential effects, and treating

and protoporphyrins in the sample absorb the light energy and fluoresce, or glow. The spectrofluorometer detects and measures fluorescence, which indicates the amount of porphyrins and protoporphyrins in the sample.

symptoms. Treatment options vary depending on the specific type of porphyria diagnosed. Gene therapy has been successful for both CEP and EPP. In the future, scientists expect development of gene therapy for the remaining porphyrias. Given the rarity of ALA dehydratase porphyria, definitive treatment guidelines for this rare type have not been developed.

For the most part, the porphyrias are attributed to inherited genes; such inheritance cannot be prevented. However, symptoms can be limited or prevented by avoiding factors that trigger symptom development.

People with a family history of an acute porphyria should be screened for the disease. Even if symptoms are absent, it is useful to know about the presence of the gene to assess the risks of developing the associated porphyria. This knowledge also reveals whether a person's offspring may be at risk. Prenatal testing for certain porphyrias is possible. Prenatal diagnosis of congenital erythropoietic porphyria has been successfully accomplished. Any prenatal tests, however, would not indicate whether a child would develop porphyria symptoms, only that they might have the potential to do so.

Acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria

Treatment for acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria follows the same basic regime. A person who has been diagnosed with one of these porphyrias can prevent most attacks by avoiding precipitating factors, such as certain drugs that have been identified as triggers for acute porphyria attacks. Individuals must maintain adequate nutrition, particularly in respect to carbohydrates. In some cases, an attack can be stopped by increasing carbohydrate consumption or by receiving carbohydrates intravenously.

When attacks occur, prompt medical attention is necessary. Pain is usually severe, and narcotic analgesics are the best option for relief. Phenothiazines can be used to counter nausea, vomiting, and anxiety, and chloral hydrate or diazepam is useful for sedation or to induce sleep. Hematin, a drug administered intravenously, may be used to halt an attack. Hematin seems to work by signaling the pathway of heme biosynthesis to slow production of precursors. Women, who tend to develop symptoms more frequently than men owing to hormonal fluctuations, may find ovulation-inhibiting hormone therapy to be helpful.

QUESTIONS TO ASK YOUR DOCTOR

- Porphyria runs in our family. How can I find out if I have the disorder or carry a defective gene for the condition?
- What are the chances that one or more of my children will inherit a form of porphyria?
- Is pregnancy a possible risk for women who have porphyria?
- If one of my children inherits porphyria, how serious is the disease likely to be?

Gene therapy is a possible future treatment for these porphyrias. An experimental animal model of AIP has been developed and research is in progress.

Liver transplant may also be necessary and successful for treating patients with life-threatening manifestation of acute intermittent porphyria.

Congenital erythropoietic porphyria

The key points of congenital erythropoietic porphyria treatment are avoiding exposure to sunlight and prevention of skin trauma or skin infection. Liberal use of sunscreens and consumption of beta-carotene supplements can provide some protection from sun-induced damage. Medical treatments such as removing the spleen or administering transfusions of red blood cells can create short-term benefits, but these treatments do not offer a cure. Remission can sometimes be achieved after treatment with oral doses of activated charcoal. Severely affected patients may be offered bone marrow transplantation, which appears to confer long-term benefits.

Porphyria cutanea tarda

As with other porphyrias, the first line of defense is avoidance of factors, especially alcohol, that could bring about symptoms. Regular blood withdrawal is a proven therapy for pushing symptoms into remission. If an individual is anemic or cannot have blood drawn for other reasons, chloroquine therapy may be used.

Erythropoietic protoporphyria

Avoiding sunlight, using sunscreens, and taking beta-carotene supplements are typical treatment options for erythropoietic protoporphyria. The drug cholestyramine may reduce the skin's sensitivity to sunlight as well as the accumulated heme precursors in the liver.

Liver transplantation has been used in cases of liver failure, but it has not provided a long-term cure of the porphyria.

Alternative treatment

Acute porphyria attacks can be life-threatening events, so attempts at self-treatment can be dangerous. Alternative treatments can be useful adjuncts to conventional therapy. For example, some people may find relief for the pain associated with acute intermittent porphyria, hereditary coproporphyria, or variegate porphyria through acupuncture or hypnosis. Relaxation techniques, such as yoga or meditation, may also prove helpful in pain management.

Prognosis

Even when porphyria is inherited, symptom development depends on a variety of factors. In the majority of cases, a person remains asymptomatic throughout life. About one percent of acute attacks can be fatal. Other symptoms may be associated with temporarily debilitating or permanently disfiguring consequences. Measures to avoid these consequences are not always successful, regardless of how diligently they are pursued. Although pregnancy has been known to trigger porphyria attacks, dangers associated with pregnancy are not as great as was once thought.

Resources

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"Porphyrias." Healthline. <https://www.healthline.com/health/porphyria> (accessed July 9, 2021).

ORGANIZATIONS

American Porphyria Foundation (APF), 4900 Woodway, Suite 780, Houston, TX 77056, (866) APF-3635 or (713) 266-9617, porphyria@aol.com, <http://www.porphyriafoundation.com>

Canadian Association for Porphyria, 13604 108 Ave. NW, Edmonton, Alberta, Canada T5M 2C8, (866) 476-2801, porphyria@cpf-inc.ca, <http://www.cpf-inc.ca>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Portosystemic venous shunt–congenital see
Patent ductus arteriosus

Potter sequence see **Oligohydramnios sequence**

Prader-Willi syndrome

Definition

Prader-Willi syndrome (PWS) is a genetic condition caused by the absence of chromosomal material from chromosome 15. The genetic basis of PWS is complex. Characteristics of the syndrome include developmental delay, poor muscle tone, short stature, small hands and feet, incomplete sexual development, and unique facial features. Insatiable appetite is a classic feature of PWS. This uncontrollable appetite can lead to health problems and behavior disturbances.

Description

The first patients with features of PWS were described by Drs. Prader, Willi, and Lambert in 1956. Since that time, the complex genetic basis of PWS has begun to be understood. Initially, scientists found that more than 70% of individuals with PWS have a portion of genetic material deleted (erased) from chromosome 15. Through a process called imprinting, genetic contributions to a child from each parent are activated so that traits from each parent are passed on. In individuals with PWS, the genetic material from chromosome 15 received from one's father is deleted. If the deletion is on the chromosome 15 inherited from one's mother, a different syndrome develops. This was an important discovery. It demonstrated for the first time that the genes inherited from one's mother can be expressed differently from those inherited from one's father.

Over time, scientists discovered that some individuals with PWS, approximately 25%, do not have a deletion of genetic material from chromosome 15. Further studies found that, rather than deleted material from chromosome 15, about 35 percent of patients inherit two copies of chromosome 15 from their mother. Normally, an individual should receive one chromosome 15 from one's

father and one chromosome 15 from one's mother. When a person receives both chromosomes from the same parent, it is called uniparental disomy. When a person receives both chromosomes from one's mother, it is called maternal uniparental disomy. For fewer than 5% of people with PWS, the chromosome 15 locus is present but silenced.

Newborns with PWS generally have poor muscle tone (hypotonia) and do not feed well. This can lead to poor weight gain and failure to thrive. Genitalia can be smaller than normal. Hands and feet are also typically smaller than normal. Some patients with PWS have unique facial characteristics, which are typically subtle and only detectable by physicians.

As children with PWS age, development is typically slower than normal. Developmental milestones, such as crawling, walking, and talking, occur later than usual. Developmental delay continues into adulthood for approximately 50% of individuals with PWS. At about one to two years of age, children with PWS develop an uncontrollable, insatiable appetite. Left to their own devices, individuals with PWS will eat until they have life-threatening obesity. The desire to eat can lead to significant behavior problems.

The symptoms and features of PWS require life-long support and care. If food intake is strictly monitored, and various therapies provided, individuals with PWS can have a normal life expectancy.

Genetic profile

To comprehend the various causes of PWS, the nature of chromosomes and genes must be well understood. Human beings have 46 chromosomes in the cells of their body. Chromosomes contain genes. Genes regulate the function and development of the body. An individual's chromosomes are inherited from their parents. A child should receive 23 chromosomes from their mother and 23 chromosomes from their father.

The 46 chromosomes in the human body are divided into pairs. Each pair is assigned a number or a letter. Chromosomes are divided into pairs based on their physical characteristics. They can only be seen when viewed under a microscope. Chromosomes within the same pair appear identical, because they contain the same genes.

Most chromosomes have a constriction near the center, called the centromere. The centromere separates the chromosome into long and short arms. The short arm of a chromosome is called the "p arm." The long arm of a chromosome is called the "q arm."

Chromosomes in the same pair contain the same genes. However, some genes work differently, depending



Colored X-ray (side view) of the elongated skull (dolichocephalic deformity) in an adult patient. This deformed skull can either characterize newborns who are born after breech presentation, or it may be found in the genetic disorder Prader-Willi syndrome. (Zephyr/Science Source)

on whether they were inherited from the egg or the sperm. Sometimes, genes are silenced when inherited from the mother. Other times, they are silenced when inherited from the father. When genes in a certain region on a chromosome are silenced, they are said to be "imprinted." Imprinting is a normal process and does not typically cause disease. If normal imprinting is disrupted, a genetic disease can develop.

Individuals should have two complete copies of chromosome 15. One chromosome 15 should be inherited from the mother, or be "maternal" in origin. The other chromosome 15 should be inherited from the father, or be "paternal" in origin.

Several genes found on the q arm of chromosome 15 are imprinted. They are normally imprinted, or silenced, if inherited from the mother. The imprinting of this group of maternal genes does not typically cause disease. The genes in this region should not be imprinted if paternal in origin. Normal development depends on these paternal genes being present and active. If these genes are deleted, not inherited, or incorrectly imprinted, PWS develops.

About 60 percent of the cases of PWS are caused when a piece of material is deleted, or erased, from the paternal chromosome 15 (DEL15). This deletion happens in region 11 through 13 on the q arm of chromosome 15. The piece of chromosomal material that is deleted contains genes that must be present for normal development. These paternal genes must be working normally, because the same genes on the chromosome 15 inherited from the mother are imprinted. When these paternal genes are missing, the brain and other parts of the body do not

develop as expected, which is what causes the symptoms associated with PWS.

Researchers have identified two specific mechanisms of genetic mutation that cause Prader-Willi syndrome. Both involve genes located on sections of chromosome 15. One specific genetic cause is a mutation of the *SNORD116* cluster genes. These genes are responsible for the production of a specific type of RNA called small nucleolar RNA (snoRNA), which is involved in the regulations of other RNA. When the snoRNA is abnormal, it leads to the symptoms of PWS. Scientists have not discovered exactly how abnormal snoRNA causes PWS.

Another cause of PWS is a mutation in the *OCA2* gene, which is also located on chromosome 15. When this gene is mutated, it leads to the characteristic light hair and fair skin of some individuals with PWS, because the *OCA2* gene is involved in producing proteins that are important in the formation of pigment in hair, eyes, and skin.

In nearly all cases of PWS caused by a deletion of genetic material, it is sporadic. This means that it happens randomly during fetal development, and there is not an apparent cause. It does not run in families. If a child has PWS due to a sporadic deletion in the paternal chromosome 15, the chance that the parents could have another child with PWS is less than 1%. In fewer than 1% of the cases of PWS, there is a chromosomal rearrangement in a family, which causes the deletion. This chromosomal rearrangement is called a translocation. If a parent has a translocation, the risk of having a child with PWS is higher than 1%.

PWS can also develop if a child receives both chromosome 15s from his or her mother. This is seen in approximately 25% of the cases of PWS. Maternal uniparental disomy for chromosome 15 leads to PWS, because the genes on the chromosome 15 that should have been inherited from the father are missing. These paternal genes must be present, since the same genes on both the chromosome 15s inherited from the mother are imprinted.

PWS caused by maternal uniparental disomy is sporadic, which means that it happens randomly, and there is no apparent cause. If a child has PWS due to maternal uniparental disomy, the chance that the parents could have another child with PWS is less than 1%.

Approximately 3% to 4% of patients with PWS have a change (mutation) in a gene located on the q arm of chromosome 15. This mutation leads to incorrect imprinting and causes genes inherited from the father to be imprinted or silenced. These genes should not normally be imprinted. If a child has PWS due to a mutation that changes imprinting, the chance that the parents could have another child with PWS is approximately 5%.

If an individual has a deletion of the same material from the q arm of the maternal chromosome 15, a different syndrome develops, called Angelman syndrome. Angelman syndrome can also occur if an individual receives both chromosome 15s from their father.

Demographics

PWS affects approximately one in 10,000 to 30,000 live births. It is the most common genetic cause of life-threatening obesity. It affects both males and females. PWS can be seen in all races and ethnic groups.

Signs and symptoms

Infants with PWS have weak muscle tone (hypotonia), which causes problems with sucking and eating. Infants with PWS may have problems gaining weight. Some are diagnosed with failure to thrive, due to slow growth and development. During infancy, babies with PWS may also sleep more than normal and have problems controlling their temperature.

Some of the unique physical features associated with PWS can be seen during infancy. Genitalia that is smaller than normal is common. This may be more evident in males with PWS. Hands and feet may also be smaller than average. The unique facial features seen in some patients with PWS may be difficult to detect in infancy. These facial features are very mild and do not cause physical problems.

As early as six months, but more commonly between one and two years of age, a compulsive desire to eat develops. This uncontrollable appetite is a classic feature of PWS. Individuals with PWS lack the ability to feel full or satiated. This uncontrollable desire to eat is thought to be related to a difference in the brain, which controls hunger. Overeating (hyperphagia), a lack of a desire to exercise, and a slow metabolism place individuals with PWS at high risk for severe obesity. Some individuals with PWS may also have a reduced ability to vomit.

Behavior problems are a common feature of PWS. Some behavior problems develop from the desire to eat. Other reported problems include obsessive-compulsive behaviors, depression, and temper tantrums. Individuals with PWS may also pick their own skin. This unusual behavior may be due to a reduced pain threshold.

Developmental delay, learning disabilities, and intellectual impairment are associated with PWS. Approximately 50% of individuals with PWS have developmental delay. The remaining 50% are described as having mild intellectual impairment, although it can occasionally be more severe.

KEY TERMS

Amniocentesis—A procedure performed at 16 to 18 weeks of pregnancy in which a needle is inserted through a woman's abdomen, into her uterus, to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about various genetic disorders and other medical conditions in the fetus.

Centromere—The centromere is the constricted region of a chromosome. It performs certain functions during cell division.

Deletion—The absence of genetic material that is normally found in a chromosome. Often, the genetic material is missing due to an error in replication of an egg or sperm cell.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

FISH (fluorescent in situ hybridization)—A technique used to detect small deletions or rearrangements in chromosomes by attempting to attach a fluorescent (glowing) piece of a chromosome to a sample of cells obtained from a patient.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found in a precise location on a chromosome.

Hyperphagia—Overeating.

Hypotonia—Reduced or diminished muscle tone.

Imprinting—A process that silences a gene or group of genes. The genes are silenced depending on whether they are inherited through the egg or the sperm.

Maternal—Relating to the mother.

Maternal uniparental disomy—A chromosome abnormality in which both chromosomes in a pair are inherited from one's mother.

Methylation testing—DNA testing that detects whether a gene is active, or whether it is imprinted.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Paternal—Relating to one's father.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosomal material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

Uniparental disomy—A chromosomal abnormality in which both chromosomes in a pair are inherited from the same parent.

Puberty may occur early or late, but it is usually incomplete. In addition to the effects on sexual development and fertility, individuals do not undergo the normal adolescent growth spurt and may be short as adults. Muscles often remain underdeveloped, and body fat is often increased.

Diagnosis

During infancy, the diagnosis of PWS may be suspected if poor muscle tone, feeding problems, small genitalia, or the unique facial features are present. If an infant has these features, testing for PWS should be performed. This testing should also be offered to children and adults who display features commonly seen in PWS (e.g., developmental delay, uncontrollable appetite, and small genitalia). There are several different genetic tests that can detect PWS. All of them can be performed from a blood sample.

Methylation testing detects 99% of the cases of PWS. It can detect the absence of the paternal genes that should be normally active on chromosome 15. Although methylation testing can accurately diagnose PWS, it cannot determine whether the PWS is caused by a deletion, maternal uniparental disomy, or a mutation that disrupts imprinting. This information is important for genetic counseling. Therefore, additional testing should be performed, depending on initial findings.

Chromosome analysis, also called karyotyping, can determine whether the PWS is the result of a deletion in the q arm of chromosome 15. It involves staining the chromosomes and examining them under a microscope. In some cases, the deletion of material from chromosome 15 can be easily seen. In other cases, further testing must be performed. FISH (fluorescent in situ hybridization) is a special technique that detects small deletions that cause PWS.

QUESTIONS TO ASK YOUR DOCTOR

- Please explain the genetic basis for Prader-Willi syndrome.
- What are the most serious medical problems associated with this disorder?
- What changes in a person's lifestyle, if any, will help in the treatment of his or her Prader-Willi syndrome?
- What is the prognosis for a person diagnosed with this condition?

More specialized DNA testing is needed to detect maternal uniparental disomy or a mutation that disrupts imprinting. This DNA testing identifies unique DNA patterns in the mother and father, which are then compared with the DNA from the child with PWS.

PWS can be detected before birth if the mother undergoes amniocentesis testing or chorionic villus sampling (CVS). This testing would only be recommended if the mother or father is known to have a chromosome rearrangement or if they already have a child with PWS syndrome.

Treatment and management

There is currently no cure for PWS. Treatment during infancy includes therapies to improve muscle tone. Some infants with PWS also require special nipples and feeding techniques to improve weight gain.

Gene editing research reveals the possibility to correct the problem of hidden genes not being read by cells. CRISPRon/off is one such method that can genetically edit DNA through epigenetic modification. By targeting the gene, small pieces of RNA can guide treatment to the target and remove methyl groups from specific genes to modify their expression.

Treatment and management during childhood, adolescence, and adulthood is typically focused on weight control. Strict control of food intake is vital to prevent severe obesity. In many cases, food must be made inaccessible. This may involve unconventional measures, such as locking the refrigerator or kitchen cabinets. A lifelong restricted-calorie diet and regular exercise program are also suggested. Unfortunately, diet medications have not been shown to significantly prevent obesity in PWS. However, growth hormone therapy has been shown to improve the poor muscle tone and reduced height typically associated with PWS.

In 2021, a study reported on success with intranasal oxytocin to help young boys with a subset of PWS (DEL15) with positive effects on social behavior and eating. The hormone oxytocin plays an important role in food intake, energy expenditure, and controlling body weight.

Special education may be helpful in treating developmental delays and behavior problems. Individuals with PWS typically excel in highly structured environments. PWS varies greatly from one individual to another, including need for behavioral and psychological treatments.

Prognosis

Life expectancy is normal, and the prognosis good if weight gain is well controlled.

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ORGANIZATIONS

International Prader-Willi Syndrome Organization, 1779 Massachusetts Avenue, NW, Suite 500, Washington, D.C.(203) 744-0100, <https://rarediseases.org/>

National Organization for Rare Disorders, Salisbury House, Station Road, Cambridge, United Kingdom+39 0444 555557, info@ipwso.org, <http://www.ipwso.org>

Prader-Willi Syndrome Association, 8588 Potter Park Drive,
Suite 500, Sarasota, FL 34238, (800) 926-4797,
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Preimplantation genetic diagnosis

Definition

Preimplantation genetic diagnosis (PGD or PIGD) is general term for the techniques used for the genetic profiling of embryos prior to implantation, or of the oocytes before fertilization.

Description

Preimplantation genetic diagnosis (PGD) is used during in vitro fertilization (IVF) to screen for genetic disorders prior to pregnancy in order to avoid implanting embryos that carry inherited disease. It is also used for selective pregnancy termination. PGD is considered an assisted reproduction technique (ART). PGD analyzes the DNA of unfertilized oocytes and fertilized embryos to select ones that meet certain criteria that improve the chances of a normal pregnancy. PGD techniques are normally used before continuing with an IVF program when chromosomal or genetic disorders occur in the family of one of the parents. This can ensure that such diseases will not be passed on in children produced from the IVF process.

Application

The first successful sex identification in blastocysts was performed in 1967 by Robert Edwards and Richard Gardner, and in 1989 the first successful births from human IVF trials were documented. PGD was used to determine the sex of the embryos used in pregnancies where the parents were carriers of X-linked disorders. Sex discrimination is important for those concerned with avoiding sex-linked disorders, but PGD can also be used to help families prepare for sex-dependent parenting or for “family balancing” when previous children are of all one gender. The latter are not considered to be medical reasons, and the ethical nature of this use of PGD is often questioned.

Couples who are carriers for monogenic disorders and are concerned about passing on disease to their future children can use PGD to identify embryos that are free of disease and use only these in IVF attempts. In cases of

KEY TERMS

Assisted reproductive technology (ART)—Medical technologies or procedures that are used during fertility treatments.

Blastocyst—An early developmental stage of a developing embryo.

DNA polymerase—An enzyme that is required for DNA replication. It functions in the addition of new nucleotides in the production of new DNA strands.

Embryo—The multicellular, developing fertilized egg of a vertebrate animal.

Eugenics—The improvement of human genetic features through the use of selective breeding or technologies that allow for genetic selection on the cellular level.

Genetic mosaicism—A mixture of cells of two or more genotypes.

In vitro fertilization (IVF)—The manual combination of egg and sperm cells in a laboratory dish to create a fertilized egg that can be implanted into a woman’s uterus. IVF is an assisted reproductive technology (ART).

Monogenetic disorder—A disorder or disease that is caused by a mutation or defect in one gene.

Oocyte—An immature ovum or egg produced during female gametogenesis.

Polar bodies—A small haploid cell that is formed during oogenesis (creation of an ovum), but that generally does not have the ability to be fertilized.

high-risk pregnancies or where embryo survival is a concern, PGD can help assess the quality of embryos that will be implanted to ensure better chances of the pregnancy leading to live births.

Predisposed cancer syndromes can be screened for such as the BRCA genes, which can contribute to hereditary breast and ovarian cancers. Additionally, HLA (human leukocyte antigen) matching may be used to allow for a second child to match that of a sick sibling. In such cases the cord-blood stem cells from the matched infant can be used to treat the disease of the sibling. Children born as a result of HLA matching through PGD are often called “savior siblings.”

Techniques used in PGD

Techniques that are used in fertility treatment are called assisted reproductive technology (ART). Along



Colored light micrograph of an IVF human embryo during preimplantation genetic testing. (Pascal Goetgheluck/Science Source)

with PGD, other ART can include controlled ovarian stimulus with hormones, transvaginal ultrasound used in oocyte retrieval, and oocyte fertilization with injected sperm DNA. PGD can be performed on embryos at different stages of development, but the common stages are:

- Unfertilized oocytes
- Fertilized embryos and polar bodies
- Three-day cleavage-stage embryos
- Blastocyst

Analysis of oocytes and early-stage embryos can only reliably test maternal contributions to the embryo. PGD of these cells can inform on X-linked disorders and anything else that may be inherited only from the mother. At later stages of embryo development the genetics from both parents can be assessed.

Fluorescent in situ hybridization (FISH)

FISH is used to detect chromosomal abnormalities in the embryo, and unlike karyotyping it can be used on interphase chromosomes, which are much less dense and compact. Fluorescent probes made from short sequences of DNA bind to complementary sequences on sample

DNA from the embryo. When the samples are exposed to particular wavelengths of light, the probes will fluoresce. If the probes bind to genes or sequences that are specifically present in certain genetic disorders, the embryo genome can be quickly analyzed for the occurrence of those genetic abnormalities.

Polymerase chain reaction (PCR)

Kary Mullis developed PCR in 1985 as a way to replicate DNA in vitro. Using thermo-stable DNA polymerases, sequences of DNA can be amplified artificially from a small amount of template DNA to produce many copies of a single sequence that can be used for further analysis. In PGD, PCR is used to amplify embryo DNA at particular sites that are associated with known disorders so that it can be further analyzed for any abnormalities.

Risks of PGD

While highly effective in assessing the genetics of embryos and helping parents at risk of passing genetic disorder on to their children, PGD is an invasive process that can damage the embryo during biopsy. Additionally,

cryopreserved embryos have a 20% chance of not surviving the thawing process, and there is some evidence that biopsied embryos have an even lower rate of survival after cryopreservation. In mouse models, offspring produced from biopsied embryos showed risks of weight gain, memory loss, and brain alterations that have been associated with neurological disorders like Down syndrome and Alzheimer's.

Analysis of PGD assumes the outcome of a biopsy of one cell is representative of a multi-cell embryo; however, the occurrence of genetic mosaicism could result in false positives or negatives, and this could lead to either normal embryos being discarded or the acceptance of abnormal embryos, respectively.

Ethics

There are conflicting opinions on the social acceptability of PGD due to its implicated contributions to eugenics. In some countries PGD is only permitted for the prevention of stillbirths and genetic diseases. Sex selection is often not considered acceptable for reasons that are not medically related. Forms of social selection like “family balancing,” when there are multiple children of one sex and parents would like a child of the opposite sex, or selection that discriminates against disabilities or intersex traits are not always considered appropriate reasons to pursue PGD.

Those that argue for wider usage of PGD state that parents have a moral obligation to select in favor of any traits that may give their future children the best life possible, including selecting for genetic traits like intelligence and beauty.

Advocates for disabled communities believe that PGD discriminates against their disabilities, while some communities argue for the use of PGD to select embryos with the traits associated with their disability.

In cases where parents explore ART to provide a cord-blood donation from a “savior sibling” to treat an existing sick child, there are questions about the ethical nature of how this exploits the unborn child who would be conceived with the intent of providing treatment for their sibling.

Policy

PGD is widely used, but many countries do not allow sex selection for nonmedical reasons. The legality and policies on ART varies from country to country.

- **Canada:** In 2012 budget cuts removed the 2004 Assisted Human Reproductive Act, and PGD became unregulated at the national level, allowing provinces to

QUESTIONS TO ASK YOUR DOCTOR

- I am/my partner is a carrier for an autosomal recessive disorder. How will PGD determine the outcome for my pregnancy?
- What other decisions can we make about the genetics of the embryos using PGD?
- What are the ethical codes and legal policies that regulate ART where I live?
- What risks are associated with ART?

make rulings about how the technology was used on their own.

- **Germany:** Since 2011 PGD is allowed only in certain cases (i.e., when there is a high instance or likelihood of stillbirth or inheritance of genetic diseases).
- **India:** PGD is regulated under a 1994 act that prohibits its use for sex selection.
- **United Kingdom:** Reproductive clinics are required to have a license if they provide PGD. A regulatory agency requires the clinics to submit an application so that the suitability of the genetic test being requested can be reviewed. The regulatory agency prohibits sex selection for social or cultural reasons, allowing it only for the identification for sex-linked disorders. This includes intersex variations, which some gender advocacy groups say is unethical.
- **United States:** There is no uniform regulation of the use of PGD on the national level and it usually falls under state law or professional guidelines. The Centers for Disease Control and Prevention (CDC) requires IVF clinics to report annual pregnancy success rates to the federal government, but this reporting does not include the use of PGD. The American Society for Reproductive Medicine states that PGD should not be used solely for sex selection.

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American Pregnancy Association, 1425 Greenway Dr., Suite 440, Irving, TX 75038, (800) 672-2296, <http://www.americanpregnancy.org>

Genetic Alliance, 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008-2369, (202) 966-5557, (202) 966-8553, info@geneticalliance.org, <http://www.geneticalliance.org>

Reproductive Health Technologies Project, 1634 Eye St. NW, Suite 650, Washington, DC 20006, (202) 530-4401, (202) 530-4404, info@rhtp.org, <http://www.rhtp.org>

Society for Assisted Reproduction Technology (SART), 1209 Montgomery Hwy., Birmingham, AL 35216-2809, (205) 978-5000, ext. 109, (205) 978-5018, <http://www.sart.org>

Emily R. Larson, PhD

Prenatal ultrasound

Definition

Prenatal ultrasound is a procedure performed during pregnancy to obtain images of the fetus.

Description

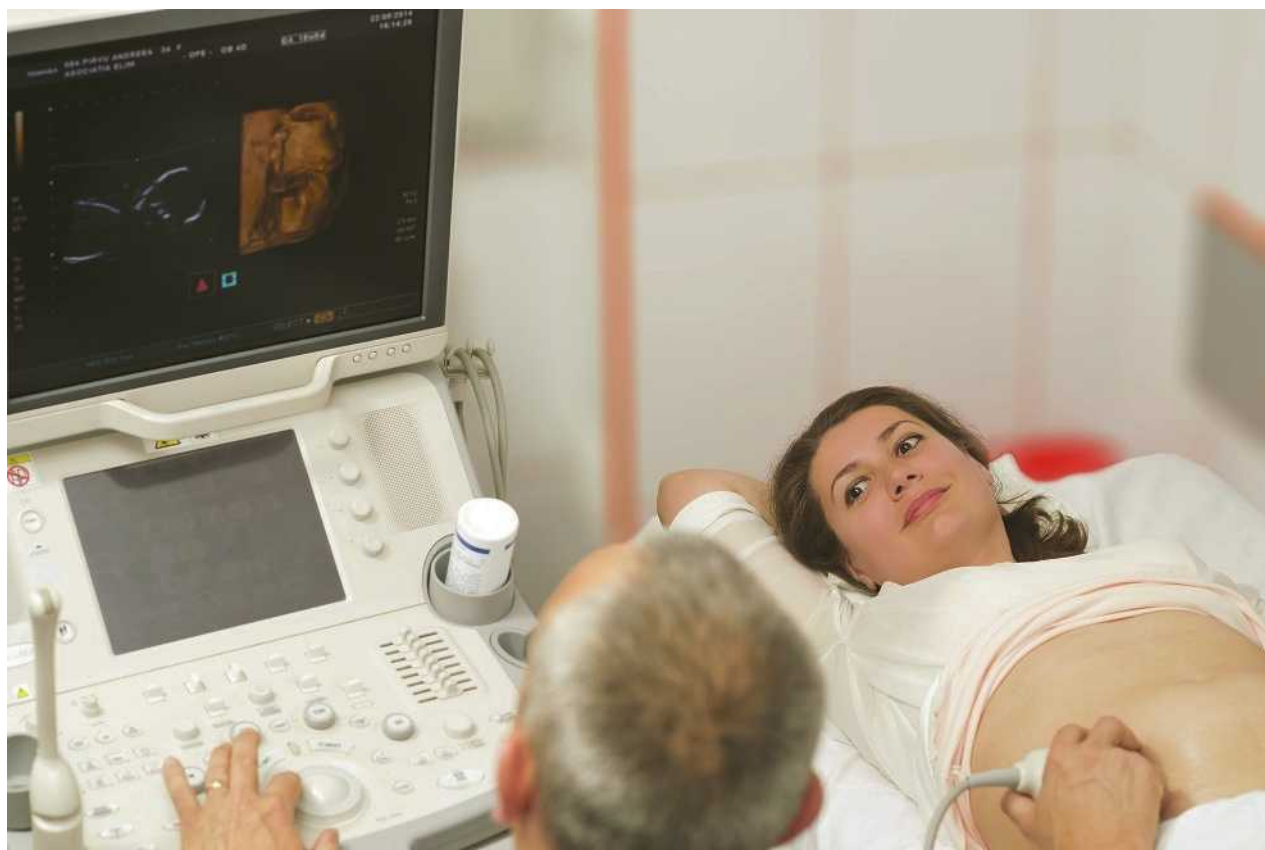
A prenatal ultrasound, also known as a sonogram, is a procedure in which a tool called a transducer is placed on a woman’s abdomen so that images of the fetus in the woman’s uterus can be viewed on a monitor. The most commonly used ultrasound produces a two-dimensional image of the fetus, although the technology exists to create a three-dimensional image as well. Electrical energy coming in to the transducer is converted to high-frequency sound waves. The sound waves reflect off of any structures they contact and return to the transducer and are converted back to electrical energy. Generally, more dense structures, like fetal bones, are seen as bright white images on the screen. Less dense tissue, like organs and fluid, shows darker on the screen. Gel placed on the woman’s abdomen acts as a medium and allows for more rapid transmission of the sound waves and a better image.

There are many reasons an obstetrician may recommend an ultrasound for a pregnant woman. Some of these reasons include getting an accurate gestational age (dating) of the pregnancy, determining viability of a fetus (i.e., heartbeat), determining if any structural changes are present in the fetus, and determining if there are problems in the fetal environment. A prenatal ultrasound is performed by a healthcare professional, including an obstetrician, a radiologist, and a maternal-fetal medicine specialist. The American Institute of Ultrasound Medicine recommends that physicians performing ultrasound complete an approved residency program, a fellowship, or postgraduate training that includes three months and 500 supervised ultrasound procedures. An ultrasound technician often performs the initial measurements and, if needed, the physician reviews the procedure and obtains additional images. Ultrasounds are sometimes referred to as either basic (level 1) or comprehensive (level 2 or 3), depending on the quality of the equipment used, the amount and detail of the fetal anatomy studied, and the training of the person performing the procedure.

Most pregnant women in the United States have one prenatal ultrasound. There is some debate about when this ultrasound should take place. Early ultrasounds, in the first trimester of pregnancy, are the most accurate way to determine how far advanced a pregnancy is and to set an accurate due date. However, these early ultrasounds do not allow for a detailed study of the fetal anatomy for any changes in development. An anatomical study of the fetus is best performed at about 18–20 weeks gestation. Women who are at increased risk for birth defects, genetic conditions, or pregnancy complications may have multiple ultrasounds. Studies have shown, and the American Institute of Ultrasound Medicine Bioeffects Committee has concluded, that there is no association between prenatal ultrasounds using sound waves and an increased chance for birth defects or other pregnancy complications. Studies have also shown that there is significant psychological benefit to parents from having ultrasounds performed. Prenatal ultrasounds provide parents with reassurance that the fetus is developing normally or identify problems that can be investigated further.

First-trimester ultrasounds

The first trimester of pregnancy is considered to be the first 12 weeks of pregnancy, or the first three months. Prenatal ultrasounds in the first trimester may be performed either on the abdomen or vaginally; however, to get the clearest images in the first trimester, a vaginal ultrasound is performed. In this type of ultrasound, a smaller transducer is placed into the vagina, up to the



A doctor performs a 3-D ultrasound on a pregnant woman. (*Marius Pirvu/Shutterstock*)

cervix. By having the transducer closer to the uterus, the fetus, which is very small in the first trimester, can be viewed more clearly.

First-trimester ultrasounds are often performed for women, unsure of the dating of their last menstrual period, who want to determine the correct gestational age. Early ultrasounds are best for dating because, early in a pregnancy, all fetuses grow at about the same rate. Therefore, measurements correspond well to gestational age. However, later in pregnancy, fetuses show more characteristics of their own growth pattern, and correlation to gestational age is not as clear. In general, first-trimester ultrasound measurements of gestational age are accurate to within about five days. Second-trimester ultrasound measurements of growth are accurate to about 8–12 days. Pinpointing a correct gestational age aids in determining an accurate due date and, consequently, in scheduling the proper tests at the proper times. One test that is offered to all pregnant women is called a maternal serum multiple marker screening test. This test screens a pregnancy to determine if there is an increased chance for Down syndrome, open spine defects, and another chromosomal condition called trisomy 18. This test can be performed between 15 and

20 weeks of pregnancy, and may result in a false-negative or false-positive result if the due date of the pregnancy is not accurate.

First-trimester ultrasounds can also be used to detect multiple pregnancies, ectopic pregnancies (pregnancies located outside of the uterus), and the location of the placenta. The placenta is the organ between the mother and fetus that allows for the crossing of nutrients and oxygenated blood. Sometimes the placenta is located over the cervix, blocking the path the fetus would normally take to exit the uterus. Complications of this condition, called placenta previa, can be avoided by performing a cesarean section rather than a vaginal delivery. Another common reason for a first-trimester ultrasound is vaginal bleeding. First-trimester ultrasounds may be able to detect a pregnancy loss or a pregnancy that is not progressing normally. In general, the fetus is too small in the first trimester to view the anatomy in detail. However, a few serious structural changes to the fetus can be identified in the first trimester. These include conditions like anencephaly (a condition in which the fetal brain and skull does not develop), cystic hygromas (large fluid-filled sacs around the fetal neck), and conjoined twins.

Nuchal translucency

First-trimester ultrasounds can also be used to screen a pregnancy for chromosomal conditions, including Down syndrome. People with Down syndrome have mild to moderate intellectual disabilities, a characteristic facial appearance, an increased chance for heart defects and other structural changes, and short stature. By measuring the translucent, or fluid-filled, area at the back of the fetal neck, it can be determined if there is an increased chance for a chromosomal change. An increased nuchal translucency indicates an increased chance for a chromosomal change. This measurement, in combination with an analysis of two proteins in the mother's blood called beta-hCG (human chorionic gonadotropin) and pregnancy-associated plasma protein A (PAPPA) in the first trimester of pregnancy, is referred to as first-trimester screening for aneuploidy (changes in chromosome number).

By performing a first-trimester screening between ten and 14 weeks of pregnancy, about 80% of fetuses with Down syndrome can be detected. Most fetuses with two other chromosomal conditions, trisomy 13 and 18, can also be detected by first-trimester screenings. Therefore, first-trimester screening for aneuploidy is considered as effective as the more traditional screening for aneuploidy performed in the second trimester. However, the American College of Obstetricians and Gynecologists recommended that individuals who perform prenatal ultrasounds and take measurements of the nuchal translucency complete additional training to ensure that they are taking this measurement correctly. The recommendation also stated that there should be ongoing monitoring of the accuracy of this measurement, that appropriate counseling about screening and testing options for aneuploidy should be provided to women wishing to have first-trimester screening, and that the screening should only be performed when further diagnostic testing indicates an increased risk for aneuploidy. The diagnostic test for chromosomal changes available in the first trimester of pregnancy is called a chorionic villus sampling (CVS). This test can be performed between ten and 12 weeks of gestation. However, CVS is not as commonly available as amniocentesis, the second-trimester test for chromosomal changes.

Screening for aneuploidy in the first trimester is a more recent event and allows women to have diagnostic testing earlier and to make decisions about continuing or discontinuing a pregnancy earlier. Ending a pregnancy in the first trimester or early second trimester is safer for the mother than later pregnancy terminations. In fetuses with an increased nuchal translucency and normal chromosomes, follow-up ultrasounds are recommended as

heart defects, other structural changes in development, and other genetic syndromes can still be present.

Second-trimester ultrasound

Ultrasounds in the second trimester of pregnancy are most often performed using the transducer on the maternal abdomen. Vaginal ultrasound may be used in situations where there is a problem with good visualization of the fetus, such as in obese women. In the second trimester, the fetus is larger, and it is possible to see more detail of the development of the fetal anatomy. Anatomy scans of the fetus are most often performed at 18–20 weeks of gestation and can also include images of the placenta, amniotic fluid, umbilical cord, and the sac containing the fetus.

It is also important to look for fetal movement. The absence of movement can indicate the presence of a condition affecting the muscles, bones, or central nervous system. There are many other fetal anomalies that can be detected as well. The finding of a structural anomaly often increases the chance for aneuploidy. Patients may be offered additional tests for more information. When one fetal anomaly is noted on ultrasound, it is important to study the fetus carefully for the presence of other anomalies, since anomalies often occur simultaneously. The prognosis for a fetus when an anomaly is found depends on the severity of the anomaly, the presence of other anomalies, and the presence of a chromosomal condition. Fetuses with mild isolated anomalies have the best prognosis.

Fetal anomalies

A detailed second-trimester ultrasound allows for the identification of structural changes in development, which, in themselves, may be a significant concern, or may be a sign that additional problems like chromosomal changes are present. About 2%–3% of all live-born infants have a birth defect.

A detailed ultrasound studies many structures in the fetal head and brain. There is a measurement of the amount of fluid in the ventricles, or areas, of cerebrospinal fluid in the brain. Too much fluid in the ventricles of the brain is a condition called hydrocephalus. Depending on the degree of hydrocephalus, there can be underdevelopment of the brain and severe intellectual disability. The presence of the two main lobes of the brain and the skull are noted to rule out a type of open spine defect called anencephaly. The lobes of the brain are studied to detect midline defects of the brain such as holoprosencephaly, in which the lobes of the brain have not divided properly. The cerebellum, an organ at the back of the brain, is studied because changes in the shape of the cerebellum or the

bones in the front of the skull are indicative of an open spine defect, or spina bifida. The size of the head is measured, because a small head size, called microcephaly, can result in intellectual disability. The face is studied for the presence of a cleft lip, a small jaw, or either widely or narrowly spaced eyes.

A study of the fetal chest and abdomen will determine if the organs are located on the normal side, or if they are reversed. Ultrasound can detect the presence of diaphragmatic hernia, in which there is a hole in the diaphragm and the intestines are herniated through it into the chest. Abdominal wall defects, in which there is an opening in the abdomen and the intestines are located outside the body, can be detected. Changes to the kidneys, such as cystic or missing kidneys, and cystic malformations of the lungs, can be detected. The heart is a particularly complex organ and can be difficult to study with ultrasound. The more severe heart defects can be identified with ultrasound, but many smaller structural changes to the heart are missed with ultrasound. When a heart defect is suspected, a more specialized ultrasound of the fetal heart, called an echocardiogram, can be performed. Ultrasound evaluation should also include views of the fetal bladder and stomach. The sex of the fetus can often be seen after 18 weeks of gestation.

A careful study of the fetal spine can detect the presence of spina bifida. Changes in the bones of the arms and legs can also be noted. In particular, an inward curving of the feet or club feet can be seen as well as missing limbs. Shortened or curved long bones are a sign of a skeletal dysplasia. There are many types of skeletal dysplasias with varying degrees of severity. Some skeletal dysplasias also include broken bones, short ribs, or changes to the bones in the spine.

Not all changes in development can be detected by ultrasound. The detection rate for individual anomalies with ultrasound varies, and centers that perform ultrasound should collect their own data before providing statistical detection rates to patients. In addition, there can be instances when a condition is diagnosed by ultrasound, but not truly present, or when a condition is misdiagnosed. Patients should be informed of the limitations of ultrasound before the procedure is performed.

Ultrasound markers

With the advancement of ultrasound technology, additional findings on ultrasound have been identified. These findings are not anomalies, or structural changes, that in themselves cause any problem in development. However, these findings have been associated with an increased chance for chromosomal changes in a fetus. Therefore, these findings have been referred to as markers,

or soft signs, of aneuploidy. For instance, fluid-filled cysts called choroids plexus cysts have been seen in fetuses with aneuploidy. The finding of a marker alone in a woman with no other increased risk for aneuploidy is not likely to be significant. Finding multiple markers does increase the chance for aneuploidy. When a marker is seen in the fetus of a woman at increased risk for aneuploidy based on advanced maternal age, maternal serum multiple marker screening, or family history, the patient should receive additional genetic counseling to discuss the finding and how it affects the risk for aneuploidy and the additional testing options. When not associated with aneuploidy, these markers are most often of no significance to the health of the fetus.

Fetuses with several chromosomal conditions can survive to full term. Those conditions include trisomy 21 (Down syndrome), trisomy 18, trisomy 13, and Turner syndrome (45,X).

About half of children with Down syndrome have a heart defect, some of which can be detected by ultrasound. In addition, fetuses with Down syndrome may have various gastrointestinal changes or a cystic hygroma (fluid-filled cyst around the neck) that may be detected by ultrasound. Ultrasound markers for Down syndrome include inward curving of the fifth finger, an increase of fluid in the kidney, short long bones in the upper arm or leg, extra skin at the back of the neck, a bright spot in either the heart or bowel, absence of the nasal bone, and fluid-filled cysts in the brain. When any of these findings is seen in a woman with an increased chance for Down syndrome, her risks may be increased. If an ultrasound is performed in a woman with an increased risk for Down syndrome, and none of these findings is seen, her risks may be lower than previously estimated. Risk reduction based on ultrasound is controversial and should not be done unless an ultrasound center has collected their own data on detection of Down syndrome with ultrasound.

Trisomy 18 is a rare, severe condition caused by the presence of an extra chromosome 18. Babies with trisomy 18 have severe neurological problems and intellectual disability and usually do not survive more than a few months. The most common ultrasound findings in fetuses with trisomy 18 include heart defects and skeletal changes. Fetuses with trisomy 18 have a characteristic hand position that can be noted, clubbed feet, an unusual shape to the feet called rocker-bottom feet, and an unusual shape to the skull called a strawberry-shaped skull. Many other anomalies of other organs have also been noted in fetuses with trisomy 18, including diaphragmatic hernia, open spine defects, and significant growth delay. Markers for trisomy 18 include a thickened nuchal fold, extra fluid in the kidneys, choroids plexus cysts, and a single umbilical artery. Most, but not all,

KEY TERMS

Aneuploidy—A change in the number of chromosomes present, so that there are additional or missing chromosomes.

Cystic hygroma—An accumulation of fluid around the head and neck caused by the blockage of drainage of lymphatic fluid.

Diaphragmatic hernia—A defect that occurs when the diaphragm does not close properly, and the intestines are able to be herniated through the diaphragm into the chest cavity.

Gestational age—An estimation of the age of a pregnancy. The beginning of gestation or pregnancy is counted from the first day of the woman's last menstrual period, although conception usually takes place about two weeks later.

Holoprosencephaly—A malformation of the brain in which the two hemispheres or lobes of the brain do not separate properly.

Hydrocephalus—The presence of extra cerebrospinal fluid in the ventricles of the brain.

Neural tube defect—A defect in closure of the bones of the spine or skull; defects of the brain and skull are called anencephaly, while defects of the spine are called spina bifida.

fetuses with trisomy 18 will have some feature of the condition identified on ultrasound.

Trisomy 13 is also a rare, severe condition caused by the presence of an extra chromosome 13 and associated with multiple birth defects, intellectual disability, and a shortened lifespan. Ultrasound findings in fetuses with trisomy 13 include heart defects, brain malformations like holoprosencephaly, small head size, cleft lip, kidney malformations, extra fingers or toes, and growth delay. Markers for trisomy 13 include an increased nuchal fold and a bright spot in the heart. Most, but not all, fetuses with trisomy 13 will have a feature of the condition noted on ultrasound.

Turner syndrome is a condition in which a female is missing the second X chromosome. Females born with Turner syndrome have an increased chance for heart defects and kidney problems. Girls with Turner syndrome have short stature and will experience infertility as adults. Many pregnancies of fetuses with Turner syndrome miscarry. Ultrasound appearance of these pregnancies often includes a large cystic hygroma and generalized fluid accumulation throughout the fetal body, called hydrops

or edema. Fetuses with Turner syndrome that survive to delivery will sometimes show heart defects, kidney problems, or a cystic hygroma on an ultrasound.

Another way to study fetal well-being is to study the fetal environment and associated pregnancy structures. If a fetus has oligohydramnios (a low amount of amniotic fluid) in the sac surrounding it, the lungs may not develop and the fetus may not survive. Oligohydramnios may occur because of absence of the kidneys, other structural defects, or due to a rupturing of the membranes or sac surrounding the fetus. Polyhydramnios (an excess of amniotic fluid) may also be a sign of structural changes, especially blockages in the urinary tract system, and can lead to premature delivery of a fetus. There can also be problems when the inner membrane of the sac that holds the fetus tears. The torn strands of amnion can wrap around the fetus and cut off blood flow to those areas. The presence of amniotic bands can disrupt the formation of limbs or any structure they wrap around and cause deformations that range from mild to lethal. There can be problems with the umbilical cord if the cord is too long or too short, has knots in it, is entangled around the fetus, has cysts in it, or is not inserted into the center of the placenta. The placenta may also cause or be associated with problems if it is too small, too large, split, located over the cervical opening, detaches from the uterus, or has tumors in it. Molar pregnancies occur when the placenta is swollen and cystic and no fetus is present. In a partial molar pregnancy, a small, malformed fetus with a chromosomal abnormality called triploidy is often present. In triploidy, a fetus has a whole extra set of chromosomes, so that the total number is 69 instead of the usual 46.

Third-trimester ultrasound

Ultrasounds in the third trimester, or last three months, of the pregnancy are often done to monitor fetal growth. If a fetus is macrosomic (large), as is often the case in maternal diabetes, then the fetus is monitored for timing of delivery. Some fetal anomalies that are present earlier do not show features until the third trimester, and some fetal anomalies, like hydrocephalus, may not develop until the third trimester. Ultrasound may be used in the third trimester for fetuses with known anomalies to monitor progression and consider delivery techniques and timing.

Another important use of ultrasound is to guide prenatal procedures such as chorionic villus sampling (CVS) and amniocentesis. In CVS, a physician inserts a catheter into the vagina, through the cervix, and into the placental tissue using ultrasound guidance. A small sample of the placental tissue can be obtained for chromosomal studies by suctioning. CVS is performed at 10–12

weeks gestation. Amniocentesis is a test performed at 15–20 weeks gestation to obtain a sample of amniotic fluid from the sac of fluid around the fetus. This fluid contains fetal cells that can be used for chromosomal analysis of the fetus. During amniocentesis, a pocket of amniotic fluid located away from the fetus is targeted. Ultrasound is used to identify a pocket of fluid and to guide the insertion of the needle into the targeted area.

Ultrasound is a useful tool in the care of pregnant women. There are many uses for prenatal ultrasound and no identified risk with the procedure.

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American Pregnancy Association, 1425 Greenway Dr., Suite 440, Irving, TX 75038, (800) 672-2296, info@americanpregnancy.org, <http://www.americanpregnancy.org>

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Primary ciliary dyskinesia

Definition

Primary ciliary dyskinesia (PCD), formerly known as Kartagener syndrome, refers to a condition that involves difficulty with clearing mucus secretions from the respiratory tract, male infertility, and the abnormal placement of abdomen and/or thoracic organs. Some individuals have situs inversus, in which the placement of organs is a mirror image of their normal placement (e.g., the heart is on the right side instead of the left side).



A researcher uses a transmission electron microscope (TEM) to examine pulmonary cilia, which can be seen in the section of the circular display area at lower left; other samples are seen at lower right. Cilia are hair-like structures that line the lungs and other organs. In the lungs, they should move in a continuous wave to clear mucus, dust, and bacteria from the lungs. In primary ciliary dyskinesia (PCD), the cilia do not function properly, causing respiratory problems. (Pascal Goetgheluck/Science Source)

Description

PCD was first reported by Manes Kartagener (1897–1975), a physician from Switzerland. In the 1930s, Kartagener and a colleague described a familial form of bronchiectasis with situs inversus and nasal polyps. This came to be known as Kartagener syndrome. PCD has also been known as Siewert syndrome, after another physician, A.K. Siewert, who described it in the early 1900s.

At one time, PCD was known as immotile cilia syndrome. That name is no longer used, because of the discovery that the cilia are actually not immotile; rather, their movement is abnormal.

PCD is caused by abnormalities of the cilia that line the respiratory tract and also form the flagella of sperm. Cilia are tiny hair-like structures that contain a bundle of small parallel tubes that form a central core. This core is called the axoneme. Ciliary movement is accomplished by the bending of the axoneme. One of the most

important associated structures that enables ciliary movement to occur is sets of tiny arms that project from each tubule. These tiny arms are called dynein arms.

Cilia line the cells of the lungs, nose, and sinuses. Before reaching the lungs, air travels through the airway, where it is moistened and filtered. The nasal passages and airway are lined with mucus membranes. The mucus covering the mucus membrane traps dirt and other foreign particles that have been breathed in. The cilia lining the membranes move in a wavelike manner, shifting the layer of mucus and carrying away the dirt and debris that has been trapped. This mucus can then be coughed out or swallowed into the stomach.

In PCD, the cilia do not move, move very little, or move abnormally. Because the cilia do not function properly, the mucus is not cleared from the respiratory tract, which leads to sinus infection (sinusitis) and chronic changes of the lung (bronchiectasis), which make it difficult to exhale. Mucus clearance from the middle ear can also be affected, and over time it can lead to hearing loss.

The male infertility in PCD is also caused by abnormal cilia movement. One spermatozoon consists of a head, midpiece, and a tail or flagellum. The tail of a spermatozoon is a long flagellum consisting of a central axoneme. This axoneme enables the movement of the flagellum so that the spermatozoon can propel its way to the fallopian tube and burrow through the egg coat to fertilize the egg. In PCD, these cilia are either immotile or are not able to move normally to complete the journey to the fallopian tubes, nor are they able to burrow through the egg coat. The result is male infertility.

Complete situs inversus involves reversal of both the abdominal and thoracic organs so that they form a mirror image of what is normal. In partial situs inversus, the thoracic organs may be reversed, while the abdominal organs are normally positioned, or vice versa. Approximately 1 in 10,000 adults has situs inversus. Only about 20% of individuals who have complete situs inversus are diagnosed with PCD. For those with complete situs inversus who are diagnosed with PCD, there is only a small risk for associated cardiac defects. Partial situs inversus may occur in individuals who have PCD as well. Partial situs inversus, also called situs ambiguus, has a higher association with other abnormalities, including polysplenia or asplenia (extra or absent spleen) and cardiac defects.

One theory behind the association of situs inversus with the underlying cause of PCD is that the lack of ciliary movement in the developing embryo may result in incorrect organ rotation in approximately 50% of affected individuals. In fact, 50% of patients with PCD will have situs inversus. However, this is a theory supported only by some researchers and remains open to debate.

Genetic profile

PCD is an autosomal recessive condition. In order to have the condition, an individual needs to inherit two copies of the gene for the condition, one from each parent. Individuals who carry only one gene for an autosomal recessive syndrome are called heterozygotes. Heterozygotes for PCD have normal ciliary function and do not have any clinical features of the condition. If two carriers of PCD have children, there is a 25% chance with each pregnancy of having a child with PCD. Prenatal testing and genetic counseling are recommended for those who have a familial history of PCD.

The components that form the cilium contain several hundred different proteins. Each is coded for by different DNA sequences, potentially on different chromosomes. A defect in any of these codes could produce an abnormal or missing protein that is a building block for the cilium and thus could cause abnormal ciliary structure and movement, resulting in PCD. Research shows that about 30% of cases of PCD are caused by mutations in two genes *DNAI1* and *DNAH5*, but changes in at least 40 genes can cause the disorder, and in many other cases the genetic cause is unknown.



X-ray of the lungs of a patient with PCD. One of the signs of this disorder is situs inversus, the inversion of the internal organs. Here, the heart (lower left) and stomach (lower left) and liver (lower right) appear on the opposite side of the body than normal. (Zephyr/Science Source)

When the same condition can be caused by different genetic abnormalities, this is known as genetic heterogeneity. In fact, several different defects in cilia have been seen in association with PCD, including overly long cilia, overly short cilia, absent cilia, and randomly oriented cilia, suggesting genetic heterogeneity. Studies have suggested that the most common defect of cilia in PCD is the lack of dynein arms. There have been rare cases in which individuals have PCD yet have no detectable abnormality of the cilia, even though the ciliary function is abnormal. Results of one study involving a genome-wide linkage search performed on 31 families with multiple individuals affected with PCD strongly suggested extensive heterogeneity. Potential regions involving genes responsible for PCD were localized on chromosomes 3, 4, 5, 7, 8, 10, 11, 13, 15, 16, 17, and 19.

Demographics

PCD occurs in approximately one in 16,000 to one in 30,000 live births, but this range is thought to be an undercount; as the disorder is often misdiagnosed, PCD is more commonly diagnosed in males because of infertility investigations. This genetic disorder does not appear to cause infertility issues in females.

Signs and symptoms

Newborns who have PCD may present with neonatal respiratory distress. Often when individuals are diagnosed with PCD in later childhood, problems such as neonatal respiratory distress may be identified in their history. Symptoms that may present in childhood include recurrent ear infections (otitis media) that can lead to hearing loss, chronic productive cough, reactive airway disease, pneumonia, chronic bronchitis, runny nose (rhinitis) with a thin discharge, and sinus infection (sinusitis). Situs inversus usually does not present symptomatically unless it is associated with a congenital heart defect.

The most common clinical expression of PCD in adults is chronic upper and lower airway disease presenting as sinusitis and bronchiectasis. Clubbing of the digits (fingers) may occur as the result of chronic hypoxia (lack of oxygen) from bronchiectasis. In males of reproductive age, male infertility is almost universal. In females who have PCD, infertility is not usually a characteristic. This difference suggests that the egg transport down the fallopian tube is associated more with muscle contractions than with ciliary movement.

Several other conditions should be considered when the aforementioned symptoms present, including cystic fibrosis (CF), immune deficiencies, and severe allergies. Although the causes of PCD and CF are completely different, the symptoms of these two diseases are very

KEY TERMS

Bronchiectasis—An abnormal condition of the bronchial tree, characterized by irreversible widening and destruction of the bronchial walls of the lungs.

Complete situs inversus—A laterality defect resulting in a mirror image of the normal organ formation with heart, spleen, and stomach on the right side, and the liver and gallbladder on the left.

Cystic fibrosis (CF)—A respiratory disease characterized by chronic lung disease, pancreatic insufficiency, and an average age of survival of 20 years. Cystic fibrosis is caused by mutations in a gene on chromosome 7 that encodes a transmembrane receptor.

Dyskinesia—Impairment of difficulty in performing voluntary movements, usually resulting in jerky or interrupted movements.

Tympanoplasty—Any of several operations on the eardrum or small bones of the middle ear to restore or improve hearing in patients with conductive hearing loss.

similar. Often when the symptoms present, children with PCD are tested for CF first, because the incidence of CF is much higher (one in 2,400). CF is also associated with male infertility.

Diagnosis

Diagnosis of PCD is confirmed by identifying the ciliary abnormalities of structure and movement. This is accomplished by biopsy of the mucus membranes of the respiratory tract and/or by examination of sperm, looking for ciliary dyskinesia. A less invasive way of diagnosing PCD is through the use of high-speed video microscopy. This technique requires special equipment and a high level of training to use. In 2021, it was not widely available. Situs inversus can be identified by x-ray or ultrasound examination. Infertility investigation may elicit the possibility of PCD in a patient who has been previously undiagnosed.

After a diagnosis is made, genetic counseling should be provided to discuss the inheritance pattern, to help identify other possible affected family members, and to discuss reproductive options.

Because PCD is an autosomal recessive disorder, individuals who have had a child with PCD have a 25% chance with each future pregnancy of having another

QUESTIONS TO ASK YOUR DOCTOR

- Please explain what the term “situs invertus” means in regard to my child.
- What is the mechanism by which PCD is inherited?
- What kinds of treatment are recommended for my child’s medical condition?
- Will our family doctor be able to deal with this medical condition, or will we have to see specialists? If so, which ones?

child with PCD. For a couple with a previously affected child, prenatal diagnosis may be possible with an ultrasound examination to identify a fetus who has situs inversus. However, if the fetus does not exhibit situs inversus, it is still possible to have PCD. It is important to remember that identifying a fetus that has situs inversus in a family not known to be at an increased risk for PCD does not mean that the fetus has PCD, because only 20% of individuals who have situs inversus have PCD.

Currently, mutations in 30 different genes have been found to be mutated in PCD. These include *DNAH5*, *CCDC39*, *DNAI1*, *CCDC40*, *DNAH11*, *DNAAF1*, *LRRC6*, *DNAI2*, and *DNAAF2*. However, one-third of patients do not have mutations in these genes.

Treatment and management

Treatment for PCD involves treatment of the symptoms. Treatment for sinusitis includes the use of antibiotics to treat and prevent recurrent infection. Occasionally, surgery to relieve the sinusitis and remove nasal polyps that may be present is necessary. Daily chest physiotherapy to loosen mucus secretions is a common therapy as well, and if started early in life it can help to prevent or delay development of bronchiectasis. Tympanoplasty in children with recurrent ear infections is often necessary.

Advances in reproductive technology allow for men who have PCD to have the opportunity to have children. A procedure called intracytoplasmic sperm injection (ICSI) now allows immotile or dysmotile sperm to fertilize an egg. ICSI involves injection of a single sperm into single eggs in order for fertilization to occur. This procedure first involves ovulation induction and egg retrieval to obtain eggs for an attempt at fertilization by ICSI. In vitro fertilization (ICSI) pregnancy rates vary from center to center. Overall, pregnancy rates utilizing these procedures of 10% to 40% have been quoted worldwide.

The chance of an affected male and his unaffected partner having a child who has PCD is small. If the disease incidence is one in 32,000, then the chance for the unaffected woman to be a carrier of PCD is approximately one in 100, and the chance of having an affected child would be expected to be approximately one in 200 (0.5%). However, all children of affected males or females will be carriers for PCD.

Prognosis

The severity of PCD is variable. With the advent of antibiotic use for infection control, the life expectancy of a patient with PCD is close to or within the normal range if there are no immediate problems in the newborn period.

Clinical trials for diagnosis and treatment of PCD are underway. Participation in a clinical trial is voluntary and at no cost to the participant. All clinical trials receiving U.S. government funding, and some supported by private industry, are posted at <https://www.clinicaltrials.gov>. Foreign trials are listed at <https://www.orpha.net>.

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ORGANIZATIONS

American Lung Association, 55 W. Wacker Drive, Suite 1150, Chicago, IL 60610, (800) 548-8252, info@lungusa.org, <http://www.lungusa.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <https://rarediseases.org>

Primary Ciliary Dyskinesia Foundation, 61 Lake Meadow Drive, Rochester, NY 14612, (844) 287-3723, info@pcdfoundation.org, <https://www.pcdfoundation.org>

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Primary familial brain calcification

Definition

Primary familial brain calcification (PFBC) is an inherited neurodegenerative disorder that results in abnormal deposits of calcium phosphate in the basal ganglia and other regions of the brain. Mutations (changes) in several different genes can result in PFBC, leading to considerable variation in the symptoms of the disorder and their severity. PFBC is frequently referred to as familial idiopathic basal ganglia calcification (FIBGC), which was formerly known as Fahr disease.

Description

PFBC is a very serious neurodegenerative disorder that typically develops in people in their 30s or 40s and progresses gradually. PFBC is characterized by deposits of calcium in the basal ganglia. These are four masses of gray matter (the cell bodies of neurons or nerve cells) that are located deep within each cerebral hemisphere of the brain. Calcium deposits may also develop in other areas of the brain. These deposits can be seen with neuroimaging, such as computed tomography (CT) scans. As the deposits grow and the disorder progresses, neuropsychiatric symptoms and movement problems develop. The neuropsychiatric symptoms often appear first and may be the most serious manifestation of PFBC. These symptoms range from slightly impaired memory and concentration to significant personality and/or behavior changes and even to psychosis and dementia. Migraine headaches are also common in people with PFBC. Movement symptoms may include clumsiness, an unsteady gait, involuntary movements, muscle cramping, fatigue, slow or slurred speech, and difficulty swallowing (dysphagia).

It is not clear exactly why brain calcification occurs or why this results in the observed symptoms. However, more severe signs and symptoms often seem to correlate with greater amounts of calcification. It has been suggested that the calcium deposits interfere with nerve signaling pathways in the brain, especially those pathways that connect the basal ganglia to the frontal lobes that are responsible for reasoning, planning, problem solving, and judgment. Areas of the brain that are involved in mood, motivation, and social behaviors can also be affected.

Genetic profile

In 2015, PFBC had been associated with mutations in four different genes: *SLC20A2*, *PDGFRB*, *PDGFB*, and *XPR1*. These genes produce proteins with very different functions in the body. The *SLC20A2* mutations are

KEY TERMS

Autosomal dominant—A trait caused by a gene located on a chromosome other than the X or Y sex chromosomes that is expressed in preference to the second copy of the same gene.

Basal ganglia—The caudate nucleus, the lentiform nucleus, the amygdala, and the claustrum.

Dystonia—Poor or disordered muscle tone.

Familial idiopathic basal ganglia calcification (FIBGC)—Fahr disease or primary familial brain calcification (PFBC).

PDGFB—The gene that encodes subunit B of the platelet-derived growth factor; a deletion in this gene causes PFBC with leukoencephalopathy.

PDGFRB—The gene that encodes a tyrosine kinase protein called platelet-derived growth factor receptor, beta polypeptide (PDGFRbeta), which is essential for activating signal-transduction pathways in cells; mutations in this gene can cause PFBC.

SLC20A2—The gene that produces a protein called sodium-dependent phosphate transporter 2 (PiT-2), which uses sodium to transport phosphate across cell membranes and is very important for regulating phosphate levels in the body; mutations in *SLC20A2* can result in PFBC.

XPR1A—The gene that encodes a receptor that is involved in exporting phosphate out of cells; mutations in this gene can cause PFBC.

responsible for almost half of all identified PFBC cases. The other mutations appear to be responsible for smaller percentages of cases.

PFBC-associated genes

The *SLC20A2* gene is named for “solute carrier family 20 (phosphate transporter), member 2,” in the solute carrier (SLC) family of genes. *SLC20A2* is located on the short arm (p) of chromosome 8 at position 11.21 (8p11.21). It produces a protein called sodium-dependent phosphate transporter 2 (PiT-2) that uses sodium to transport phosphate across cell membranes. Phosphate is required for many different bodily functions, including metabolism, the production of nucleic acids for DNA, signaling between cells, and fat production. PiT-2 is very important for maintaining phosphate homeostasis—consistent levels of phosphate in the body. About 20 different *SLC20A2* mutations are known to cause PFBC. Most of the PFBC-associated mutations in *SLC20A2*

change single amino-acid building blocks in the PiT-2 protein; these changes make the protein unable to effectively transport phosphate into cells. A large deletion in this gene also has been found to cause PFBC. All of these mutations result in high levels of phosphate in the blood and excess phosphate in the brain that combines with calcium to form calcium phosphate deposits. The *SLC20A2* gene is active (produces protein) in cells throughout the body, but the most PiT-2 protein is produced in the basal ganglia and other brain regions that are affected in PFBC.

The *PDGFRB* gene is located on the long arm (q) of chromosome 5 at position 33.1 (5q33.1). It belongs to two families of genes within the immunoglobulin gene superfamily: the “immunoglobulin-like domain containing” and the “I-set domain containing” families. The *PDGFRB* gene produces a protein called platelet-derived growth factor receptor, beta polypeptide (PDGFRbeta). This protein is a member of a family of proteins called receptor tyrosine kinases that are responsible for transmitting signals into the interior of cells from the cell surface. PDGFRbeta is located in the outer membrane of certain types of cells. It is a receptor for platelet-derived growth factor and is activated when this growth factor binds to it. This binding causes PDGFRbeta to activate signaling pathways made up of other proteins inside the cell. It activates these pathways by adding phosphate groups to the proteins in a process called signal transduction. The signaling pathways activated by PDGFRbeta affect many different cell processes, including growth and cell division (proliferation), cell survival, and cell movement. At least two different mutations in the *PDGFRB* gene can result in PFBC. These mutations change single amino-acid building blocks within the protein, but it is unclear how these changes result in PFBC. Presumably, the mutations alter signaling within the cells. This may cause cells that line the blood vessels in the brain to take in too much calcium, which leads to calcification of the blood vessel linings or an increase in phosphate levels that leads to the formation of calcium phosphate deposits. However, since the *PDGFRB* gene is active throughout the body, it is not clear why these mutations appear to only affect the brain.

The *PDGFB* gene produces the subunit B of the platelet-derived growth factor, the protein that binds to and activates the receptor encoded by the *PDGFRB* gene. Mutations in the *PDGFB* gene probably affect the same signaling pathways as mutations in the *PDGFRB* gene. A deletion has been identified in the *PDGFB* gene that causes PFBC with leukoencephalopathy, a disease that affects the white matter (nerve cell projections called axons) in the brain.

In 2015, researchers identified mutations in the *XPRI* gene in several families affected by PFBC. *XPRI*

produces a protein that is important for exporting phosphate from cells, as well as acting as a receptor for retroviruses. The identified PFBC-associated mutations alter phosphate export. This further suggests that dysregulation of phosphate levels may be involved in the development and progression of PFBC.

Inheritance pattern

PFBC is inherited as an autosomal dominant trait. This means that a single copy of a mutated PFBC-associated gene inherited from one parent is sufficient to cause the disorder, even if the corresponding gene inherited from the other parent is normal. Most people with PFBC have one parent who was affected by the disorder. Each child of a PFBC-affected individual has a 50% chance of inheriting the mutation and developing the disease. PFBC-causing mutations may also arise *de novo* (called sporadic or somatic mutations); that is, neither parent carried the mutated gene or was affected by PFBC. However, it is not known how often *de novo* mutations occur.

Demographics

PFBC is believed to be rare, with only about 60 affected families reported in the medical literature. However, since sophisticated imaging of the brain is required to detect calcium deposits, it is likely that PFBC is underdiagnosed or misdiagnosed as a different disorder that causes similar symptoms. Thus, it is likely that there are many more families affected by PFBC.

Signs and symptoms

Signs and symptoms of PFBC most often develop in the fourth decade of life. The severity of the disorder varies considerably. A few affected people have no symptoms related to brain calcification, whereas others have severe psychiatric and movement difficulties. Symptoms also can include migraines and seizures. This variability in symptoms may be a reflection of the different genes and the different mutations in each gene that can result in PFBC.

It is estimated that 20%–30% of people with PFBC have psychiatric and behavioral symptoms, including the following:

- concentration problems
- memory loss
- personality changes
- psychosis (a distorted view of reality)
- dementia (a decline in cognition or intellectual functioning)

Movement symptoms include the following:

- involuntary muscle contractions or tensing (dystonia)
- poor coordination (ataxia)

QUESTIONS TO ASK YOUR DOCTOR

- How is PFBC diagnosed?
- Should I have genetic testing for PFBC? Should my family members be tested?
- What are the chances that I will pass PFBC on to my children?
- Is prenatal testing available for PFBC?
- What is the prognosis for a person diagnosed with PFBC?

- uncontrolled limb movements (choreoathetosis)

Diagnosis

Diagnosis of PFBC is based on the following:

- neuroimaging with CT scans that shows calcification of the basal ganglia on both sides of the brain (bilateral)
- progressive neurologic dysfunction
- absence of other causes for the symptoms, such as a metabolic disorder, infection, exposure to toxins, or brain trauma
- a family history of PFBC exhibiting autosomal dominant inheritance (a parent with the disorder)

Magnetic resonance imaging (MRI) or x-rays of the brain can also detect calcification. Rarely, patients with symptoms and from families with PFBC have no signs of calcification on brain imaging.

Genetic testing is available for mutations in the *SLC20A2* gene, although these mutations account for only about 40% of cases. In some instances in which no known gene mutation has been identified but at least two family members of different generations are affected by PFBC, a type of test called linkage analysis may be available. Prenatal testing is available for families in which a PFBC-associated mutation has been identified.

Treatment and management

There is no standard treatment for PFBC; rather, treatments are aimed at specific symptoms. Patients usually have annual neurologic and neuropsychiatric assessments. Drug treatments include the following:

- medications for treating anxiety, depression, and obsessive-compulsive behaviors
- medications for tremors, dystonia, or other movement disorders, although levodopa is usually not effective for Parkinsonian-like symptoms caused by PFBC

- antiepileptic drugs for seizures
- oxybutynin or other anticholinergic drugs for urinary incontinence (lack of bladder control)
- migraine drugs for both prevention and treatment of headaches

Prognosis

PFBC has a poor prognosis. It is a progressive disorder without a cure, meaning that the symptoms will gradually increase in their severity.

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National Institute of Neurological Disorders and Stroke, PO Box 5801, Bethesda, MD 20824, (301) 496-5751 or (800) 496-5751, <http://www.ninds.nih.gov>

Parkinson's Disease Foundation, 1359 Broadway, Suite 1509, New York, NY 10018, (212) 923-4700 or (800) 457-6676, (212) 923-4778, info@pdf.org, <http://www.pdf.org>

Margaret Alic, PhD

Primordial dwarfism

Definition

Primordial dwarfism (PD) refers to a group of very rare genetic disorders marked by severe proportionate dwarfism. The term "primordial" means that the disorder begins during the earliest stages of embryonic life, as distinct from having its onset in later stages of development. "Proportionate" means that all the parts of the person's

body are smaller or shorter than normal, in contrast to disproportionate dwarfism, in which the head is significantly larger than the rest of the body, or the trunk is of average size but the limbs are disproportionately large or long. Children diagnosed with primordial dwarfism are extremely small for their age even as fetuses.

There are about 200 different types of dwarfism that had been identified, including primordial dwarfism. Most types of dwarfism are caused by disorders of the endocrine system or the skeleton; all known subtypes of primordial dwarfism, however, are caused by mutations in a number of different genes.

Description

There are five major subtypes of primordial dwarfism commonly recognized by researchers. The number of genetic syndromes considered to represent primordial dwarfism is constantly changing, however, as a result of advances in research and reports of new cases of PD. It is possible that the current classification will undergo further revision. In addition to the fluidity of classifying PD, some individuals are difficult to assign to any of the five recognized subtypes and so may be diagnosed simply as having primordial dwarfism not otherwise specified (PD-NOS).

The five subtypes of PD recognized by geneticists are as follows:

- **Microcephalic osteodysplastic primordial dwarfism type 1 (MOPD1):** This subtype of primordial dwarfism is characterized by microcephaly (an abnormally small head), intellectual disability, and other neurological abnormalities. Most patients die in early childhood. This form of PD has a number of alternate names, including Majewski osteodysplastic primordial dwarfism type 1, after the Polish researcher who described several cases in 1976; cephaloskeletal dysplasia; Taybi-Linder syndrome; and low-birth-weight dwarfism with skeletal dysplasia. MOPD1 is an example of the changes in PD classification: at one time researchers thought they had identified a form of PD that they labeled MOPD type 3, but the present consensus holds that MOPD type 1 and MOPD type 3 are the same entity.
- **Microcephalic osteodysplastic primordial dwarfism type 2 (MOPD2):** As in MOPD type 1, children with this form of PD have abnormally small heads, but they also have distortions of the shape of the pelvis, disproportionately short forearms and legs in early childhood, and severely retarded growth after, as well as before, birth. Other names for MOPD type 2 include Majewski osteodysplastic primordial dwarfism type 2. Persons with this subtype of PD have been reported to live into adolescence or their early 20s.



Charlotte Garside, a five-year-old girl with primordial dwarfism, is held by her mother. She stands just 68 centimeters tall (a little more than two feet) and weighs less than nine pounds. (Kippa Matthews/Barcroft Media/Getty Images)

- **Meier-Gorlin syndrome (MGORS):** Also known as ear, patella, short stature syndrome (EPS) and microtia, absent patellae, micrognathia syndrome, MGORS is characterized by unusually small ears (microtia), the absence of kneecaps in the knee joint, and an underdeveloped jaw (micrognathia). Children with this form of PD usually have normal intelligence and may live into their early 20s.
- **Seckel syndrome (SCKL):** Seckel syndrome is a very rare type of PD characterized by microcephaly, a narrow bird-like face with a nose resembling a bird's beak, and severe intellectual disability. It is also known as bird-headed dwarfism, Virchow-Seckel dwarfism, and nanocephalic dwarfism. The syndrome is named for Helmut Paul George Seckel, who first reported on a case series of the syndrome in 1960.
- **Silver-Russell syndrome (SRS):** Known as Russell-Silver syndrome in the United Kingdom, SRS is characterized by extreme intrauterine growth retardation, very low birth weight, feeding difficulties, failure to thrive, persistent vomiting, a deformity of the little finger known as clinodactyly, and various facial deformities that include a triangle-shaped face. About half of SRS patients have learning disabilities, with the other half being of normal intelligence. SRS was first identified in 1953.

Genetic profile

All known forms of PD are inherited in an autosomal recessive pattern, which means that the person must

inherit a defective gene from both parents. PD affects males and females equally.

- **MOPD type 1:** MOPD type 1 is caused by mutations in the *RNU4ATAC* gene on the long arm of chromosome 2 at 1q14.2. It is not yet clear, however, how mutations in this gene lead to the characteristic features of MOPD type 1.
- **MOPD type 2:** MOPD type 2 is caused by a mutation in the *PCNT* gene on the long arm of chromosome 21 at 21q22.2. The gene codes for a protein called pericentrin, which is important in the process of cell division and multiplication. A mutation in the *PCNT* gene leads to impaired cell division, a reduction in the total number of cells, and the overall short stature and delayed growth characteristic of MOPD type 2.
- **Meier-Gorlin syndrome:** MGORS can be caused by mutations in any one of several genes involved in the pre-replication complex, which regulates the copying (replication) of DNA before cells divide. The specific genes associated with Meier-Gorlin syndrome include *ORC1* on chromosome 1 at 1p32.3, *ORC4* on chromosome 2 at 2q22, *ORC6* on chromosome 16 at 16q12, *CDT1* on chromosome 16q, and *CDC6* on chromosome 17 at 17q21. Researchers are still unsure as to why these mutations lead to the characteristic features of MGORS, although some think that the mutations slow down the process of cell division, which in turn leads to slow growth of the bones and other tissues during the child's prenatal development.
- **Seckel syndrome:** Seckel syndrome may result from mutations in any of six different genes: the *ATR* gene on chromosome 3 at 3q23, the *RBBP8* gene on chromosome 18 at 18q11.2, the *CEP152* gene on chromosome 15 at 15q21, the *CEP63* gene on chromosome 3 at 3q22, the *NIN* gene on chromosome 14 at 14q22, and the *CENPJ* gene on chromosome 13 at 13q12. The *ATR* gene is essential to the cell's DNA repair mechanism. It is not yet known how the other genes associated with Seckel syndrome contribute to the characteristic features of the disorder.
- **Silver-Russell syndrome:** The genetics of SRS are complex. Some cases result from loss of a process called methylation (the attachment of methyl groups to specific segments of DNA) to the *IGF2* and *H19* genes on chromosome 11. Loss of methylation disrupts the function of these genes, which direct normal cell and tissue growth. Other cases of SRS are caused by uniparental disomy (UPD), a condition in which the child inherits both copies of a chromosome from one parent and no copies from the other. In SRS, the child receives two copies of chromosome 7 from the mother alone, with no contribution from the father. It is possible

that other genes that have not been identified also play a role in the development of Silver-Russell syndrome.

In March 2015, an international team of scientists reported an association between the *XRCC4* gene on chromosome 5 at 5q14.2 and primordial dwarfism. This gene codes for a protein that is important in repairing double-strand breaks in DNA. Mutations in *XRCC4* are already known to be associated with increased susceptibility to breast cancer, lymphoma, bladder cancer, and multiple myeloma. It is thought that mutations in this gene may also lead to increased cell death, reduced cell growth and replacement, and the other growth failures associated with primordial dwarfism. The researchers did not, however, identify the *XRCC4* mutations with any of the specific subtypes of PD.

Demographics

Dwarfism by itself is not a particularly rare condition; estimates of the number of people in North America diagnosed with some form of dwarfism vary between 100,000 and 500,000. By contrast, primordial dwarfism is a rare occurrence. Silver-Russell syndrome is thought to occur in 1 in every 50,000 to 1 in every 100,000 live births; other subtypes of PD, for example MOPD type 2, are estimated to affect fewer than 100 persons worldwide, or less than 1 person in 3 million. Estimates of the number of persons with all subtypes of PD in Canada and the United States range between 100 and 1,000.

There is no indication that PD is more common in some racial or ethnic groups than in others, although further research may provide new evidence.

Signs and symptoms

While all subtypes of primordial dwarfism are marked by growth delays before and after birth, each of the subtypes has its own constellation of features.

MOPD type 1

Children with this type of PD typically have dry, aged-looking skin; thin, sparse hair on the scalp; and scanty eyebrows and eyelashes. In addition to microcephaly, their brains lack a corpus callosum, the band of nerve fibers that joins the two cerebral hemispheres. They also suffer from seizures and difficulty breathing. Some patients have defects in their hearing and vision, including glaucoma and proptosis (outward bulging of the eyes).

Skeletal abnormalities include hip displacement, abnormally short neck, bowing of the long bones in the legs, elongated collarbones, and reduced height of the spinal vertebrae.

KEY TERMS

Autosomal recessive—A pattern of inheritance in which two copies of a defective gene on a nonsex chromosome must be present for a disease or inherited trait to develop in an individual.

Autosome—Any human chromosome other than a sex chromosome.

Clinodactyly—A birth defect in which a finger (most often the little finger) is bent at an angle toward the neighboring finger (usually the fourth finger).

Craniosynostosis—A condition in which one or more of the fibrous joints in an infant's skull turns to bone prematurely. As the child's head continues to grow, the growth pattern of the skull is affected, resulting in a misshapen head and often deformed facial features.

Dwarfism—In general, a condition in which a person is unusually short in stature (adult height shorter than 4 ft. 10 in.) as the result of a genetic disorder, endocrine disorder, or skeletal abnormality. There are about 200 different conditions that can cause dwarfism.

Frontal bossing—The medical term for an unusually prominent forehead, often associated with an abnormally heavy brow ridge.

Intrauterine growth retardation (IUGR)—The slow or poor growth of a fetus during the mother's pregnancy. It can be caused by malnutrition or lack of an adequate oxygen supply to the fetus, as well as by genetic disorders.

Microcephaly—A neurological disorder in which the infant's or child's head is abnormally small. There is no universally accepted measurement for microcephaly, but it is commonly defined as a head circumference more than two standard deviations below the mean for the child's age and sex.

Microdontia—Abnormally small teeth.

Micrognathia—The medical term for an undersized or underdeveloped jaw.

Microtia—A birth defect in which the external ear is underdeveloped. The condition is called anotia if the outer ear is completely missing.

Osteodysplasia—A general term for a disorder of bone development.

Patella (plural, patellae)—The medical term for the kneecap.

Primordial—Referring to conditions that begin before birth or are characteristic of the embryo's earliest stages of development.

Proportionate dwarfism—Dwarfism in which the person's body parts are all smaller or shorter than normal but remain in proportion to one another.

Proptosis—Bulging of the eye outward from the orbit of the eye. It is also known as exophthalmos.

Uniparental disomy—A condition in which both members of a chromosome pair or segments of a chromosome are inherited from one parent without any contribution from the other parent.

MOPD type 2

Many patients with MOPD type 2 are born prematurely, either spontaneously or due to early induction of labor in response to fetal distress (indications that the fetus may not be well). Children with MOPD type 2 typically have more health problems than those with other forms of PD. These problems include abnormally small teeth (microdontia); unusually widely spaced teeth; a high-pitched, squeaky voice; sleep disorders in early life; frequent infections; farsightedness; feeding difficulties; and breathing difficulties. Some patients develop areas of abnormally light or dark skin pigmentation. Other patients have malformations in the blood vessels in the brain that lead to aneurysms (localized bulges in the wall of a blood vessel) and an increased risk of stroke. Girls with MOPD type 2 sometimes undergo precocious puberty, but this symptom has not been reported in boys with MOPD type 2.

Skeletal abnormalities include shortening of the forearms, premature closure of the epiphyses (the rounded ends of long bones), an abnormally narrow angle between the hip bone and the femur (the long bone in the thigh), scoliosis, loose ligaments, and dislocated joints. Another common feature is delayed bone age; that is, the maturation of the bones is slowed and may be as much as two to five years behind the child's chronological age.

Meier-Gorlin syndrome

Children with MGORS typically have curved collarbones and habitual dislocation of the elbow joints, as well as absent kneecaps and underdeveloped external ears. Bone age is usually delayed, and the epiphyses of the long bones are often flattened rather than rounded.

Meier-Gorlin syndrome can be distinguished from the other subtypes of PD by the fact that the child usually

attains a greater final height. Abnormalities in sexual development may occur in both boys and girls. Males may have undescended testicles (cryptorchidism), while females may have underdeveloped labia majora (external genital folds) and small breasts.

Seckel syndrome

In addition to a beak-like nose, other facial features characteristic of Seckel syndrome include abnormally large eyes, a narrow face, a receding forehead, misshapen ears, and micrognathia. Some patients have cleft palate, improper positioning of the teeth, erosion of the tooth enamel, or uneven development of the two sides of the face (facial asymmetry). Many children with Seckel syndrome develop disorders of the blood, including anemia (a low level of circulating red blood cells) and pancytopenia (a low level of circulating white blood cells, red blood cells, and platelets).

Skeletal abnormalities include craniosynostosis, malformation of the hip bones, scoliosis, dislocation of the forearm bones, clubfoot, and clinodactyly. In addition, some patients have only 11 pairs of ribs rather than the normal 12 pairs.

Silver-Russell syndrome

Children with SRS often have problems with low blood sugar (hypoglycemia) and increased sweating, along with delayed motor development resulting from lack of muscle mass and strength. In contrast to other subtypes of PD, children with SRS may appear to have relatively large heads compared to the small size of the rest of the body. About half of children with SRS have asymmetrical (uneven) growth.

Distinctive facial features include frontal bossing (broad and prominent forehead), a small chin, crowding of the teeth, and a thin upper lip. Other abnormalities include webbing between the toes (syndactyly) and a high-pitched voice. Males with SRS often have cryptorchidism and hypospadias (abnormal location of the urinary opening in the penis). Children with SRS are also at increased risk of certain forms of cancer, including Wilms' tumor and hepatocellular carcinoma.

Diagnosis

The diagnosis of primordial dwarfism can be made before birth by ultrasound imaging between 13 and 20 weeks gestation. Intrauterine growth retardation becomes evident at that point and becomes progressively worse over the course of the pregnancy. Molecular genetic testing can also be done before birth. The University of Chicago Genetic Services offers a comprehensive primordial dwarfism sequencing panel that includes sequence

QUESTIONS TO ASK YOUR DOCTOR

- Which subtype of primordial dwarfism does my child have?
- How long is my child likely to live?
- What are our chances of having another child with primordial dwarfism?
- Will my child have normal intelligence?
- What treatments and management will you recommend?

analysis of 16 different genes known to be associated with the five major subtypes of PD. The cost is \$4500. The department also offers sequence testing for individual genes.

In some cases, the diagnosis of primordial dwarfism is not made until after the infant is born. Such clinical signs as very low birth weight (as little as 3 lb.), short body length (less than 16 in.), facial deformities, and premature closure of the soft spots (fontanelles) in the skull indicate PD. The pediatrician may also order x-rays of the limbs to evaluate bone age; skeletal deformities like clinodactyly, dislocated joints, and scoliosis; and abnormalities of the skull and facial bones.

Some features of PD may not be fully apparent until the child is two or three years of age. One is delayed growth; for example, it can take a child with MOPD type 2 between two and five years to reach the body length of an average newborn. In addition, intellectual disability is easier to identify when the child is closer to school age.

Treatment and management

Treatment of children with primordial dwarfism varies according to the subtype of PD. As infants with MOPD type 1 rarely live beyond the first year of life, treatment is supportive only. Children with MOPD type 2 require careful monitoring that includes regular eye examinations for farsightedness, regular brain scans to detect aneurysms as early as possible, and yearly blood tests for blood sugar levels and other early signs of type 2 diabetes, beginning at age five.

Treatment of Meier-Gorlin syndrome and Seckel syndrome is highly individualized because the severity of specific symptoms varies from case to case. Surgery may be used to treat some dental and skeletal abnormalities. Most children with MGORS will require physical therapy; some will require special education. Children

with Seckel syndrome are rarely capable of attending school, as over 50% have an IQ below 50.

Silver-Russell syndrome is the one subtype of primordial dwarfism in which children may benefit from administration of growth hormone after age two. Recombinant human growth hormone is given on a daily basis by subcutaneous injection. The child typically requires physical therapy and special education in later childhood. Children with severe feeding difficulties may require surgical placement of a feeding tube.

Prognosis

The prognosis for children with primordial dwarfism is poor, as there was no cure for any of the subtypes. Life expectancy is limited, with patients with MOPD type 1 having the shortest expectancy. Patients with all types of PD, however, have reduced life expectancies, with only a few patients known to have lived past 30 years of age.

Resources

BOOKS

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Griffiths, Anthony J. F., et al., eds. *Introduction to Genetic Analysis*. 12th ed. New York: Macmillan, 2020.

PERIODICALS

Duker, Angela L., et al. "Microcephalic Osteodysplastic Primordial Dwarfism Type II Is Associated with Global Vascular Disease." *Orphanet: Journal of Rare Diseases* 16, no. 1 (May 20, 2021): 231. DOI: 10.1186/S13023-021-01852-Y.

WEBSITES

Hecht, Marjorie. "What Is Primordial Dwarfism?" Healthline. October 24, 2018. <https://www.healthline.com/health/primordial-dwarfism> (accessed August 15, 2021).

"Overview of Primordial Dwarfism." verywellhealth. <https://www.verywellhealth.com/primordial-dwarfism-2860989> (accessed June 17, 2021).

ORGANIZATIONS

Little People of America (LPA), 250 El Camino Real, Suite 211, Tustin, CA 92780, (714) 368-3689 or (888) LPA-2001, (714) 368-3367, info@lpaonline.org, <http://www.lpaonline.org>

Magic Foundation, 6645 W. North Ave., Oak Park, IL 60302, (708) 383-0808, contactus@magicfoundation.org, <https://www.magicfoundation.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Rebecca J. Frey, PhD

Prion diseases

Prion(pronounced PREE-on) diseases are a class of degenerative central nervous system disorders. They are unique in that while some prion diseases have a genetic component, they may also be transmitted, and the infectious agent of the disease is a protein. Dr. Stanley Prusiner coined the term "prion," meaning "proteinaceous infectious particle," in 1982. His controversial, but finally accepted, research in the area of prion diseases led to his winning the Nobel Prize in Medicine in 1997.

Prion Diseases in Humans

There are five forms of prion disease known to occur in humans: kuru, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS), fatal familial insomnia (FFI), and new variant Creutzfeldt-Jakob disease, popularly known as "mad cow disease." Three of these, familial CJD, GSS, and FFI, are inherited disorders caused by mutations in a single gene on chromosome 20, while kuru and variant CJD are considered acquired prion diseases.

The prion diseases are also called transmissible spongiform encephalopathies (TSEs), because they can be transmitted between unrelated individuals and sometimes cause a sponge-like encephalopathy (degeneration of the brain tissue) in which vacuoles (holes) and other abnormal structures are formed in the brain. Prion diseases have also been identified in animals and include scrapie in sheep and goats, bovine spongiform encephalopathy (BSE) in cows, feline spongiform encephalopathy in cats, and chronic wasting disease in mules, deer, and elk.

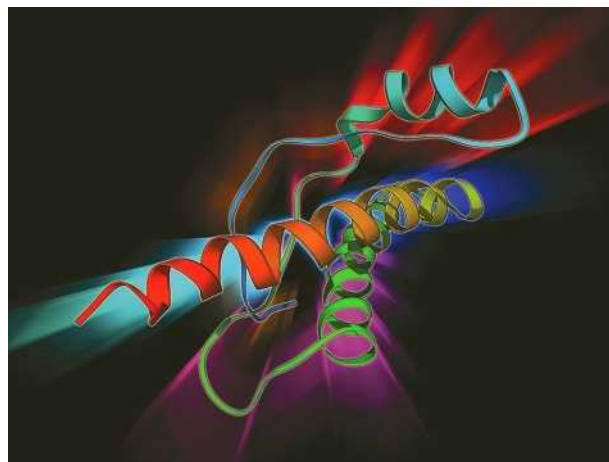


Illustration of a prion protein. (Laguna Design/Science Photo Library/Alamy)

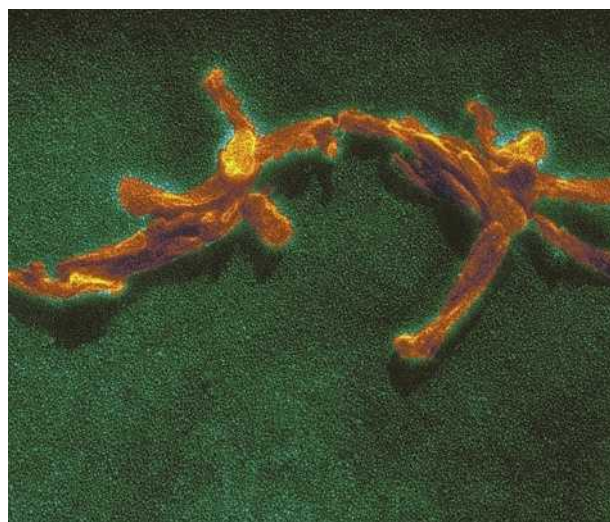
Prion diseases have all been associated with the function of a specific cellular protein called the prion protein (PrP). Like all cellular proteins, PrP is a long-chain molecule consisting of linked amino acids. A protein can assume many shapes: twisted into a spiral helix, extended into linear strands, or folded into sheets of aligned strands. Different shapes of the same molecular sequence are called isomers. It is theorized that the normal form of cellular PrP is a compact shape consisting mainly of four helix regions, whereas in the abnormal isomer (the prion), the protein is refolded into a sheet-helix combination. Furthermore, this prion triggers the conversion of normal PrP to the abnormal shape through an unknown mechanism. The abnormal isomer acts as a template to change more and more normal PrP to the abnormal structure. Therefore, once the protein exists in the abnormal form, it is an infectious agent that can be transmitted from one person to another.

Normal proteins are processed by proteases, which are enzymes present in the body that act to break down excess proteins in a process called proteolysis. However, the abnormal isomer of the prion protein is protease-resistant and cannot be broken down by the body's protease enzymes. Therefore, the abnormal prion protein continues to be produced without being processed. This condition leads to an accumulation of the abnormal protein in the body.

In several forms of prion disease, the abnormal prion protein aggregates in deposits, or plaques, in the brain tissue. It is believed that once the abnormal prion protein accumulates to a certain level in the body, the physical symptoms of impaired mental and physical functioning begin to show themselves. However, the exact mechanisms by which the abnormal isomer causes disease are not known. The onset of symptoms may not occur until the patient is age 60 or older, suggesting that either the rate of accumulation of the abnormal protein is initially slow or that some triggering event late in life causes the initial formation of the abnormal isomer, after which the disease can spread.

The normal function of the prion protein is not completely understood, but it is known to be involved with the functions of the synapses (nerve connections) in the brain. PrP is found in the highest concentrations in the brain. It is also found in the eyes, lungs, heart, kidney, pancreas, testes, and blood, and in the neuromuscular junction. The conversion of normal PrP to the infectious abnormal isomer form may disrupt the normal functions of the prion protein, and this process may be another cause of the degenerative symptoms of the disease.

Body tissues containing the abnormal isomer are a source of transmission of the disease between people



Color enhanced transmission electron micrograph of prions. These protein molecules are often found in direct connection with illnesses of the nervous system. The prions in this image were isolated from the brain of a hamster infected with scrapie-associated fibril. Other illnesses caused by prions include bovine spongiform encephalopathy (mad cow disease) in cattle, and Kuru and Creutzfeldt-Jakob disease in humans. (*Eye of Science/ Science Source*)

and even across species. Prion diseases are also found in animals, and in animal studies it has been shown that the disease can be spread through the ingestion of infected brain tissue. The transmission can also cross the species barrier; cows have become affected by prion disease after eating feed contaminated with infected sheep brain tissue. It is widely speculated that the outbreak of “mad cow” disease, the most publicized prion disease, was caused by infection from affected cows in the United Kingdom, although the mode of transmission has still not been determined. Transmission through oral ingestion was also shown to be the cause of kuru in the Fore tribe of New Guinea. After the Fore abandoned their practice of ritual cannibalism in which they consumed the brain tissue of ancestors, the incidence of kuru all but disappeared.

Other cases of human infection have been shown to be iatrogenic, or transmitted inadvertently during medical treatment. Most of these iatrogenic cases involve direct contact with brain and nervous system tissue. For example, CJD has been reported to result from the use of contaminated surgical instruments, corneal implants, implantation of dura mater or electrodes in the brain, and the injection of human growth hormones derived from cadaverous pituitary glands.

Other modes of transmission have been shown to be less efficient in animal studies. The recent outbreak of

new variant CJD caused increased concern about possible transmission through blood transfusions and plasma-derived products, but no case of new variant CJD has been proven to result from blood transfusion. Laboratory and epidemiological evidence supporting a strong risk of the spread of prion disease through blood transfusion have not been found, even though this area has been studied intensively.

Genetic profile

The gene that encodes the prion protein has been mapped to the short arm of chromosome 20 at 20p13. It has been named the *PRNP* gene. Mutations in the *PRNP* gene can cause alterations in the chemical sequence of amino acids in the prion protein, and this change is believed to make the protein more susceptible to assuming the abnormal conformation. Over 30 different mutations of the gene have been identified, encompassing point mutations (one base pair substituted for another in the gene sequence), insertions (additions to the gene sequence), and deletions (missing parts of the gene sequence). Depending on the specific mutation, different types of prion disease can appear in the patient.

It is estimated that 10% to 15% of prion disease cases are caused by inherited mutations of the *PRNP* gene. Because of the delayed onset of the disease and the wide variation in symptoms, more exact statistics are difficult to determine. The inheritance pattern is autosomal dominant, meaning that if either parent passes the mutated gene to their offspring, the child will be affected by the disease. A parent with prion disease has a 50% probability of passing on the mutated gene to his or her child.

Another genetic factor important in diagnosing prion disease is the genetic sequence of the *PRNP* gene. Like all genes, the *PRNP* gene is made up of two strands of DNA. Each DNA strand consists of a sequence of chemical structures called bases, and the two strands together form a sequence of base pairs. Three base pairs together form a unit called a codon, and each codon codes for a specific amino acid. At codon 129 of the *PRNP* gene, either the amino acid methionine (Met) or valine (Val) can be encoded. Because one copy of the *PRNP* gene is inherited from each parent, an individual may either be homozygous, having two of the same amino acids (Met-Met or Val-Val) at this position, or heterozygous, having different amino acids (Met-Val). Individuals who are homozygous appear to be more susceptible to infection of prion diseases, because it has been shown that a greater percentage of those infected are homozygous than in the general population.

In addition, the clinical symptoms (phenotype) of the prion disease can vary based on whether the individual is

Met-Met or Val-Val homozygous, and whether the individual has Met or Val on the same gene as another mutation. For example, a specific point mutation at codon 178 has been found to cause familial CJD if the individual has valine at codon 129 on the mutated gene, while the same mutation causes FFI when the individual has methionine at codon 129. In the case of GSS, the substitution of the amino acid leucine for proline at codon 102 has been found in most individuals diagnosed with GSS, and it is thought that this substitution is necessary for the development of GSS. In the case of FFI, the affected person must have asparagine at codon 178 instead of the usual aspartic acid.

Epidemiology

Prion diseases occur worldwide with a rate of one to two cases per one million. CJD is the most common of the prion diseases, while GSS and FFI are extremely rare, and kuru is now virtually non-existent due to the abandonment of the practice of cannibalism. There are 30 to 40 cases of familial CJD diagnosed each year in the United States. Males and females are equally susceptible to prion diseases. Several forms of prion disease usually do not cause identifiable symptoms until the individual is more than 60 years old, although other forms, such as FFI, have an earlier onset and are seen in teenagers and young adults.

Since prion disease can be either inherited or transmitted through infection, the demographics of the disease have both familial and environmental patterns. Inherited CJD is found with high frequency in Libyan Jews and also in other descendants of Sephardic Jews in Greece, Tunisia, Israel, Italy, Spain, and perhaps South America. Other genetic clusters have been identified in Slovakia, Poland, France, and Germany. Fatal familial insomnia has been linked to family pedigrees in Italy, Australia, the United States, and elsewhere. Families with GSS syndrome have been found in several countries in North America and Europe; the Indiana kindred, a family spanning eight generations, was the largest GSS family identified, with 57 members diagnosed with GSS.

The environmental clusters of acquired prion disease include the Fore, a remote tribe of New Guinea, in which kuru was transmitted through the practice of ritual cannibalism; a group of over 80 cases in Japan resulting from dura mater (brain membrane) grafts from a single surgical supply company; over 100 cases resulting from cadaveric human growth hormone injections in Europe and the United States; and, most famously, the 40-plus cases of new variant CJD or “mad cow” disease in the United Kingdom.

Signs and Symptoms

Prion disease primarily affects the brain and central nervous system, so its associated symptoms are all related to neurological function. These symptoms may include loss of muscular coordination and uncontrollable body movements (ataxia), visual problems, hallucinations, behavioral changes, difficulty in thinking clearly or remembering, sleep disturbances, speech impairment, and insanity. Such general complaints as headache, diminished appetite, and fatigue may occur prior to the onset of the more serious symptoms. The exact combination and severity of these symptoms vary widely among cases and types of prion disease.

Inherited Prion Diseases

FAMILIAL CREUTZFELDT-JAKOB DISEASE. CJD, named for the two German neuropathologists—Hans Gerhard Creutzfeldt (1885–1964) and Alfons Maria Jakob (1884–1931)—who first described it, is the most common of the inherited human prion diseases. It is characterized by a rapid deterioration in mental function from confusion and memory loss into severe dementia, accompanied by loss of muscular control (ataxia) and twitching or spasmodic motion (myoclonus). One distinctive feature of the dementia associated with the familial form of CJD is its startling speed of progression; family members will often say that they can see their loved one's mental abilities decline literally from one day to the next. Other symptoms include vision and speech impairment; patients with fCJD may go completely blind. A scan of electrical activity in the brain, called an electroencephalogram (EEG), will often show an abnormal periodic spike pattern. The onset of symptoms usually occurs when the patient is over age 50, and death follows within one to five years. Microscopic holes, called vacuoles, form within the brain tissue and give it a "spongiform" appearance characteristic of CJD.

GERSTMANN-STRÄUSSLER-SCHINKER DISEASE. Gerstmann-Sträussler-Scheinker disease (GSS) is named for the three Austrian neurologists who first described it in 1936: Josef Gerstmann (1887–1969), Ernst Sträussler (1872–1959), and Ilya Scheinker (1902–1954). The first mutation of the prion protein gene *PRNP* was identified in a GSS family in 1989.

GSS encompasses a variety of disorders. One form of the disease (the ataxic form) is first characterized by an unsteady walk, sometimes accompanied by leg pains. These motor problems get worse over several years and are finally accompanied by mental and behavioral breakdown. By contrast, dementia is the main characteristic of the telencephalic form of GSS, accompanied by rigidity, the inability to make facial expressions, tremors, and

stuttering or stammering. In another form of the disease, GSS with neurofibrillary tangles, the main features are loss of muscle coordination (ataxia), tremors, and progressive insanity. As in CJD, the affected individuals are usually in their 50s or older, and the progression of the disease may take from two to as long as 13 years. GSS is the most slowly progressing of the inherited prion diseases.

FATAL FAMILIAL INSOMNIA. FFI is the rarest of the inherited prion diseases. First reported in an Italian man in 1765, the disorder has been identified in fewer than 40 families worldwide. In the late 1990s, it was reported that there are about 25 families around the world who carry mutations for FFI: eight in Germany; five in Italy; four in the United States; two each in France, Australia, and England; and one each in Japan and Austria. In 2011, another family in the Netherlands was identified as carrying an FFI mutation.

The most noticeable sign of FFI is the untreatable and progressively worse difficulty in sleeping. The affected individual then begins to experience complex hallucinations that are often enacted dreams. Excessive sweating, irregular heartbeat, high blood pressure, and hyperventilation are other symptoms. Motor impairment may be present. Shortened attention span and memory loss has been observed. In the terminal stages, stupor and coma precede death. The average age at onset of symptoms is the mid-40s, and the disease progresses rapidly, with death resulting after about one year. Autopsy reveals the formation of dense tangles of neural fibers and astrocytes in the thalamus region of the brain. Genetic testing and counseling are considered essential for FFI, because the mutation that causes the disorder can now be identified by testing and because initial symptoms of the disorder do not appear until the person has reached childbearing age.

Acquired Prion Diseases

KURU. Kuru was called the "shivering disease" by the Fore tribe members, because its primary symptom was twitching and shaking of the body. This twitching began slowly and was not present when the person was completely still, but it then progressively worsened until any attempt at motion led to drastic and uncontrollable body movements, and the individual could no longer stand or walk. Mental insanity usually did not appear until the terminal stages of the disease. The onset of symptoms usually occurred in middle-aged individuals, and the course of the disease was short: three to 12 months.

VARIANT CREUTZFELDT-JAKOB DISEASE. The early signs of variant CJD (vCJD) are most often psychiatric

disturbances. Abnormal sensations of prickling or itching (paresthesia) or pain even from light touches (dysesthesia) are often present. So far, individuals affected with new variant CJD are much younger in age, typically teenagers and young adults. The duration of the disease is one to two years. As in familial CJD, vacuoles are present in the brain, but they are associated with dense deposits (plaques) of the abnormal PrP isomer.

The incidence of vCJD peaked in 2000, declining to about two cases per year since 2008. As of 2015, there had been about 177 cases of vCJD reported since 1996, with four cases reported in the United States.

Diagnosis

Because of the many different forms of prion disease and the overlap in symptoms with those of other, more common syndromes, prion diseases are often difficult to diagnose. Patients who are eventually identified with prion disease have been initially diagnosed with many other diseases, including Alzheimer's disease, Huntington's disease, Parkinson's disease, schizophrenia, multiple sclerosis, and myoclonic epilepsy. The number of possible diagnoses illustrates the difficulty in identifying the disease, and the importance of careful diagnosis to avoid unnecessary treatments.

A diagnosis of prion disease should be considered in any adult patient with signs of neurological impairment such as uncontrollable body movements, confusion, loss of memory, and cognitive degeneration, or psychiatric abnormality. Periodic discharges of brain waves, as observed on an EEG, are present in many, but not all, cases of prion disease. A magnetic resonance imaging (MRI) scan of the brain can rule out other causes of brain disease and potentially identify some abnormalities associated with prion disease. A biopsy, or sampling, of brain tissue can reveal the presence of abnormal PrP, although this procedure is generally not used in elderly patients because of the risk to the surgeon and other healthcare professionals.

Because the early symptoms of a prion disease are similar to those of such infectious disorders of the brain as neurosyphilis, encephalitis, or meningitis, doctors may begin the diagnostic process by taking a spinal tap in order to rule out infection as a cause of the patient's symptoms.

Genetic testing can reveal those cases of prion disease that are caused by mutations. The Centers for Disease Control and Prevention (CDC) has stated criteria for a diagnosis of fCJD as follows: a diagnosis of probable or possible fCJD in the patient, coupled with a diagnosis of possible or probable fCJD in a first-degree

QUESTIONS TO ASK YOUR DOCTOR

- What is a prion?
- How does a person "catch" a prion? Is the process similar to a viral or bacterial infection?
- How are prion infections treated?
- What is the direction of current research on prion diseases?

relative (parent, sibling, or child), plus detection of a mutation in the *PRNP* gene on molecular genetic testing.

Bismuth, mercury, or lithium poisoning result in symptoms quite similar to those of prion disease. These poisonings can be differentially diagnosed by blood tests.

The diagnosis of prion disease can be definitively confirmed by the transmission of the disease to an animal host such as a genetically engineered mouse. However, the transmission period may be quite long, as much as six to seven months. After death, prion disease can also be validated by autopsy of the brain tissue.

Treatment and management

At present, there is no known treatment that can prevent or reverse the transformation of the prion protein into its aberrant form. All treatments for prion disease are directed toward management of the symptoms. These treatments may include psychoactive drugs, electroconvulsive therapy (ECT), and professional care to ensure that the loss of physical and mental functions do not lead to accidental injury or death. Affected persons may wish to consider hospice care as the disease progresses toward complete incapacitation. Research into more advanced treatments is focusing on the application of gene therapies to block the formation of infectious PrP and drugs, which could act to stabilize the normal PrP structure. As with any inherited disease, genetic counseling is important in the management of the familial forms of prion disease.

Prognosis

Since the forms of prion diseases vary widely, the age at onset and rate of worsening of symptoms are also quite variable, but all prion diseases are incurable and fatal, with duration ranging from a few months to several years after onset. Some patients with GSS have been reported to live as long as 13 years after symptom onset, but this length of the disease course is exceptional.

Mechanism of Prion Misfolding and Downstream Effects

In 2021, scientists used sophisticated imaging techniques to visualize the location where misfolding of the prion protein begins. They then developed antibodies to the location of initial misfolding. With the help of the antibodies that bound to the location of initial misfolding, the misfolding stopped, and aggregation of prions stopped. This work has yielded insight into the pathology and a possible target for drug research.

Also in 2021, researchers announced that a protein implicated in other neurodegenerative diseases, TREM2, was at elevated levels in the blood and cerebrospinal fluid of prion disease patients. Working with laboratory models, scientists have determined that in some brain regions, TREM2 is transcribed from its gene at higher levels and that in some regions, the TREM2 message is translated at a higher rate than in controls. The function of TREM2 is unknown. This discovery may allow for diagnosis of a prion disease through a blood test, and it offers a potential target for drug development.

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ORGANIZATIONS

- CJD Aware!, 2527 South Carrollton Avenue, New Orleans, LA 70118, info@cjdaware.com, <http://www.cjdaware.com/index.html>
- Creutzfeldt-Jakob Disease Foundation, Inc., 341 West 38th Street, Suite 502, New York, NY 10016, (212) 719-5100 or (800) 659-1991, <http://www.cjdfoundation.org>
- National Institute of Neurological Disorders and Stroke (NINDS), P.O. Box 5801, Bethesda, MD 20824, (301) 496-5751 or (800) 352-9424, <http://www.ninds.nih.gov>
- National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

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Revised by Kimberly Napoli

Propionic acidemia

Definition

Propionic acidemia is an inborn error of metabolism: a rare inherited disorder in which the body is unable to break down and use certain proteins properly. As a result, massive amounts of organic compounds (such as propionic acid, ketones, and fatty acids) build up in the blood and urine, interfering with normal body functions and development.

Description

Propionic acidemia, first described in 1961, usually shows up in the first few weeks after birth and, if untreated, results in mental and physical impairment. The disorder can have a broad range of clinical outcomes, ranging from the severe form that is fatal to newborns to the mild, late-onset form associated with periodic attacks of ketoacidosis, when organic compounds build up in the blood and urine. Other names for the disorder include ketotic hyperglycinemia, hyperglycinemia with ketoacidosis and lactic acidosis (propionic type), and propionyl CoA carboxylase (PCC) deficiency, types I and II.

Propionic acidemia can occur in isolation, or it can be a feature of multiple carboxylase deficiency, a condition involving abnormal production of many enzymes—all of which need biotin (a form of vitamin B)—as the result of an abnormality in biotin metabolism. Propionic acidemia is characterized by deficiency of an enzyme, propionyl CoA carboxylase, which the body requires to break down the amino acids isoleucine, valine, threonine,

and methionine (chemical building blocks of proteins). The deficiency can be caused by abnormal genes for making propionyl CoA carboxylase (isolated propionic acidemia) or by abnormal genes for metabolizing biotin (propionic acidemia resulting from multiple carboxylase deficiency).

Genetic profile

Propionic acidemia is an autosomal recessive disorder; that is, if a man and woman each carry one abnormal gene, then 25% of their children are expected to be born with the disorder. Two genes, *PCCA* and *PCCB*, code for the two parts (alpha and beta subunits) of the propionyl CoA carboxylase molecule.

The *PCCA* gene controls the production of alpha subunit and is on chromosome 13. Alterations in the *PCCA* gene result in type I propionic acidemia.

Researchers have identified 19 disease-causing mutations in the *PCCA* gene. Eight of these mutations result in an incomplete alpha subunit. Six mutations prevent the alpha subunit from binding biotin, which is required for propionyl CoA carboxylase to work properly, and results in multiple carboxylase deficiency. People who inherit two abnormal *PCCA* genes (homozygotes) produce only 1%–5% of the normal amount of propionyl CoA carboxylase. People who inherit one normal and one abnormal *PCCA* gene (heterozygotes) produce 50% of the normal amount of enzyme.

The *PCCB* gene, which controls the production of beta subunit, is on chromosome 3. Mutations in this gene are responsible for type II propionic acidemia.

Twenty-eight disease-causing mutations have been found in the *PCCB* gene. In people of Caucasian, Spanish, and Latin American heritage, researchers have found the most frequent mutation in about 32% of those with propionic acidemia. In people of Japanese heritage, two other mutations are most prevalent, occurring in 25% and 31% of Japanese patients. Homozygotes for the *PCCB* gene produce propionyl CoA carboxylase in amounts similar to homozygotes for the *PCCA* gene, but heterozygotes for the *PCCB* gene produce nearly normal amounts of propionyl CoA carboxylase. This is probably because many more beta subunits (four to five times more) are produced than alpha subunits, so even with decreased *PCCB* gene activity, enough beta subunits are available to combine with alpha subunits to make a complete molecule of propionyl CoA carboxylase.

Demographics

The frequency with which propionic acidemia occurs throughout the world is unknown because it is a rare

KEY TERMS

Amino acid—Organic compounds that form the building blocks of protein. There are 20 types of amino acids (eight are “essential amino acids” that the body cannot make and must therefore be obtained from food).

Biotin—A growth vitamin of the vitamin B complex found naturally in liver, egg yolks, and yeast.

Ketoacidosis—A condition that results when organic compounds (such as propionic acid, ketones, and fatty acids) build up in the blood and urine.

Multiple carboxylase deficiency—A type of propionic acidemia characterized by an inability to metabolize biotin.

Propionic acid—An organic compound that builds up in the body if the proper enzymes are not present.

Propionyl CoA carboxylase—An enzyme that breaks down the amino acids isoleucine, valine, threonine, and methionine.

disorder. However, in the United States, it affects roughly 1 in 100,000 people. Its occurrence does not appear to be specific to any particular population group. Considered to be prevalent among Inuits in Greenland, propionic acidemia has also been identified in other populations, including Austrian, Spanish, Latin American, Saudi Arabian, Amish, and Japanese people. Males and females are equally likely to be affected.

Signs and symptoms

Newborns with propionic acidemia are typically small and pale with poorly developed muscles. Symptoms that usually appear in the first weeks of life include poor feeding, vomiting, listlessness (lethargy), and ketoacidosis. Less often, infants with the disorder experience loss of body fluids (dehydration), seizures, and enlarged livers.

In some patients, the disorder appears later in life. Signs include facial abnormalities, such as puffy cheeks and an exaggerated “Cupid’s bow” upper lip. Patients with late-onset propionic acidemia may have acute inflammation of the brain (encephalopathy) or be developmentally delayed. These patients may have periodic attacks of ketoacidosis, usually brought on by eating too much protein, becoming constipated, or having frequent infections.

Patients with propionic acidemia as the result of having multiple carboxylase deficiency often have ketoacidosis and their urine may have a distinct “tom cat’s urine” odor. These patients may also have skin rash and loss of hair (alopecia).

Diagnosis

Physicians have only a few tests available that allow them to differentiate propionic acidemia from other inborn errors of metabolism. Tests that are absolutely specific for the disorder involve the measurement of propionyl CoA carboxylase and chemicals related to the reactions it affects. These tests are fairly uncommon and do not have published normal values.

Prenatal diagnosis of propionic acidemia is possible using cells obtained by amniocentesis. The cells can be tested for decreased activity of propionyl CoA carboxylase, for their ability to bind propionic acid, or for their methylcitrate levels.

In a newborn child, propionyl CoA carboxylase activity can be measured in white blood cells (leukocytes) from cord blood (blood from the umbilical cord). The infant’s blood and urine can be tested for increased levels of propionic acid. These levels are tested as well in older children and adults who are suspected of having the disorder.

Physicians can use genetic tests to analyze DNA and identify the specific gene, *PCCA* or *PCCA*, that is abnormal.

Treatment and management

The accepted treatment for propionic acidosis is a low-protein diet. Daily protein intake must be limited to 0.5–1.5 g/kg. Patients should eat frequent meals and avoid fasting, because fasting increases the body’s need for propionyl CoA carboxylate.

A low-protein diet keeps the number of ketoacidosis attacks to a minimum; however, such a diet does not prevent attacks. Physicians treat attacks of ketoacidosis by removing all protein from the patient’s diet and giving the patient sodium bicarbonate and glucose. If the attack is severe, proteins may be removed from the patient’s stomach by peritoneal dialysis.

Some patients may respond to a single oral dose (100 mg/kg) of L-carnitine, an organic compound. Others may be helped by antibiotics, which reduce the number of bacteria that produce propionic acid in the stomach. These are experimental treatments and have not been tested for long-term effects.

Patients with multiple carboxylase deficiency may receive biotin supplements (10 mg daily), which provide immediate, long-lasting improvement. Biotin supplements

QUESTIONS TO ASK YOUR DOCTOR

- What does the term “propionic acidemia” mean?
- What medical problems are associated with this disorder?
- One of my relatives was diagnosed with late-onset propionic acidemia. Is there a way to determine whether my children are at risk for this disorder?
- What information can a genetic counselor provide about this condition?

are not effective, however, for patients with other types of propionic acidemia.

Prognosis

The future of patients with propionic acidemia depends on the severity of the disorder. Left untreated, propionic acidemia in infants results in coma and death. With early diagnosis and treatment, some children are intellectually normal, while others’ lives may be complicated by intellectual disability and abnormal physical development. Some with propionic acidemia may be identified only during family studies. For patients with late-onset propionic acidemia, the disease can be controlled to some extent by diet, but many of these patients will also be mentally and physically delayed.

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ORGANIZATIONS

Organic Acidemia Association, 9040 Duluth St., Golden Valley, MN 55427, (763) 559-1797, mkstagni@gmail.com, <http://www.oaanews.org>

Linnea E. Wahl, MS

Propionyl CoA carboxylase (PCC) deficiency
see **Propionic acidemia**

Prostate cancer

Definition

The prostate, a gland found only in men, is part of the reproductive system. Prostate cancer is a disease in which the cells of the prostate become abnormal and start to grow uncontrollably, forming tumors. Tumors that can spread to other parts of the body are called malignant tumors or cancers. Tumors that are not capable of spreading are called benign.

Description

The prostate is a gland that produces semen, the fluid that contains sperm. The prostate is about the size of a walnut and lies just beneath the urinary bladder. Usually prostate cancer is slow growing, but it can grow fast in some instances. As the prostate cancer grows, some of the cells break off and spread to other parts of the body through the lymphatic or the blood systems. This is called metastasis. The most common sites of spreading are the lymph nodes and various bones in the spine and pelvic region.

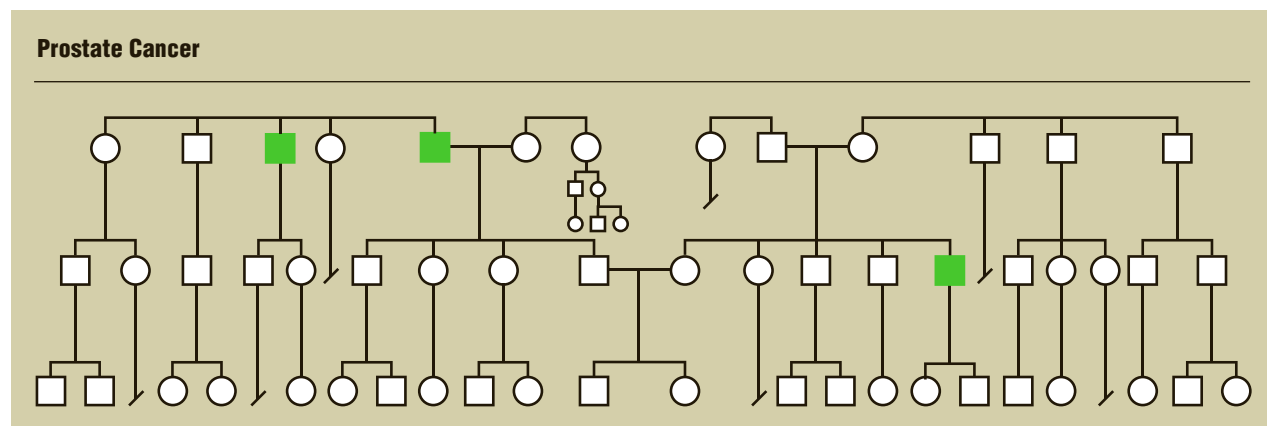
The cause of prostate cancer is not clear; however, several risk factors are known. The average age at diagnosis of prostate cancer is around 72. In fact, 80% of prostate cancer cases occur in men over the age of 65.

As men grow older, the likelihood of their getting prostate cancer increases. Hence, age is one of the more important risk factors for prostate cancer. Race may be another contributing factor. African Americans have the highest rate of prostate cancer in the world, while the rate in Asians is one of the lowest. Although the rate of prostate cancer in native Japanese is low, the rate in Japanese Americans is closer to that of white American men. This pattern suggests that environmental factors also play a role in prostate cancer.

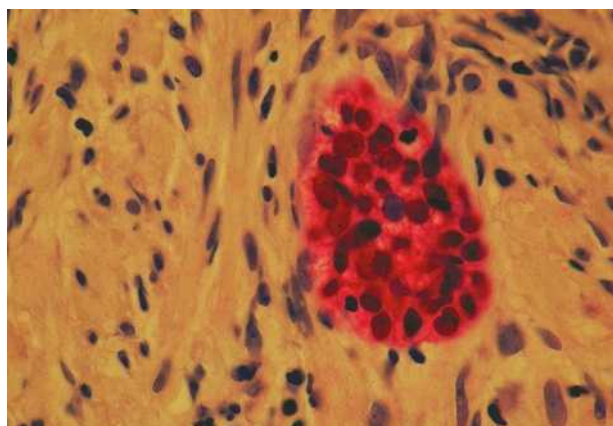
There is some evidence to suggest that a diet high in fat increases the risk of prostate cancer. Studies also suggest that nutrients such as soy isoflavones, vitamin E, selenium, vitamin D, and carotenoids (including lycopene, the red color agent in tomatoes and beets) may decrease prostate cancer risk. Vasectomy may be linked to increased prostate cancer rates. Similarly, workers in industries, such as welding, with exposure to the metal cadmium appear to have a higher than average risk of prostate cancer. Male sex hormone levels may also be linked to the rate of prostate cancer. In addition, some studies have linked increased prostate cancer risk to smoking.

Genetic profile

An estimated 5%–10% of prostate cancer is due to a hereditary cause. Among men with early prostate cancer, a hereditary cause is likely in up to one-third of cases before age 60, and almost half of men diagnosed at age 55 or younger. Studies have found around a two-to-three-fold increased rate of prostate cancer in close relatives of men with the disease. Hereditary prostate cancer is likely in a family if there are three cases of prostate cancer in close relatives or three affected generations on either the mother's or father's side or two relatives with prostate cancer before age 55.



Prostate cancer: pedigree analysis chart (Gale)



Light micrograph of a test for prostate cancer. Dye is injected into the prostate gland and binds to proteins altered by prostate cancer cells (red). (Michael Abbey/Science Source)

Studies suggest that hereditary prostate cancer is likely to be caused by several different genes instead of a single gene. The, *HPC1* (hereditary prostate cancer gene 1), located on the first chromosome pair at 1q24-25, was the first gene found to cause hereditary prostate cancer. At least four other genes have been reported, including one thought to increase the risk of both prostate and brain tumors. Other genes known to increase the risk of other cancers, such as breast cancer, are also linked to prostate cancer. These genes include *BRCA1*, *BRCA2*, and *HOXB13*. When a mutation in one or more of these genes is inherited, it is inherited in an autosomal dominant pattern. *BRCA1* and *BRCA2* are genes that code for tumor suppressor proteins. When these genes are not coded correctly, the proteins are unable to suppress the overgrowth of cells, thus leading to tumors and cancer. The *HOXB13* gene is responsible for coding proteins that regulate activities of other genes, also likely a tumor suppressor. Other tumor suppressor genes associated by studies to prostate cancer are *CAVI*, the *CDKIs*, *CCNA1*, *CCNA2*, *DAPK*, *FHIT*, *HIC1*, *LPL*, and others. Common variations in certain genes also may increase susceptibility to prostate cancer, including genes linked to androgen, a sex hormone, and *PSA* and *TMPRSS2-ETS*. Since no clear cause has been identified for the majority of hereditary prostate cancer, genetic testing is typically done through research studies. Ongoing research seeks to determine the relationship among the approximately 40 genes that may have a role in prostate cancer.

Demographics

Prostate cancer is the most common cancer among men in the United States and is the second leading cause of cancer deaths. One in seven men in the United States

will be diagnosed with prostate cancer at some point in their lives, most after the age of 65. Prostate cancer affects African American men about twice as often as it does Caucasian men, and the mortality rate among African Americans is also higher. African Americans have the highest rate of prostate cancer in the world. The prostate cancer rate varies considerably around the world. The highest rates are in North America and Western Europe; by contrast, the rates are moderate in Africa and lowest in Asia. It is unclear what roles genetics, diet, economics, and healthcare access play in these rates.

Signs and symptoms

Frequently, prostate cancer has no symptoms, and the disease is diagnosed when the patient goes for a routine screening examination. However, occasionally, when the tumor is larger or the cancer has spread to the nearby tissues, the following symptoms may occur:

- weak or interrupted urine flow
- frequent urination (especially at night)
- difficulty starting urination
- inability to urinate
- pain or burning sensation when urinating
- blood in the urine
- persistent pain in lower back, hips, or thighs (bone pain)
- difficulty having or keeping an erection (impotence)

Diagnosis

Although prostate cancer may be slow-growing, it can be quite aggressive, especially in men under the age of 40. When the disease is slow-growing, it may go undetected. Because it may take many years for the cancer to develop, men with the disease are likely to die of other causes rather than from the cancer.

Prostate cancer is frequently curable when detected early. However, because the early stages of prostate cancer may not have symptoms, it often remains undetected until the patient goes for a routine physical examination. Diagnosis of the disease is made using some or all of the following tests.

Digital rectal examination (DRE)

In order to perform this test, the doctor puts a gloved, lubricated finger (digit) into the rectum to feel for any lumps in the prostate. The rectum lies just behind the prostate gland, and a majority of prostate tumors begin in the posterior region of the prostate. If the doctor does detect an abnormality, he or she may order more tests in order to confirm these findings.

Cancer biomarkers

Cancer biomarkers are molecules in the body that can be tested to predict outcome, confirm diagnosis, and provide treatment recommendations. Depending on the biomarker, they can be detected in the blood, urine, or from a biopsy of the prostate. One of the most commonly tested biomarkers is prostate-specific antigen (PSA), which can be measured in the blood. The cells lining the prostate generally make this protein, and a small amount can be detected in the bloodstream. Prostate cancers typically produce a lot of this protein, and it can be easily detected in the blood. Hence, when PSA is found in the blood in higher than normal amounts, cancer may be present. PSA can also be used in monitoring treatment. Although PSA tests can be useful, sometimes they indicate that individual has prostate cancer when he does not, and sometimes they miss a diagnosis. PSA testing cannot tell how serious the prostate cancer is.

Urine biomarkers look at changes in genes and proteins that are specific to prostate cancer that are shed from the prostate. These types of biomarkers help to determine if a biopsy is necessary. Other biomarkers are DNA, mRNA, and protein types and levels found in tumor tissue that are associated with prostate cancer. These typically help monitor tumor aggressiveness, how well treatment is working, and whether a negative biopsy is correct.

Transrectal ultrasound

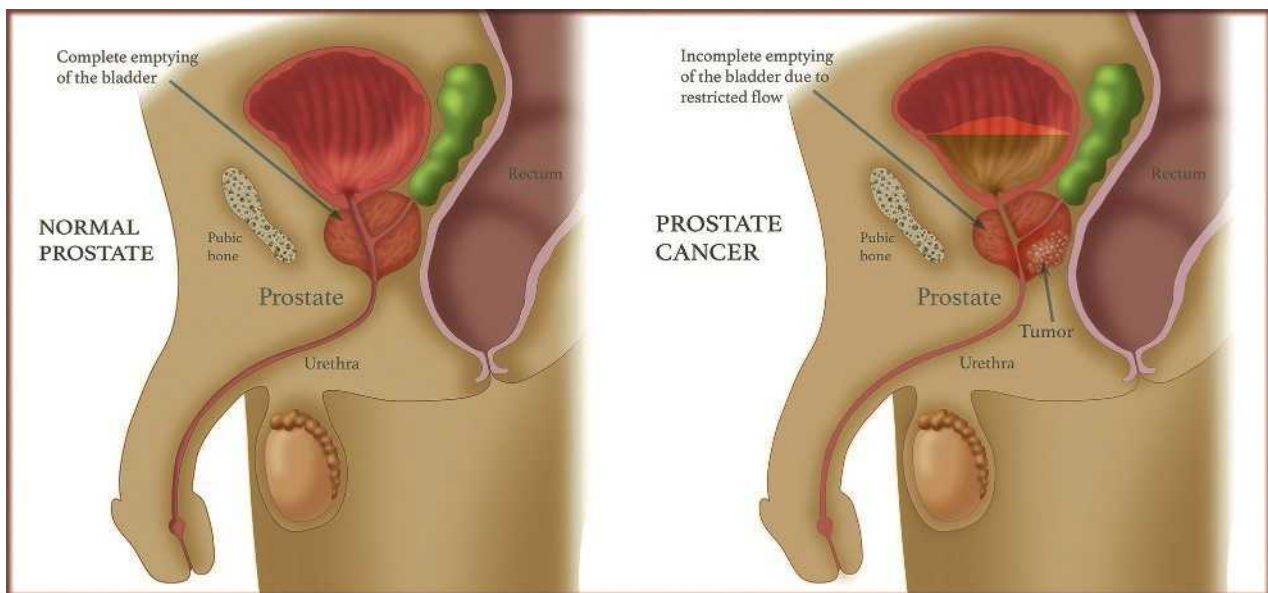
A small probe is placed in the rectum and sound waves are released from the probe. These sound waves

bounce off the prostate tissue, and an image is created. Since normal prostate tissue and prostate tumors reflect the sound waves differently, the test can be used to detect tumors. Though the insertion of the probe into the rectum may be slightly uncomfortable, the procedure is generally painless and takes only about 20 minutes.

Prostate biopsy

If cancer is suspected from the results of any of the above tests, the doctor will remove a small piece of prostate tissue with a hollow needle. This sample is then checked under a microscope for the presence of cancerous cells. Prostate biopsy is the most definitive diagnostic tool for prostate cancer.

If cancer is detected during the microscopic examination of the prostate tissue, the pathologist will “grade” the tumor. This means that the tumor will be scored on a scale of 2–10 to indicate how aggressive the tumor is. Tumors with a lower score are less likely to grow and spread than are tumors with higher scores. This method of grading tumors is called the Gleason system. This is different from “staging” of the cancer. When a doctor stages a cancer, the doctor gives it a number that indicates whether it has spread and the extent of spread of the disease. In Stage I, the cancer is localized in the prostate in one area, whereas in the last stage, Stage IV, the cancer cells have spread to other parts of the body.



On the left, a normal prostate. On the right, a prostate with cancer. A tumor may constrict urine flow from the bladder. (Monica Schroeder/Science Source)

KEY TERMS

Anti-androgen drugs—Drugs that block the activity of the male hormone.

Benign—A noncancerous tumor that does not spread and is not life-threatening.

Benign prostatic hyperplasia (BPH)—A noncancerous condition of the prostate that causes growth of the prostate tissue, thus enlarging the prostate and blocking urination.

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Cancer biomarkers—A molecule found in the body like a protein or gene that can suggest prognosis and what type of therapies would be best. In some cases they can even predict the risk of cancer in people who do not have cancer.

Chemotherapy—Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of the cancerous cells or by killing the cancer cells.

Estrogen—A female sex hormone.

Hormone therapy—Treatment of cancer by changing the hormonal environment, such as testosterone and estrogen.

Lymph node—A bean-sized mass of tissue that is part of the immune system and is found in different areas of the body.

Malignant—Describes a tumor growth that spreads to another part of the body, usually cancerous.

Metastasis—The spreading of cancer from the original site to other locations in the body.

Prostatectomy—The surgical removal of the prostate gland.

Radiation therapy—Treatment using high-energy radiation from x-ray machines, cobalt, radium, or other sources.

Rectum—The end portion of the intestine that leads to the anus.

Semen—A whitish, opaque fluid released at ejaculation that contains sperm.

Seminal vesicles—The pouches above the prostate that store semen.

Testicles—Two egg-shaped glands that produce sperm and sex hormones.

Testosterone—Hormone produced in the testicles that is involved in male secondary sex characteristics.

Transrectal ultrasound—A procedure in which a probe is placed in the rectum. High-frequency sound waves that cannot be heard by humans are sent out from the probe and reflected by the prostate. These sound waves produce a pattern of echoes that are then used by the computer to create sonograms or pictures of areas inside the body.

X-rays and imaging techniques

X-ray studies may be ordered to determine whether the cancer has spread to other areas. Imaging techniques (such as computed tomography scans and magnetic resonance imaging), for which a computer is used to generate a detailed picture of the prostate and areas nearby, may be done to get a clearer view of the internal organs. A bone scan may be used to check whether the cancer has spread to the bone.

The American Cancer Society and other organizations recommend that PSA blood testing and DRE be offered to men with at least a ten-year life expectancy beginning at age 50. Men at higher risk for prostate cancer, such as those with a family history of the disease or African American men, may wish to consider screening at an earlier age such as 45. A low-fat diet may slow the progression of prostate cancer. Hence, the American Cancer Society recommends a diet rich in fruits, vegetables, and dietary fiber, and low in red meat and saturated fats, in order to reduce the risk of prostate cancer.

Treatment and management

The doctor and the patient decide on the treatment after considering many factors. For example, the patient's age, the stage of the tumor, the patient's general health, and the presence of any coexisting illnesses have to be considered. In addition, the patient's personal preferences and the risks and benefits of each treatment method are also taken into account before a decision is made. Molecular genetic analysis using biomarkers is a recent approach to treatment and management of prostate cancer. Biomarkers that indicate gene variants can provide information on what genes to target in terms of pharmaceuticals.

Surgery

For early-stage prostate cancer, surgery is frequently considered. Radical prostatectomy involves complete removal of the prostate. During the surgery, a sample of the lymph nodes near the prostate is removed to determine whether the cancer has spread beyond the prostate gland.

Because the seminal vesicles (the gland where sperm is made) are removed along with the prostate, infertility is a side effect of this type of surgery. In order to minimize the risk of impotence (inability to have an erection) and incontinence (inability to control urine flow), a procedure known as “nerve-sparing” prostatectomy is used.

In a different surgical method, known as the transurethral resection procedure (TURP), only the cancerous portion of the prostate is removed, by using a small wire loop that is introduced into the prostate through the urethra. This technique is most often used in men who cannot have a radical prostatectomy due to age or other illness, and it is rarely recommended.

Radiation therapy

Radiation therapy involves the use of high-energy x-rays to kill cancer cells or to shrink tumors. It can be used instead of surgery for early-stage cancer. The radiation can either be administered from a machine outside the body (external beam radiation), or small radioactive pellets can be implanted in the prostate gland in the area surrounding the tumor.

Hormone therapy

Hormone therapy is commonly used when the cancer is in an advanced stage and has spread to other parts of the body. Prostate cells need the male hormone testosterone to grow. Decreasing the levels of this hormone, or inhibiting its activity, may cause the cancer to shrink or stop growing. Hormone levels can be decreased in several ways. Orchiectomy is a surgical procedure that involves complete removal of the testicles, leading to a decrease in the levels of testosterone. Alternatively, drugs (such as *LHRH* agonists or anti-androgens) that bind to the male hormone testosterone and block its activity can be given. Another method tricks the body by administering the female hormone estrogen. When this is given, the body senses the presence of a sex hormone and stops making the male hormone testosterone. However, there are some side effects to hormone therapy. Men may have hot flashes, enlargement and tenderness of the breasts, or impotence and loss of sexual desire, as well as blood clots, heart attacks, and strokes, depending on the dose of estrogen.

Chemotherapy

Chemotherapy is the use of drugs to kill cancer cells. The drugs can either be taken as a pill or injected into the body through a needle that is inserted into a blood vessel. This type of treatment is called systemic because the drug enters the blood stream, travels through the whole body, and kills the cancer cells that are outside the prostate. Chemotherapy is sometimes used to treat prostate cancer

QUESTIONS TO ASK YOUR DOCTOR

- Why is prostate cancer designated as a genetic disorder?
- Are genetic tests available to determine whether a person is at risk for prostate cancer?
- What kind of tests should a man have to determine if he has early-stage prostate cancer, and at what age should he have those tests?
- What is the prognosis for a man diagnosed with prostate cancer, and what factors affect this prognosis?

that has recurred after other treatment. Research is ongoing to find more drugs that are effective for the treatment of prostate cancer.

Immunotherapies

Immunotherapy uses the person’s own immune system to kill cancer cells. Immunotherapies include vaccines that target cancer cells. Other immunotherapies use antibodies that attack the cancer cells. Although immunotherapy is promising, it is still in the early stages of research and development and is not widely used.

Focal ablation of prostate cancer

Focal ablation of prostate cancer destroys a targeted region of cancer using extreme cold, high-intensity ultrasound, light therapy with a light sensitive drug, lasers, or magnets. This type of therapy is still in the early stages of development. It shows promise as it can have fewer side effects than other treatments.

PARP Inhibitors

PARP inhibitors are medications that block PARP, an enzyme found in the body that can help cancer cells grow by repairing their DNA. By blocking PARP, these medications can result in targeted death of the cancer cells. These medications are typically used for men who are not responsive to traditional treatments with specific gene variations in the BRCA gene.

Watchful waiting

Watchful waiting means no immediate treatment is recommended, but doctors keep the patient under careful observation. This option is generally used in older patients when the tumor is not aggressive and the patients have other, more life-threatening illnesses. Prostate cancer in

older men tends to be slow-growing. Therefore, the risk of the patient dying from prostate cancer, rather than from other causes, is relatively small.

Prognosis

According to the American Cancer Society, the survival rate for all stages of prostate cancer combined has increased from 50% to 87% between 1990 and 2020. Due to early detection and better screening methods, nearly 60% of the tumors are diagnosed while they are still confined to the prostate gland. The five-year survival rate for early-stage cancers is almost 99%. Sixty-three percent of the patients survive ten years, and 51% survive 15 years after initial diagnosis. Studies on the prognosis of hereditary prostate cancer are ongoing. One study found that the mortality for African Americans with prostate cancer, after surgery for removal of the prostate, is 20% higher relative to Caucasians of similar education, income, and health insurance. Asian Americans and Pacific Islanders, by contrast, had a 35% lower mortality than Caucasians.

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ORGANIZATIONS

- American Cancer Society, 250 Williams St. NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org>
- National Cancer Institute, Office of Communications, 9609 Medical Center Dr., Bethesda, MD 20892-9760, (800) 422-6237, <http://www.cancer.gov>
- Urology Care Foundation, 100 Corporate Blvd., Linthicum, MD 21090, (410) 689-3700, (410) 689-3998, info@urologyhealth.org, <http://www.urologyhealth.org>

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Protein C deficiency

Definition

Protein C deficiency is a lack of sufficient functioning protein C in the blood. Protein C is a substance that helps to prevent blood clots. Persons with this disorder may have no symptoms, mild symptoms, or severe and even life-threatening symptoms.

Description

Protein C deficiency was discovered in 1981, just six years after protein C was first isolated. In a 1981 paper published in the *Journal of Clinical Investigations*, researchers described a connection between low concentrations of protein C in the blood plasma (the liquid portion of the blood) and blood clotting. It is now known that protein C plays a crucial role in the series of steps involved in blood clotting. One of protein C's roles in this pathway is to regulate the blood-coagulation protein thrombin. With too little properly functioning protein C to control thrombin's activity, multiple clots can form.

Low levels of protein C may have explicit effects, and in some individuals, these include dark, reddish-purple blotches, which sometimes extend over considerable areas of the body. Such blotching is known as purpura fulminans. Newborns with severe protein deficiency may display considerable blotching, as well as painful black sores, particularly on the back of the head and the buttocks. This is a life-threatening condition.

KEY TERMS

Deep vein thrombosis—A blood clot in a deep vein, usually in the legs.

Eschars—Painful patches of dead, blackened tissue.

Mesentery—Double-layered fold in the peritoneum.

Parenchyma—Functional (rather than structural) tissues of an organ.

Pulmonary embolism—A blood clot in the lungs.

Purpura fulminans—Dark, reddish-purple patches of dying tissue that result from clots in small blood vessels that would otherwise feed that tissue.

Venous thromboembolism—A blood clot that breaks free of its location in a vein and moves elsewhere in the body.

While in the past many young patients died from the effects of severe protein C deficiency, medical advancements coupled with a better understanding of protein C have led to intensive treatment and monitoring options that allow many patients to survive and thrive.

Genetic profile

Protein C deficiency often results from an abnormal *protein C* gene, which is located on chromosome 2. Hereditary protein C deficiency is inherited in an autosomal dominant manner, which means that an individual need only inherit the abnormal gene from one parent. This circumstance often occurs when one parent is heterozygous for the trait or has one normal copy of the gene and one abnormal copy of the gene. When such is the case, that parent's children have a 50% chance of inheriting the abnormal gene. If both parents are heterozygous for the trait, a child's chance of inheriting the abnormal gene jumps to 75%, but the child also has a 25% chance of inheriting two copies of the abnormal gene—one from each parent. A child with two copies of the abnormal gene is said to have homozygous protein C deficiency.

Demographics

Many people have some level of protein C deficiency, although they have no symptoms. It is estimated that 1 in 200–500 individuals has such a deficiency. Significant protein C deficiency is much rarer, occurring in just 1 person of every 20,000. The most severe form of the disorder, homozygous protein C deficiency, occurs

when an individual inherits an abnormal *protein C* gene from each parent. Homozygous protein C deficiency is exceptionally rare. Estimates for the incidence of homozygous protein C deficiency range from 1 in 500,000 to less than one per million.

Signs and symptoms

Protein C deficiency comes in two types:

- Type I protein C deficiency occurs when an individual has perfectly functioning protein C but has too little of it. Kidney disease or a number of other diseases can prompt an individual's body to produce too little protein C. Type I may also result when individuals have inherited one abnormal *protein C* gene from one of their parents. Regardless of its cause, people who have too low a level of protein C cannot control thrombin, and this situation causes blood clots to form.
- Type II protein C deficiency occurs when individuals are able to make sufficient protein C, but the protein C that is made does not function correctly and cannot play its proper role in the coagulation cascade. Genetic mutations can cause the production of nonfunctioning protein C.

Scientists have found that protein C not only interacts with thrombin, but also with other molecules involved in blood clotting, and they have identified more than 270 mutations that can occur in the *protein C* gene.

Symptoms

The symptoms of homozygous protein C deficiency and severe heterozygous protein C deficiency are typically evident very soon after birth. They include:

- Appearance and rapid progression of purpura fulminans, which often begin as large red to purple lesions, often at the back of the head or on the buttocks. Purpura fulminans result from clots in small blood vessels that would otherwise feed that tissue. They typically develop quickly into black scabs of dead tissue known as eschars, which are extremely painful.
- Blindness due to blood clots in the veins of the retina.
- Blood clots in large blood vessels, including those of the kidneys.

As patients with severe protein C deficiency age, they typically have recurring problems with purpura fulminans, particularly following injuries, infections, or changes in anticoagulating therapeutic regimens.

Individuals with moderately severe protein C deficiency may not have their first symptoms until they reach their teens or older. These symptoms may include:

- Recurring venous thromboembolism, which is a blood clot that breaks free of its location in a vein and moves elsewhere in the body, sometimes into the lungs (a pulmonary embolism).
- Deep vein thrombosis, or a blood clot in a deep vein, usually in the legs.
- Clots in organ tissues (parenchyma).
- Blood-clotting proteins that become overly active and disseminated (intravascular coagulation).

In the mild form of protein C deficiency, the patient's body makes functional protein C but makes it in insufficient amounts. Some people who have this condition may experience no problems at all. Others may have one or more of the following symptoms:

- recurring blood clots that may affect blood flow and may lead to a pulmonary embolism
- deep vein thrombosis
- arterial ischemic stroke, due to a blood clot in an artery that feeds the brain
- clots in the mesentery, a double-layered fold in the peritoneum of the abdomen
- blood clots that occur during pregnancy

Diagnosis

Examination

Doctors will suspect protein C deficiency in infants born with obvious purpura fulminans, particularly those who quickly develop eschars. They may also suspect this disorder in older patients who develop the reddish-purple patches or who experience recurring blood clots.

Tests

Doctors will order blood tests to measure the amount of functional protein C and/or to measure the total amount of protein C—functional or not—in the bloodstream. The doctor may repeat the test to make sure that the measured rate is not fluctuating. Another test that a doctor may order involves making tiny nicks in the arm to measure how long the patient continues to bleed and to learn about the clotting activity in the patient.

Treatment and management

Individuals who have protein C deficiency can take various measures to reduce the occurrence of blood clots. These include making typical healthy-lifestyle choices such as eating a balanced diet, remaining physically active, maintaining a healthy weight, and refraining from tobacco use. Avoiding prolonged immobility, such as sitting still on long car rides or plane trips, can

QUESTIONS TO ASK YOUR DOCTOR

- I have mild protein C deficiency and would like to have a baby. Am I at risk for developing venous thrombosis and, if so, what precautions can I take? Are there other risks I should know about?
- My child has just been diagnosed with protein C deficiency, but my other children seem fine. At what age should they be tested for this disorder?
- I understand that several tests are available to test for protein C deficiency. Which do you recommend and why?
- I have protein C deficiency and am going to undergo surgery that will keep me off my feet for more than a week. What special care should I expect at the hospital, and what precautions can I follow once I return home to avoid blood clots while I am recovering?

also be helpful. Persons who are (or expect to be) bedridden due to surgery or illness should discuss with their doctor options for reducing their risk of blood clots. The treatment for patients with protein C deficiency varies based on the severity of the disorder and the individual's symptoms.

Traditional

The doctor may order the administration of protein C, usually as fresh frozen plasma or as protein C concentrate. This is a typical treatment for patients with infantile protein C deficiency.

Drugs

Some patients may receive anticoagulants, such as a form of heparin or warfarin, to counter current clots and, in some cases, to help prevent future clots.

Prognosis

Individuals who have homozygous protein C deficiency often experience fatal thrombosis unless they receive replacement protein C through fresh frozen plasma or through protein C concentrate. Patients who have milder forms of the disorder and have associated symptoms typically have a good outcome with treatment, although they may experience symptoms now and again. Many people who have protein C deficiency never have any symptoms and lead normal lives.

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ORGANIZATIONS

- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Leslie A. Mertz, PhD

Protein S deficiency

Definition

Protein S deficiency is a disorder caused by an insufficient amount of functioning protein S in the blood. Protein S is a substance that helps to prevent blood clots. Normally, the body has a balance between components that promote clotting and those that prevent it, so that clots form only under certain conditions. In individuals with protein S deficiency, too many clots occur. Some people are born with this deficiency, whereas others develop it because of liver disease or due to a lack of vitamin K. Some people with protein S deficiency never have symptoms, but others experience blood clots, embolisms, miscarriages, and, in a few cases, death.

Description

Protein S is a relatively new discovery. Researchers first identified it in the late 1970s. This protein is vitamin K-dependent, which means that vitamin K is necessary for its production. Protein S plays an important role in the steps necessary to control coagulation in the human body, and without it, blood clotting becomes abnormal. In particular, protein S is involved in the action of various

KEY TERMS

Deep vein thrombosis—A blood clot in a deep vein, usually in the legs.

Pulmonary embolism—A blood clot in the lungs.

Purpura fulminans—Dark, reddish-purple patches of dying tissue that result from clots in small blood vessels that would otherwise feed that tissue.

Thrombophlebitis—Inflammation of veins due to blood clots.

Vitamin K—A vital substance that is obtained by eating certain foods, such as leafy greens, but mainly through bacterial manufacture in the large intestine.

blood-clotting substances (such as protein C, factor V, and factor VIII). When the levels of protein S are too low, blood clots can occur. People can obtain vitamin K by eating certain foods, such as leafy greens, but they mainly get their vitamin K from bacteria in the large intestine. These bacteria actually make vitamin K, and they usually make plenty to provide all the vitamin K that a person needs.

The main health problem associated with protein S deficiency is blood clotting, or thrombosis. Protein S is important in the blood-clotting pathway because it is one of a number of anticoagulation proteins that keep the blood from clotting abnormally. In particular, protein S joins with another anticoagulant, protein C, to shut down the clotting action of the enzyme thrombin. Without enough functioning protein S, protein C alone cannot stop thrombin's clotting activity, and it is left to produce clots when it should not. These clots can lodge in blood vessels, where they can limit or stop blood flow. This hindrance of blood flow can be dangerous, and even lethal. Fortunately, various treatments exist to treat abnormal blood clotting.

Genetic profile

Protein S deficiency can result from liver disease or insufficient vitamin K, but it is often a congenital condition resulting from at least one mutated protein S gene that is inherited from a parent.

Hereditary protein S deficiency results from mutations in the protein S gene *PROS1*. *PROS1* is located on chromosome 3. Two of the known mutations of this gene—and several others probably exist—include deletions of parts of the gene such that the mutated gene's

instructions for making the protein are no longer complete. A short, improperly functioning protein results.

Hereditary protein S deficiency is inherited in an autosomal dominant manner, which means that an individual need inherit the abnormal gene from only one parent. This situation often occurs when one parent is heterozygous for the trait or has one normal copy of the gene and one abnormal copy of the gene. When such is the case, that parent's children have a 50% chance of inheriting the abnormal gene. If both parents are heterozygous for the trait, the child's chance of inheriting the abnormal gene not only jumps to 75%, but the child also has a 25% chance of inheriting two copies of the abnormal gene—one from each parent. A child with two copies of the abnormal gene is said to have homozygous protein S deficiency.

Demographics

Protein S deficiency occurs in about 1 of every 20,000 individuals. Some individuals may have no symptoms and, therefore, be unaware they have the condition. In others, first symptoms may not appear until adulthood, but they usually materialize before middle age. A much rarer form of the protein S deficiency is the hereditary form of the disorder, known as homozygous protein S deficiency. Homozygous protein S deficiency generally makes its presence known in newborns or infants as purpura fulminans, which is the formation of purplish patches of dying tissue on the body that can sometimes be quite large. These patches are caused by blood clots in small blood vessels that would otherwise feed that tissue.

Signs and symptoms

Symptoms

Many individuals with protein S deficiency never experience any symptoms, and some only become aware that they have it when they undergo testing because a close relative develops the disorder. Among those who do experience problems associated with the disorder, symptoms can range from mild to severe. Symptoms may include the following:

- purpura fulminans, mainly in individuals with homozygous protein S deficiency
- recurring blood clots that may affect blood flow and may move into the lungs (pulmonary embolism)
- blood clot in a deep vein, usually in the legs (deep vein thrombosis)
- inflammation of veins due to blood clots (thrombophlebitis)
- miscarriage
- swelling and pain in the legs due to venous thrombosis

QUESTIONS TO ASK YOUR DOCTOR

- I have protein S deficiency, and the doctor has prescribed heparin. Am I still at any risk of having a dangerous blood clot?
- Will I have to take anticoagulants for the rest of my life?
- What are the signs of blood clots, and should I consult a doctor if I find any of these signs?
- What is the chance that I will pass my own protein S deficiency to any children I may have in the future? Is it prudent for me to pursue a pregnancy?
- Would it be beneficial to eat a diet high in food rich in vitamin K?

Diagnosis

Examination

Doctors may want to test a patient for protein S deficiency when they learn of a family history of the disorder, particularly when it is combined with the presence of one or more of the following symptoms:

- deep vein thrombosis
- thrombophlebitis
- purpura fulminans
- swelling and pain in the legs, possibly accompanied by redness
- recurring blood clots, particularly in individuals of middle age or younger
- cord-like, hard veins, which are indicative of clotting

Tests

Doctors will order blood tests to measure the amount of functional protein S and/or to measure the total amount of protein S—functional or not—in the bloodstream. Doctors may repeat the test to make sure that the measured rate is not fluctuating. Another test that may be ordered involves making small nicks in the arm to measure how long the patient continues to bleed and, therefore, to provide information about the patient's clotting activity.

Treatment and management

Individuals who have protein S deficiency can take various measures to reduce the occurrence of blood clots. These include making typical healthy-lifestyle choices such as eating a balanced diet, remaining physically

active, maintaining a healthy weight, and refraining from tobacco use. Avoiding prolonged immobility, such as sitting still on long car rides or plane trips, can also be helpful. Persons who are (or who expect to be) bedridden due to surgery or illness should discuss with a doctor options for reducing the risk of blood clots. Women who are considering a pregnancy or beginning birth control or certain types of hormone-replacement therapies should consult a doctor first.

The treatment for protein S deficiency varies based on the patient's symptoms. Symptoms are wide-ranging because numerous protein S mutations can occur, and these can have different effects.

Traditional

For patients diagnosed with protein S deficiency, doctors typically recommend that the person follow a healthy lifestyle in terms of diet and exercise to lower the risk of blood clots. To treat an already existing clot, a doctor may recommend that the patient receive fresh frozen human plasma, which contains protein S.

Drugs

Some patients may receive anticoagulants, such as a form of heparin or warfarin, to counter current clots and, in some cases, to help prevent future clots. The use of such drugs is particularly common for women who are pregnant, because even in a person without this disorder, the level of protein S dips during pregnancy. In addition, women who take some forms of birth control pills or certain types of hormone-replacement therapies may experience additional drops in protein S.

Prognosis

Some individuals with mild forms of this disorder never experience any symptoms and have no problems associated with the condition. Others may have symptoms ranging from mild to severe. Many people with protein S deficiency have a good outcome, particularly when they follow the advice of a physician. Even with the use of anticoagulants, however, life-threatening blood clots do occur occasionally, and some patients die from them.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Leslie A. Mertz, PhD

Proteus syndrome

Definition

Proteus syndrome is characterized by excessive growth of cells. This can result in asymmetrical growth, benign (noncancerous) tumors, and pigmented skin lesions.

Description

Proteus syndrome is a rare condition that was first described by Michael Cohen in 1979. Hans-Rudolf Wiedemann named the condition after the Greek god Proteus who could assume many forms. The disorder gained wide recognition when it became publicized that Joseph (John) Merrick, the person depicted in the movie *The Elephant Man*, was suspected of having Proteus syndrome.

The excess growth of tissue that characterizes Proteus syndrome is progressive and tends to affect some tissues but not others. This can result in asymmetrical growth in the body such as the skull, bones, spine, hands, feet, fingers, and toes. Proteus syndrome often results in overgrowth of one side of the body and not the other. Benign tumors on the surface of the skin or inside the body may also occur. Raised brown patches on the skin and an overgrowth of tissues on the soles of the feet or the palms of the hands are common. The types of tissues and organs that are affected and the severity of the effects vary from person to person and within the course of a lifetime. Proteus syndrome is sometimes associated with mental delay.

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Benign tumor—An abnormal proliferation of cells that does not spread to other sites.

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Connective tissue—A group of tissues responsible for support throughout the body; includes cartilage, bone, fat, tissue underlying skin, and tissues that support organs, blood vessels, and nerves throughout the body.

Cyst—An abnormal sac or closed cavity filled with liquid or semisolid matter.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Gene—A building block of inheritance that contains the instructions for the production of a particular protein and is made up of a molecular sequence found on a section of DNA. Each gene is found at a precise location on a chromosome.

Mosaicism—A genetic condition resulting from a mutation, crossing-over, or nondisjunction of

chromosomes during cell division and causes a variation in the number of chromosomes in the cells.

Nevus (plural: nevi)—Any anomaly of the skin present at birth, including moles and various types of birthmarks.

Protein—Important molecules composed of amino acids that are involved in the formation of cellular structures and controlling the basic functions of the human body.

Spleen—Organ located in the upper abdominal cavity that filters out old red blood cells and helps fight bacterial infections. It is responsible for breaking down spherocytes at a rapid rate.

Spontaneous—Occurring by chance.

Thymus gland—An endocrine gland located in the front of the neck that houses and transports T cells, which are part of the immune system and help to fight infection.

Tissue—Group of similar cells that work together to perform a particular function. The four basic types of tissue include muscle, nerve, epithelial, and connective tissues.

Vascular malformation—Abnormality of the blood vessels that often appears as a red or pink patch on the surface of the skin.

Vertebra—One of the 23 bones that compose the spine. *Vertebrae* is the plural form of vertebra.

Genetic profile

The specific cause of Proteus syndrome is unclear. Proteus syndrome appears to occur randomly, which suggests that it is not inherited. Research shows that Proteus syndrome results from an unknown gene that is mutated in some cells but normal in other cells of the body. This type of gene expression is called mosaicism.

The tissues and organs that are affected in Proteus syndrome and the severity of effects can depend on how many cells contain the mutated gene and what types of cells contain it. Someone with many cells containing the changed Proteus gene is more likely to have more severe effects than someone with only a few affected cell types. Someone with many cells changed in a particular part of the body such as the hand are more likely to have excessive growth in that area. During fetal development, the

mutated Proteus gene will affect cell growth even after the fetus is fully formed, as cell division continues to take place and is necessary for the growth of tissues and organs and for the replacement of damaged cells. The mutated Proteus gene mainly results in excessive growth from infancy to adolescence.

Demographics

Only 100 to 200 cases of Proteus syndrome have been reported around the world. Both males and females are equally likely to be affected with Proteus syndrome.

Signs and symptoms

Individuals with Proteus syndrome can have a wide range of manifestations. The effects can also range from

mild to severe. The most common manifestations of Proteus syndrome include:

- overgrowth of hands, feet, fingers, or toes (gigantism)
- overgrowth of one side of the limbs, face, or body (hemihypertrophy)
- overgrowth of the connective tissue on the soles of the feet or palms of the hand or, less commonly, in the abdomen or nose (connective tissue nevi)
- darkened, discolored, and often rough or raised patches of skin (skin surface nevi)
- benign tumors on the skin surface and under the skin
- benign tumors of the fat cells (lipoma) or areas of significantly decreased or increased body fat
- abnormalities of the skull resulting in a large or asymmetrical head
- benign bony growths projecting outward from the ends of the bones (exostosis)

People with Proteus syndrome can have curvature of the spine. They may also have an enlarged spleen or thymus. Approximately 12%–13% of people with the disorder have cystic abnormalities of the lungs, which can interfere with the normal functioning of the lungs. Abnormalities in the blood vessels called vascular malformations appear as pink or red patches on the surface of the skin are common. About one-third of people with Proteus syndrome are mentally impaired; skull abnormalities are often seen in those with impairment. People with Proteus syndrome can have a distinctive facial appearance, with a long and narrow face, down-slanting eyes, wide and forward-tipping nostrils, a low nose bridge, and a mouth that remains open when at rest.

Sometimes mild or moderate effects of Proteus syndrome such as benign tumors are present at birth. As a person grows and develops, the tissue overgrowth progresses and changes. This progression is often irregular and is characterized by periods of major overgrowth and other periods of absent overgrowth. The effects therefore change over the course of a lifetime. However, most changes occur before adolescence since tissue overgrowth tends to plateau at that time.

Diagnosis

There is no blood test available to diagnose Proteus syndrome. A diagnosis can be made only by careful observation of the individual, perhaps over a period of time and through imaging studies. These may include x-ray evaluations of the skull and skeletal system; magnetic resonance imaging (MRI) of the limbs, nervous system, and abdomen; and computed tomography (CT) scans of the chest.

QUESTIONS TO ASK YOUR DOCTOR

- What are the physical symptoms typically associated with Proteus syndrome?
- How is Proteus syndrome diagnosed?
- What is the latest information from research studies about the progressions of Proteus syndrome?
- Are there organizations interested in providing information and support for people with Proteus syndrome and the general public?

The great variability of Proteus syndrome from person to person makes it hard to diagnose. There are no definitive and universal diagnostic guidelines.

Treatment and management

There is no cure for Proteus syndrome and treatment largely involves the management of effects of the disorder, such as the removal of tumors or bony overgrowths. Removal of tumors is not recommended unless they are causing major problems, since these tumors usually grow back. Surgery to remove an overgrown portion of the bone should be performed only if it affects normal functioning. Bony overgrowths in the ear, for example, may need to be removed if they are interfering with hearing. This type of surgery, however, can sometimes increase the growth of the remaining bone. Psychological counseling to help children with Proteus syndrome deal with the disorder should be considered. In order for counseling to be effective it is preferable that it begins at a young age.

Prognosis

The long-term prognosis of Proteus syndrome is not known. The life expectancy is likely to vary greatly in each occurrence of the syndrome. Those with tumors and bony overgrowths affecting critical organs are likely to have a poorer prognosis.

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ORGANIZATIONS

Proteus Syndrome Foundation, 6235 Whetstone Dr., Colorado Springs, CO 80918, (719) 264-8445, <http://www.Proteus-syndrome.org>

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PRPS1 gene mutation— progressive hearing loss

Definition

The *PRPS1* gene encodes the instructions for producing an enzyme called phosphoribosylpyrophosphate synthetase 1 (PRPP synthetase 1). Although mutations (changes) in the *PRPS1* gene can cause several different syndromes, specific mutations cause a type of nonsyndromic, sensorineural, progressive hearing loss that primarily affects males. The disorder is nonsyndromic because it is not associated with any visible abnormalities in the external ear or with any other related medical problems. Sensorineural hearing loss is caused by malfunction of the cochlea of the inner ear. X-linked disorders are caused by mutations in genes, such as *PRPS1*, that are located on the X sex chromosome. They primarily affect males, because males have only one X chromosome. Females have two X chromosomes, so even if one X chromosome contains a mutated gene, a corresponding normal gene on the other X chromosome can often compensate for the mutation.

Description

More than 100 different genes have been associated with hereditary hearing loss and deafness, and it is expected that more hearing loss-associated genes will be identified in the future. Nonsyndromic progressive hearing loss caused by mutations in the *PRPS1* gene appears to be a rare form that is postlingual, meaning that the hearing loss develops after language acquisition.

The type of X-linked sensorineural nonsyndromic hearing loss (NSHL) caused by *PRPS1* gene mutations is also known as isolated X-linked sensorineural deafness, DFNX1 (for DeaFNess X-linked 1), or DFN2 because it was originally mapped to the DFN2 locus (site) on the X chromosome. Mutations in a second gene on the X chromosome, *POU3F4*, can also cause X-linked NSHL and were originally mapped to the DFN3 or DFNX2 locus. DFN3 hearing loss is a mixed type (a combination of conductive and sensorineural) and prelingual (occurring before language acquisition) and progresses to profound hearing loss. Mutations in a third gene on the X chromosome, *SMPX*, can cause postlingual, sensorineural, progressive NSHL that ranges from mild to profound. *PRPS1* gene mutations can also cause several different syndromes with multiple signs and symptoms that can include neurological problems and sensorineural hearing loss:

- Arts syndrome
- X-linked recessive Charcot-Marie-Tooth disease 5
- PRPP synthetase superactivity with PRPS-related gout

PRPP synthetase 1, produced by the *PRPS1* gene, is involved in making (synthesizing) phosphoribosylpyrophosphate (PRPP). PRPP is required to make new purine and pyrimidine nucleotides. These are the building blocks of the nucleic acids DNA and RNA, as well as ATP and GTP that are energy sources for cells. Cells can salvage or recycle purines and pyrimidines from the breakdown of DNA and RNA, which is much more energy efficient than producing new nucleotides. However, PRPP synthetase 1 and PRPP are also required for the purine salvage pathway. Sensorineural hearing loss, as well as the neurological symptoms of *PRPS1*-associated syndromes, is believed to result from reduced levels of GTP and possibly ATP, as well as other purine nucleotides. However, two other PRPS genes have been identified. *PRPS2* is also located on the X chromosome. *PRPS3*, located on chromosome 7, is believed to be active only in the testes.

Genetic profile

NSHL caused by *PRPS1* mutations is generally progressive and postlingual. However, the first family with NSHL that mapped to the DFN2 locus was a large, four-generational, British-American family with members who had congenital (present at birth and, therefore, prelingual) profound NSHL. The female carriers of mutations at the DFN2 locus had mild to moderate NSHL, especially at higher frequencies of sound. The second identified DFN2 family included five affected males with severe, progressive, postlingual hearing impairment in the low and middle frequencies and less impairment at high frequencies and with hearing loss first diagnosed

between the ages of seven and 20 years. This American family included two female carriers of the mutation with less severe hearing impairment. Since then, several large Chinese families have been identified with X-linked, postlingual NSHL mapping to the DFN2 locus. In 2010, researchers reported on a large, five-generational, Chinese family (106 members) with X-linked, mild-to-profound NSHL affecting 17 members. Nine affected males had progressive, severe to profound hearing loss beginning between the ages of five and 15. Seven of eight female carriers had mild to moderate hearing loss in one or both ears. Five of the women had hearing loss diagnosed between the ages of 47 and 64. One woman had severe to profound bilateral hearing loss at age 71. One female carrier had normal hearing at age 52. The researchers identified were able to identify an NSHL-associated mutation in the *PRPS1* gene.

The *PRPS1* gene is located on the long arm (q) of the X chromosome at Xq22.3. Mutations that cause progressive hearing loss in males and later-onset hearing loss in females have been identified as *PRPS1* gene mutations that change an amino acid within functional portions of the PRPP synthetase 1 protein and result in the loss of its enzymatic activity. Several identified NSHL-associated mutations change single nucleotides in the *PRPS1* gene sequence that result in changes in evolutionarily highly conserved amino acids in the enzyme. This means that many different organisms, including humans, have the same amino acids at these locations in the enzyme, indicating that these amino acids are very important for enzyme function.

Different mutations in the *PRPS1* gene that change different amino acids in the PRPP synthetase 1 enzyme have been identified as causing *PRPS1*-associated syndromes. PRPP synthetase 1 superactivity is caused by mutations that interfere with the regulation of the enzyme, resulting in *PRPS1*-related gout and, occasionally, neurological problems, developmental delay, and NSHL. Other *PRPS1* gene mutations that decrease PRPP synthetase I activity have been identified as causing Arts syndrome, which is characterized by intellectual disability, delayed motor development, and other serious problems in males, as well as NSHL. Females affected by Arts syndrome tend to have milder symptoms. Additional *PRPS1* gene mutations that change an amino acid in PRPP synthetase 1 have been identified as causing Charcot-Marie-Tooth X-linked neuropathy, which includes hearing loss and visual impairment. The *PRPS1* mutations that result only in progressive NSHL, although they change single amino acids in the enzyme, are not predicted to cause major structural changes in the PRPP synthetase 1 enzyme. This may explain why they cause only NSHL, in contrast to *PRPS1* mutations that may

KEY TERMS

Cochlea—The spiral-shaped, fluid-filled hearing apparatus of the inner ear.

Decibel (dB)—A logarithmic unit for expressing loudness or intensity; normal speech is typically in the range of 20–50 dB.

DFN2 or DFNX1—A DeaFNess gene locus associated with nonsyndromic, progressive, X-linked hearing loss, now identified as the *PRPS1* gene locus.

Hearing level (HL)—Hearing threshold; the sound level that can just barely be heard.

Hertz (Hz)—A measurement of sound frequency; 1 Hz equals to one cycle per second.

Nonsyndromic hearing loss (NSHL)—Hereditary hearing loss that is not part of another underlying genetic disorder.

Phosphoribosylpyrophosphate (PRPP)—A molecule that is required for making new purine and pyrimidine nucleotides and for salvaging and recycling purines; PRPP synthesis requires phosphoribosylpyrophosphate synthetase 1 (PRPP synthetase 1), which is encoded by the *PRPS1* gene.

Purines—Bases such as adenine and guanine; adenine and guanine nucleotides are building blocks of DNA and RNA, as well as ATP and GTP that are cellular energy sources and have other important roles in cellular function.

Sensorineural hearing loss—Hearing loss caused by an abnormality in or permanent damage to the inner ear, the auditory nerve, or the auditory center of the brain.

X-linked—A gene located on the X sex chromosome.

have much more severe effects on enzyme function and result in syndromes characterized by multiple neurological problems. Tests of *PRPS1* activity in cells from patients with X-linked progressive NSHL have indicated that PRPP synthetase 1 activity is reduced to approximately 50% of normal.

Demographics

The incidence of *PRPS1*-associated nonsyndromic progressive hearing loss in males is unknown, but it is presumed to be rare. Although more than 70% of hereditary hearing loss and deafness are nonsyndromic,

X-linked hearing loss and deafness accounts for less than 2% of NSHL and can be caused by genes other than *PRPS1*.

Signs and symptoms

The symptom of *PRPS1*-associated NSHL is postlingual, progressive, severe to profound, sensorineural hearing loss at all frequencies. In males, it appears to usually develop in childhood or adolescence. Female carriers of the *PRPS1* mutations may have no symptoms or have hearing loss that develops later in life.

Diagnosis

Genetic forms of hearing loss are diagnosed by an ear exam, hearing tests (audiometry), a physical exam, personal and family medical histories, imaging studies such as computed tomography (CT) scans of the temporal bone, and molecular genetic testing. NSHL is usually readily distinguishable from syndromic hearing loss by the absence of other signs and symptoms, which are usually neurological with *PRPS1*-associated syndromic hearing loss. Other diagnostic tests may include:

- auditory brain stem response testing to evoke responses in the auditory nerve and brain stem
- auditory steady-state testing
- evoked otoacoustic emissions to determine the activity of the outer hair cells of the cochlea
- acoustic immittance testing to assess the peripheral auditory system, including middle-ear pressure
- various specialized types of audiometry

Hearing is generally tested using earphones. Sounds are sent into the earphones at various decibel (dB) and frequency (hertz, Hz) levels to determine the amount of hearing loss in dB and the range of hearing loss in Hz. Each ear is tested independently, since hearing loss is not necessarily the same in both ears. Hearing loss is categorized by the hearing threshold or hearing level (HL)—the level of sound that can just barely be heard, measured in dB and defined as 0 dB for a healthy young adult with normal hearing.

- Normal hearing is an HL up to 25 dB.
- Mild hearing loss is an HL of 26–40 dB.
- Moderate hearing loss is an HL of 41–55 dB.
- Moderately severe hearing loss is an HL of 56–70 dB.
- Severe hearing loss is an HL of 71–90 dB.
- Profound hearing loss is an HL greater than 90 dB.

The average person speaking English in a conversational tone tends to speak in the 30–60 dB range, depending on the particular sounds. People with mild hearing

QUESTIONS TO ASK YOUR DOCTOR

- Why do you think my hearing loss is due to a *PRPS1* gene mutation?
- Is genetic testing available for *PRPS1* mutations?
- Should my family members be tested for *PRPS1* gene mutations or screened for hearing loss?
- What is the risk that I will pass on progressive hearing loss to my sons or daughters?

loss are generally able to hear and understand one-on-one conversations if they are close to the speaker, but they may have difficulty hearing a speaker who is far away, has a soft voice, or is surrounded by background noise. People with moderate hearing loss may have problems hearing conversational speech, even at relatively close range and in the absence of background noise. People with severe hearing loss have difficulty hearing in most situations, unless the speaker is talking loudly and is relatively close. People with profound hearing loss may not hear loud speech or environmental sounds.

Hearing loss is generally plotted on a graph called an audiogram of frequency versus HL. The normal hearing frequency range for humans is approximately 100–8,000 Hz. The normal frequency of sounds in English falls between approximately 240 Hz and 7,500 Hz. With progressive sensorineural hearing loss, any of the three frequency ranges (high, medium, or low) may be lost first.

A diagnosis of sensorineural rather than conductive or mixed hearing loss, the age of onset, and the degree of progressiveness, as well as a family history of hearing loss affecting younger males, may suggest *PRPS1*-associated NSHL. Sensorineural versus conductive hearing loss is distinguished using a device called a bone vibrator. The bone vibrator sends auditory signals through the bones of the ear, bypassing the ear canal and the ossicles of the middle ear. With conductive hearing loss, the affected individual can hear sounds at a lower dB level with the bone vibrator than with earphones, because the problem is in the outer or middle ear. With sensorineural hearing loss, the affected individual generally hears sounds through the bone vibrator at the same dB level as with earphones, because the problem lies within the inner ear, the auditory nerve, or the auditory center of the brain. The audio profile of hearing loss, as well as clinical presentation, can clearly distinguish NSHL associated with *PRPS1* mutations from NSHL caused by *POU3F4* mutations. Genetic testing

may be available for *PRPS1* mutations. Children who are at risk for hereditary hearing loss should have genetic testing, if possible, as well as regular screening audiometry.

Treatment and management

Most people with progressive NSHL benefit from hearing aids. Children over 12 months of age with severe to profound hearing loss may be candidates for cochlear implants. Regular audiologic examinations are used to measure the stability or progression of hearing loss and to identify any additional factors that may be contributing to hearing loss, such as middle ear problems. It is important for people with NSHL to avoid exposure to noise.

Prognosis

PRPS1-associated NSHL is generally progressive, meaning that hearing will continue to deteriorate. However, hearing aids can be very helpful.

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ORGANIZATIONS

Alexander Graham Bell Association for the Deaf and Hard of Hearing, 3417 Volta Pl. NW, Washington, DC 20007, (202) 337-5220, (202) 337-8314, info@agbell.org, <http://www.listeningandspokenlanguage.org>

American Society for Deaf Children, 800 Florida Ave. NE, #2047, Washington, DC 20002-3695 or (800) 942-2732 (ASDC), (410) 795-0965, <http://www.deafchildren.org>

National Association of the Deaf, 8630 Fentor St., Suite 820, Silver Spring, MD 20910, (301) 328-1443, (301) 587-1791, <http://nad.org>

National Institute on Deafness and Other Communication Disorders, 31 Center Dr., MSC 2320, Bethesda, MD 20892-2320, (301) 496-7243 or (800) 241-1044, (301) 402-0018, nidcdinfo@nidcd.nih.gov, <http://www.nidcd.nih.gov>

Margaret Alic, PhD

Prune-belly syndrome

Definition

Prune-belly syndrome is characterized by the following three findings: lack of abdominal muscles, undescended testes, and abnormal development of the urinary tract. Also known as Eagle-Barrett syndrome, this rare disorder was first described in 1839.

Description

Prune-belly syndrome displays a wide range of severity. Affected individuals will have little to no muscle in their abdominal wall. The abdomen will appear wrinkled, like a prune. In male infants, the testicles, although present, are usually not seen. They remain inside the infant's abdomen instead of moving to the normal position during development of the fetus. Undescended testes are a risk factor for infertility and testicular cancer later in life.

There are a variety of urinary tract abnormalities that occur in this syndrome. The kidneys may not fully form, and the level of development of the kidneys varies. The ureters, the tubes that connect the kidneys to the bladder, may be very large. In the portions that are very large, urine may not be able to flow as well as normal. The bladder, the organ that holds urine, may also be very large. A connection between the umbilicus and bladder may be present as well. The urethra may have areas that are very dilated and others that are very narrow. The narrowing may not allow the urine to flow out well. This blockage causes the bladder to become very large. The drainage of the fetus's bladder is what makes up the amniotic fluid during pregnancy. If the bladder cannot be drained, then not enough amniotic fluid will be present. The lack of amniotic fluid, or oligohydramnios, can cause poor formation of the fetus's lungs. The bladder in these patients may become so large that a mass can be seen and felt on the baby.

Ten percent of cases may have various abnormalities of the heart or large blood vessels. A percentage of cases have abnormalities of the musculoskeletal system such as dislocation of the hips, abnormal indentation of the chest,

malformed feet or fingers, and a spine that is not aligned properly.

Genetic profile

A specific genetic defect is unknown. Multiple cases in families are rare but have been reported. The risk of recurrence in future pregnancies is unknown but is thought to be low.

Demographics

Despite the lack of a specific genetic defect or pattern of inheritance, over 95% of affected individuals are male. The incidence of this syndrome is estimated at 1 in 40,000 births.

Signs and symptoms

There are many symptoms that infants may experience in the newborn period. Most of these depend on the extent of damage that exists in the lungs and urinary tract. Infants who have poorly developed lungs may be unable to breathe on their own at birth. They may also develop a collapsed lung or pneumothorax. If the infant

KEY TERMS

Creatinine—A normal component of blood kept in low levels in urine by functioning kidneys.

Pyelonephritis—Inflammation of the kidney commonly caused by bacterial infections.

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.

does not have a normal ribcage, then his or her ability to move air into and out of the lungs is impaired. This can lead to infections in the lung.

Since infants may not be able to eliminate all their urine, they are at risk of having repeated urinary tract infections.

Diagnosis

At birth, the syndrome is easily diagnosed based on the three findings that have been described. There is no specific



Eleven-month-old Lance Witterder has prune-belly syndrome, which means he has no abdominal muscles; the disorder also destroyed his kidneys. He underwent surgery to receive a kidney from his father. (ZUMA Press, Inc./Alamy)

QUESTIONS TO ASK YOUR DOCTOR

- How did this disorder get its name?
- What information is available about the genetic basis of this disease?
- What treatments are available for prune-belly syndrome, and what risks, if any, are associated with those treatments?

prenatal or genetic test that can diagnose prune-belly syndrome. The diagnosis of prune-belly syndrome can be made in the prenatal period by ultrasound, which can show some of the findings in this syndrome, such as distended bladder and ureters, oligohydramnios, and cryptorchidism. An enlarged bladder can be seen in other syndromes besides prune-belly; however, these findings on ultrasound should alert a physician to prune-belly as a possible cause.

Treatment and management

The potential treatments for prune-belly syndrome depend upon whether the diagnosis is made at birth or *in utero*. It also varies depending upon how severe the abnormalities are. Various surgical procedures have been performed on fetuses in an attempt to correct the urinary tract obstructions that occur. One of these procedures is the vesicoamniotic shunt. This procedure relieves bladder obstructions by placing a tube in the fetal bladder, allowing amniotic fluid to be produced as usual. The production of amniotic fluid allows for normal development of the lungs. There is not much information regarding the long-term outcomes for persons who receive these shunts. In infants who survive but have renal failure, kidney transplantation has been attempted with some success.

Prognosis

Approximately 20% of patients with this syndrome are stillborn. Thirty percent of infants do not survive past two years due to renal failure or infection. The remaining 50% of the infants will have a variety of urinary tract problems. Developing pyelonephritis (infection and inflammation of the kidney) at some point in time, having an elevated baseline creatinine, and having both kidneys look abnormal on an ultrasound are predictive for developing renal failure.

Resources

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ORGANIZATIONS

National Institute of Diabetes and Digestive and Kidney Diseases, 9000 Rockville Pike, Bethesda, MD 20892, <http://www.niddk.nih.gov>

Prune Belly Syndrome Network, PO Box 16071, Philadelphia, PA 19154, (855) 275-7276, <http://prunebelly.org>

David Elihu Greenberg, MD

Pseudo-Gaucher disease

Definition

Pseudo-Gaucher disease is a rare lysosomal storage disease caused by a genetic mutation with characteristics very different from those of Gaucher disease, but caused by the same genetic mutation as that responsible for Gaucher disease. The condition is transmitted as an autosomal recessive trait. The disorder is also known as Gaucher-like disease and is also referred to as Gaucher, type IIIC and is distinct from Gaucher disease and its other subtypes due to the presence of neuropathy and cardiovascular calcifications.

Description

Pseudo-Gaucher disease is a well-studied genetic disorder transmitted as an autosomal recessive trait. It has a wide variety of manifestations, involving a number of different body systems. It is classified as the most common lysosomal storage disease caused by an abnormal accumulation of lipid glucocerebroside within lysosomes and macrophages, affecting a wide range of organs and body systems including the nervous system and the immune system. It has traditionally been divided into three major types, based on significant differences in those manifestations. Since the mid-1980s, a handful of cases have been reported in patients with some Gaucher-like symptoms, but other symptoms—especially cardiovascular calcification—that appear to justify its

KEY TERMS

Aortic valve—Valve joining the left ventricle to the aorta in the heart.

Arrhythmia—Irregular heartbeat.

Autosomal recessive—Genetic trait that appears only when two copies of a mutated gene are present.

Calcification—Accumulation of calcium minerals on soft tissues, causing them to become hard and rigid.

Enzyme—A protein that catalyzes biochemical changes in the body without itself undergoing permanent change.

Genotype—Genetic constitution of an organism for any given characteristic.

Mitral valve—Valve joining the left ventricle and left atrium in the heart.

Phenotype—Observable characteristic or trait of an organism.

Prevalence—Number of individuals living with a particular illness within a particular population at any given time. Prevalence is often expressed in terms of the number of individuals per 100 or per 1,000 members of the population.

classification as a distinct form of genetic disorder, now called Gaucher disease type IIIC, or pseudo-Gaucher disease.

Genetic Profile

Pseudo-Gaucher disease is caused by one or more mutations on the *GBA* (glucosidase, beta; acid [includes glucosylceramidase]) gene, the same gene that is responsible for other forms of Gaucher disease. The *GBA* gene is responsible for production of the enzyme beta-glucocerebrosidase, which catalyzes the breakdown of a large lipid molecule, glucocerebroside, into glucose and ceramide, a simpler lipid molecule. More than 200 mutations in the *GBA* gene have been implicated in the development of various forms of Gaucher disease. A specific mutation in the same gene has also been found to be associated with the development of pseudo-Gaucher disease. That mutation occurs at position 409 with the substitution of a histidine amino acid for aspartic acid. Although the genotypes of the four forms of Gaucher disease, types I, II, III, and IIIC (pseudo-Gaucher) are similar, the phenotypes produced are very different for the first three categories and pseudo-Gaucher.

Demographics

The prevalence of pseudo-Gaucher disease is roughly 1 in 50,000 to 1 in 100,000 people worldwide, with type I having a higher incidence. Type I occurs more frequently in the Jewish population of central and eastern European decent, affecting roughly 1 in 500 to 1 in 1,000 people of this Jewish population.

Signs and symptoms

The distinguishing characteristic of pseudo-Gaucher disease, as opposed to other forms of Gaucher disease, is cardiovascular calcification, primarily of the aortic and mitral valves. Neurological dysfunction of the eyes, resulting in corneal opacity, and enlargement of the spleen has also been observed in a small number of cases. Other signs of pseudo-Gaucher disease include skeletal abnormalities and seizures. Type 3 Gaucher disease is also distinguished from other types of Gaucher disease because it is a juvenile, chronic, and more mild form.

Diagnosis

The presence of cardiovascular insufficiency and ocular opacity are initial indications of the possibility of Gaucher-like disease. Further standard cardiac tests, such as diastolic murmur, cardiac enlargement, and arrhythmia, may suggest the presence of cardiovascular disease. A confirmatory test for the disorder consists of a genetic test for the presence of a mutation at position 409 in the *GBA* gene.

Treatment and management

No treatments are available for the cure of pseudo-Gaucher disease. Heart valve replacement has been attempted for the most severe cases of valve calcification, but generally without success. Three Spanish sisters who received this surgery all died, at the ages of 13, 15, and 16. Other forms of treatment include enzyme replacement therapy (ERT), which has had some success for other forms of Gaucher disease but not for pseudo-Gaucher disease because ERT is not capable of effecting anything across the blood-brain barrier, and therefore does not alter the effect the disease has on the brain and central nervous system.

Prognosis

Prognosis is generally poor for pseudo-Gaucher disease, since no successful treatment for manifestations of the disorder has been developed. A number of individuals with the disorder have died during childhood or adolescence, though recent data have shown those diagnosed with pseudo-Gaucher disease to live into the teenage years or early adulthood. No steps can be taken to prevent the occurrence of pseudo-Gaucher disease among individuals

QUESTIONS TO ASK YOUR DOCTOR

- What tests are available for diagnosing pseudo-Gaucher disease?
- Have any treatments been developed for extending the life of individuals with the condition?
- What is the status of gene therapy research for possible use with carriers of the mutation GBA gene?
- What type of Gaucher disease do I have, and what is my prognosis?

who carry the characteristic genotype. Early detection of the disease may make possible early intervention that may prolong the life of an affected individual.

Resources

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ORGANIZATIONS

- National Gaucher Foundation, 61 General Early Dr., Harpers Ferry, WV 25425, (800) 504-3189, rhonda@gaucherdisease.org, <http://www.gaucherdisease.org/gaucher-disease-type2-type3.php>

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Pseudo-Hurler disease see **GM1-gangliosidosis**

Pseudoachondroplasia

Definition

Pseudoachondroplasia is moderately severe skeletal dysplasia characterized by disproportionate short stature, hypermobile joints, normal head size, and normal length and appearance at birth. Individuals with this condition are usually not diagnosed until early childhood. Complications of this disorder include early-onset arthritis of the weight-bearing joints and other orthopedic complications. This genetic disorder has autosomal dominant inheritance.

Description

Pseudoachondroplasia is a rare genetic skeletal dysplasia first described by Drs. Maroteaux and Lamy in 1959. It is sometimes also referred to as pseudoachondroplastic dysplasia and pseudoachondroplastic spondyloepiphyseal dysplasia and is one of more than 200 rare skeletal dysplasias. Skeletal dysplasias are a group of disorders that result from problems in bone growth and formation. The term "dwarfism" is losing favor to the more technical term of skeletal dysplasia. There are many causes of growth problems, including hormone imbalances, metabolic problems, and problems with bone growth.

Pseudoachondroplasia is one of the most common skeletal dysplasias. Individuals with pseudoachondroplasia have normal growth parameters (height and weight) at birth, and it usually is not until the second year of life that growth retardation becomes evident. During this phase, their body proportions resemble those of individuals with achondroplasia—the most common form of skeletal dysplasia. Because of this resemblance, this type of skeletal dysplasia was termed "pseudo" achondroplasia.

As the name implies, pseudoachondroplasia was once thought to be closely related to achondroplasia. However, geneticists have since learned otherwise. In appearance, individuals with pseudoachondroplasia share the same height as those with achondroplasia, but their head size is the same as that of average-size people, and they lack the distinct facial features characteristic of achondroplasia. Children with pseudoachondroplasia are usually not diagnosed until they are two or three years old when their growth parameters become abnormal. The most serious complications of pseudoachondroplasia are short stature, orthopedic problems, and early-onset osteoarthritis of the weight-bearing joints. Many individuals with pseudoachondroplasia experience significant joint pain and undergo multiple orthopedic surgeries and joint replacements.

Pseudoachondroplasia is easily recognizable. Individuals with pseudoachondroplasia have disproportionate short stature, a normal-sized head, normal facial features, joint laxity, and disproportionate shortening of their limbs. Most individuals with pseudoachondroplasia have a normal IQ. The early motor development of infants with pseudoachondroplasia is normal until the advent of walking when a waddling gait is often noted. Individuals with pseudoachondroplasia can have medical complications that range from mild to severe. Because of the differences in their bone structure and their joints, they are at increased risk to develop osteoarthritis at an early age (sometimes in their teens and usually by their 20s). They also have a small risk for neurologic problems caused by spinal cord compression due to abnormal vertebra and joint laxity.

The short stature of pseudoachondroplasia can be socially isolating and physically challenging. Most public places are not adapted to individuals of short stature, and this can limit their activities. Children and adults with pseudoachondroplasia can be socially ostracized due to their physical appearance. Many individuals erroneously assume that people with pseudoachondroplasia have limited abilities.

Genetic profile

Pseudoachondroplasia is caused by a mutation, or change, in the cartilage oligomeric matrix protein 3 gene (*COMP*) that is located on the short arm of chromosome 19 (19p13.1).

Genes contain the instructions that tell a body how to form. They are composed of four different chemical bases: adenine (A), thymine (T), cytosine (C), and guanine (G). When these bases are arranged in a specific order, they provide the instructions that a cell needs to form a protein. Every three bases codes for one amino acid. Amino acids are the building blocks of proteins.

The *COMP* gene provides the instruction for the formation of a particular protein that is made by cartilage cells and is then transported into the cellular matrix surrounding these cells. Cartilage plays a very important role in bone formation. Because of abnormalities in the formation of this protein, the protein cannot be transported out of the cell. This results in a deficiency of the protein in the cartilage matrix and a build-up of the protein within the cartilage cells. This leads to the development of pseudoachondroplasia. Because cartilage plays a role in the normal growth and development of bones, any problems with cartilage will lead to problems with bone growth.

Pseudoachondroplasia is caused by mutations in the *COMP* gene. One specific mutation accounts for approximately 30% of the cases of pseudoachondroplasia. The

COMP gene comprises 757 amino acids. In a normal (nonmutated) gene, amino acid 372 codes for aspartic acid. In most individuals with pseudoachondroplasia, this amino acid has been deleted. Other mutations have been detected in the *COMP* gene, most of which are small substitutions or deletions of base pairs.

Mutations in the *COMP* gene are inherited in an autosomal dominant manner. Every individual has two *COMP* genes: one from their father and one from their mother. In an autosomal dominant disorder, only one gene has to have a mutation for the person to have the disorder. Most individuals with pseudoachondroplasia are born to parents with average stature. Their pseudoachondroplasia is the result of a *de novo*, or new, mutation. No one knows the cause of *de novo* mutations or why they occur so frequently in pseudoachondroplasia. However, once a couple has had a child with pseudoachondroplasia, there is a 4% recurrence risk to have a second similarly affected child. This increased recurrence risk is due to germline mosaicism, or the chance that the *de novo* mutation is present in others of their sperm and egg cells.

An individual with pseudoachondroplasia has a 50% chance of passing on their mutated gene to their children. Often individuals with short stature will marry other individuals with short stature. If the partner of a person with pseudoachondroplasia also has an autosomal dominant inherited skeletal dysplasia, then there is a 25% chance that they will have a child with average stature, a 25% chance that they will have a child with one pseudoachondroplasia gene (a heterozygote), a 25% chance that their child will have the other autosomal dominant skeletal dysplasia (a heterozygote), and a 25% chance that a child will get a double dose of the gene for pseudoachondroplasia and the gene for the other skeletal dysplasia (a double heterozygote). Babies with two skeletal dysplasias (double dose) can be much more severely affected than babies with a single pseudoachondroplasia gene. Couples with skeletal dysplasias should seek genetic counseling to understand their exact risks before undertaking a pregnancy.

Demographics

The exact prevalence of pseudoachondroplasia is unknown, but it is estimated to occur in about 1 in 30,000 individuals. Pseudoachondroplasia affects males and females in equal numbers. Most individuals with pseudoachondroplasia are born to parents with average stature. This is due to a new mutation that occurs on the *COMP* gene of the child with pseudoachondroplasia.

Signs and symptoms

Individuals with pseudoachondroplasia have disproportionate short stature, normal-sized heads, limb

differences, and rhizomelic shortening of their limbs; rhizomelic means “root limb.” Rhizomelic shortening of the limbs means that those segments of a limb closest to the body (the root of the limb) are more severely affected. In individuals with pseudoachondroplasia, the upper arms are shorter than the forearms, and the upper leg (thigh) is shorter than the lower leg.

In addition to shortened limbs, individuals with pseudoachondroplasia have other characteristic limb differences. They have a limited ability to rotate and extend their elbows. They also have joint laxity, particularly of the hands, ankles, and knees. Because of this joint laxity, they can be bow-legged or knock-kneed and may have in-turned toes. Their hands and feet are short and broad, as are their fingers and toes. Their fingers and other joints are hyperextensible, or very flexible.

In addition to limb differences, individuals with pseudoachondroplasia have other characteristic skeletal differences. Because of malformed vertebra and lax ligaments, individuals with pseudoachondroplasia can have spinal problems, including kyphosis (hunchback), lordosis (swayback), and scoliosis.

Individuals with pseudoachondroplasia have normal facial features and a normal-sized head. This is one of the major features that differentiate pseudoachondroplasia from achondroplasia. Individuals with pseudoachondroplasia have shortening of their long bones. The average adult height of individuals with pseudoachondroplasia ranges from 32–52 in. (80–130 cm).

Diagnosis

Pseudoachondroplasia is diagnosed by a combination of physical exam, x-rays, and molecular testing. The characteristic findings of short stature and rhizomelic shortening of the limbs become apparent around two years of age and become more pronounced over time. In addition to being diagnosed by physical examination, individuals with pseudoachondroplasia have some specific bone changes that can be seen on an x-ray. A DNA blood test to look for mutations in the *x* gene may also help clarify the diagnosis.

Unlike other skeletal dysplasias, pseudoachondroplasia cannot be diagnosed by a prenatal ultrasound or sonogram because the characteristic changes in the bones and the growth delays do not appear until the child is two years of age.

The diagnosis of pseudoachondroplasia can be made prenatally by DNA testing if the mutation for that family has been characterized. A sample of tissue from a fetus is obtained by either chorionic villi sampling (CVS) or by amniocentesis. Chorionic villi sampling is generally done between ten and 12 weeks of pregnancy, and

amniocentesis is done between 14 and 18 weeks of pregnancy. Chorionic villi sampling involves removing a small amount of tissue from the developing placenta. The tissue in the placenta contains the same DNA as the fetus. Amniocentesis involves removing a small amount of fluid from around the fetus. This fluid contains some fetal skin cells from which DNA can be isolated. The fetal DNA is then tested to determine if it contains the mutation that is responsible for pseudoachondroplasia in that family.

Prenatal DNA testing for pseudoachondroplasia is not routinely performed in low-risk pregnancies. This type of testing is generally limited to high-risk pregnancies, such as those in which both parents have pseudoachondroplasia or one in which one parent has pseudoachondroplasia and the other parent has another autosomal dominant form of skeletal dysplasia. It is particularly helpful in determining if a fetus has received two dominant skeletal mutations. Infants who have inherited two autosomal dominant skeletal dysplasias may have very severe complications that may result in death.

DNA testing can also be performed on blood samples from children or adults. This is usually done as part of a genetic work-up to establish the exact form of skeletal dysplasia. Many skeletal dysplasias can be hard to differentiate from one another, and DNA testing can often clarify the diagnosis.

Treatment and management

There is no cure for pseudoachondroplasia. All children with pseudoachondroplasia should have their height, weight, and head circumference measured and plotted on growth curves specifically developed for children with pseudoachondroplasia. The most common medical complication is early-onset osteoarthritis and other orthopedic problems. Some patients experience significant pain that can be controlled by analgesics, although the effectiveness of various forms of analgesics has not been thoroughly studied in pseudoachondroplasia. Early-onset osteoarthritis is caused by malformations of the weight-bearing joints and deficient cartilage production. Approximately 50% of patients with pseudoachondroplasia will require hip replacements. By being aware of the potential medical complications and by taking some preventative measures, it may be possible to avoid or delay the onset of some of the long-term consequences of these complications.

Weight management is extremely important for an individual with pseudoachondroplasia. Excess weight can exacerbate many of the potential orthopedic problems, such as bowed legs, curvature of the spine, and joint and lower back pain. Excess weight can also contribute to sleep apnea problems. Development of good eating habits and appropriate exercise programs should

KEY TERMS

Cartilage oligomeric matrix protein gene—A gene that codes for a specific protein involved in the formation of cartilage.

Rhizomelic—Term meaning “root limb,” which refers to the disproportionate shortening of the upper part of a limb compared to the lower part.

be encouraged in individuals with pseudoachondroplasia. However, because of the potential for spinal cord compression, care should be used in choosing appropriate forms of exercise.

The social adaptation of children with pseudoachondroplasia and their families should be closely monitored. Children with visible physical differences can have difficulties in school and socially. Support groups such as Little People of America can be a source of guidance on how to deal with these issues. It is important that children with pseudoachondroplasia not be limited in activities that pose no danger. In addition to monitoring their social adaptation, every effort should be made to physically adapt their surroundings for convenience and to improve independence. Physical adaptations can include step stools to increase accessibility and lowering of light switches and counters.

The two treatments that have been used to try to increase the final adult height of individuals with pseudoachondroplasia are limb-lengthening and growth hormone therapy.

Limb-lengthening involves surgically attaching external rods to the long bones in the arms and legs. These rods run parallel to the bone on the outside of the body. Over a period of 18–24 months, the tension on these rods is increased, which results in the lengthening of the underlying bone. This procedure is long, costly, and has potential complications, including pain, infections, and nerve problems. Limb-lengthening can increase overall height by 12–14 in. (30.5–35.6 cm) in some skeletal dysplasias. It does not change the other physical manifestations of pseudoachondroplasia, such as the appearance of the hands and feet. This is an elective surgery, and individuals must decide for themselves if it would be of benefit to them. The optimal age to perform this surgery is not known.

Growth hormone therapy has been used to treat some children with pseudoachondroplasia. Originally, there was doubt about the effectiveness of this treatment because children with pseudoachondroplasia are not growth-hormone deficient. This doubt has proven to be

justified. While this treatment seems to have some success for individuals with other forms of skeletal dysplasia, at least one study has found that it actually decreases the height of children with pseudoachondroplasia. Growth hormone therapy is not recommended for pseudoachondroplasia.

Prognosis

The prognosis for most people with pseudoachondroplasia is very good. In general, they have minimal medical problems, normal IQ, and most achieve success and have a long life, regardless of their stature. The most serious medical barriers to an excellent prognosis are the orthopedic complications and early-onset arthritis that can limit the activities of an individual and cause significant pain. Most individuals with pseudoachondroplasia will have multiple orthopedic surgeries over their lifetime.

Successful social adaptation plays an important role in the ultimate success and happiness of an individual with pseudoachondroplasia. It is very important that the career and life choices of an individual with pseudoachondroplasia not be limited by preconceived ideas about their abilities.

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Human Growth Foundation, 997 Glencove Ave., Suite 5, Glenhead, NY 11545, (800) 451-6434, hgf1@hgfound.org, <http://www.hgfound.org>

Little People of America, 250 El Camino Real, Suite 211, Tustin, CA 92780, (714) 368-3689, info@lpaonline.org, <http://www.lpaonline.org>

Kathleen A. Fergus, MS, CGC

Pseudothalidomide syndrome see **Roberts SC phocomelia**

Pseudoxanthoma elasticum

Definition

Pseudoxanthoma elasticum (PXE) is an inherited connective tissue disorder in which the elastic fibers present in the skin, eyes, and cardiovascular system gradually become calcified and inelastic.

PXE was first reported in 1881 by Rigal, but the problem with elastic fibers was described in 1896 by Darier, who gave the condition its name. PXE is also known as Grönblad-Strandberg-Touraine syndrome and systemic elastorrhexis.

Description

The course of PXE varies greatly between individuals. Typically, it is first noticed during adolescence as yellow-orange bumps on the side of the neck. Similar bumps may appear at other places where the skin bends a lot, like the backs of the knees and the insides of the elbows. The skin in these areas tends to get thick, leathery, inelastic, and acquire extra folds. These skin problems have no serious consequences, and for some people, the disease progresses no further.

Bruch's membrane, a layer of elastic fibers in front of the retina, becomes calcified in some people with PXE. Calcification causes cracks in Bruch's membrane, which can be seen through an ophthalmoscope as red, brown, or gray streaks called angioid streaks. The cracks can eventually (e.g., in ten to 20 years) cause bleeding, and the usual resultant scarring leads to central vision deterioration. However, peripheral vision is unaffected.

Arterial walls and heart valves contain elastic fibers that can become calcified. This leads to a greater susceptibility to the conditions that are associated with hardening of the arteries in the normal aging population—high blood pressure, heart attack, stroke, and arterial obstruction—and, similarly, mitral valve prolapse. Heart disease and hypertension associated with PXE have been reported in children as young as four to 13 years of age. Although often appearing at a younger age, the overall incidence of these conditions is only slightly higher for people with PXE than it is in the general population.

Arterial inelasticity can lead to bleeding from the gastrointestinal tract and, rarely, acute vomiting of blood.

Genetic profile

PXE is caused by changes in the genetic material, called mutations, which are inherited in either a dominant or recessive mode. A person with the recessive form of the disease (which is most common) must

possess two copies of the PXE gene to be affected, and, therefore, must have received one from each parent. In the dominant form, one copy of the abnormal gene is sufficient to cause the disease. In some cases, a person with the dominant form inherits the abnormal gene from a parent with PXE. More commonly, the mutation arises as a spontaneous change in the genetic material of the affected person. These cases are called “sporadic” and do not affect parents or siblings, although each child of a person with sporadic PXE has a 50% risk to inherit the condition.

Both males and females can develop PXE, although the skin findings seem to be somewhat more common in females.

The actual genetic causes of this condition were not discovered until 2000. The recessive, dominant, and sporadic forms of PXE all appear to be caused by different mutations or deletions in a single gene called *ABCC6* (also known as *MRP6*), located on chromosome 16. Although the responsible gene has been identified, how it causes PXE is still unknown.

Genetic researchers have since identified mutations in a number of persons with PXE, most of whom have been found to have the recessive type. Affected individuals in these families had mutations in both copies of the gene and parents, who are obligate carriers, had a mutation in only one copy. Contrary to the usual lack of symptoms in carriers of recessive genes, some carriers of recessive PXE have been found to have cardiovascular symptoms typical of PXE.

Although the recessive type is the most common, there are also familial and sporadic cases that have been found to be caused by dominant mutations in the *ABCC6* gene.



Light micrograph of PXE. This disease causes the elastic fibers in the skin, eyes, and cardiovascular system to become calcified. (Biophoto Associates/Science Source)

Demographics

PXE is rare and occurs in about 1 in every 50,000 people in the general population. PXE is twice as common in females as in males.

Signs and symptoms

A wide range in the type and severity of symptoms exists between people with PXE. The age of onset also varies, although most people notice initial symptoms during adolescence or early adulthood. Often, the first symptoms to appear are thickened skin with yellow bumps in localized areas such as the folds of the groin, arms, knees, and armpits. These changes can also occur in the mucous membranes, most often in the inner portion of the lower lip. The appearance of the skin in PXE has been likened to a plucked chicken or Moroccan leather.

Angioid streaks in front of the retina are present in most people with PXE and an ophthalmologic examination can be used as an initial screen for the condition. Persons with PXE often complain of sensitivity to light. Because of the progressive breakdown of Bruch's membrane, affected persons are at increased risk for bleeding and scarring of the retina, which can lead to decreased central vision but does not usually cause complete blindness.

Calcium deposits in the artery walls contribute to early-onset atherosclerosis, and another condition called claudication, inadequate blood flow that results in pain in the legs after exertion. Abnormal bleeding, caused by calcification of the inner layer of the arteries, can occur in the brain, retina, uterus, bladder, and joints but is most common in the gastrointestinal tract.

Diagnosis

The presence of calcium in elastic fibers, as revealed by microscopic examination of biopsied skin, unequivocally establishes the diagnosis of PXE.

Treatment and management

PXE cannot be cured, but plastic surgery can treat PXE skin lesions, and laser surgery is used to prevent or slow the progression of vision loss. Excessive blood loss due to bleeding into the gastrointestinal tract or other organ systems may be treated by transfusion. Mitral valve prolapse (protrusion of one or both cusps of the mitral heart valve back into the atrium during heartbeat) can be corrected by surgery, if necessary.

Measures should be taken to prevent or lessen cardiovascular complications. People with PXE should control their cholesterol and blood pressure and maintain normal weight. They should exercise for cardiovascular

KEY TERMS

Angioid streaks—Gray, orange, or red wavy branching lines in Bruch's membrane.

Bruch's membrane—A membrane in the eye between the choroid membrane and the retina.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Claudication—Pain in the lower legs after exercise caused by insufficient blood supply.

Connective tissue—A group of tissues responsible for support throughout the body; includes cartilage, bone, fat, tissue underlying skin, and tissues that support organs, blood vessels, and nerves throughout the body.

Deletion—The absence of genetic material that is normally found in a chromosome. Often, the genetic material is missing due to an error in replication of an egg or sperm cell.

Dominant trait—A genetic trait where one copy of the gene is sufficient to yield an outward display of the trait; dominant genes mask the presence of recessive genes; dominant traits can be inherited from a single parent.

Elastic fiber—Fibrous, stretchable connective tissue made primarily from proteins, elastin, collagen, and fibrillin.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Mitral valve—The heart valve that prevents blood from flowing backward from the left ventricle into the left atrium. Also known as bicuspid valve.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Recessive trait—An inherited trait or characteristic that is outwardly obvious only when two copies of the gene for that trait are present.

health and to prevent or reduce claudication later in life. They should also avoid the use of tobacco, thiazide anti-hypertensive drugs, blood thinners like Coumadin, and nonsteroidal anti-inflammatory drugs like aspirin and

QUESTIONS TO ASK YOUR DOCTOR

- What is the meaning of the name “pseudoxanthoma elasticum”?
- What is the probability that this genetic disorder will be transmitted from parents to children?
- On what basis is pseudoxanthoma elasticum syndrome diagnosed?
- What ongoing medical attention is needed to monitor the progress of this disease?

ibuprofen. In addition, they should avoid strain, heavy lifting, and contact sports, since these activities could trigger retinal and gastrointestinal bleeding.

People with PXE should have regular eye examinations by an ophthalmologist and report any eye problems immediately. Regular check-ups with a physician are also recommended, including periodic blood pressure readings.

Some people have advocated a calcium-restricted diet, but it is not yet known whether this aids the problems brought about by PXE. It is known, however, that calcium restriction can lead to bone disorders.

Prognosis

The prognosis is for a normal lifespan with an increased chance of cardiovascular and circulatory problems, hypertension, gastrointestinal bleeding, and impaired vision. Now that the gene for PXE has been identified, the groundwork for research to provide effective treatment has been laid. Studying the role of the *ABCC6* protein in elastic fibers may lead to drugs that will improve or prevent the problems caused by PXE.

Genetic tests are now available that can provide knowledge needed to both diagnose PXE in symptomatic persons and predict it prior to the onset of symptoms in persons at risk. Prenatal diagnosis of PXE, by testing fetal cells for mutations in the *ABCC6* gene, can be done in early pregnancy by procedures such as amniocentesis or chorionic villus sampling. For most people, PXE is compatible with a reasonably normal life, and prenatal diagnosis is not likely to be highly desired.

Genetic testing to predict whether an at-risk child will develop PXE may be helpful for medical management. A child who is found to carry a mutation can be monitored more closely for eye problems and bleeding

and can begin the appropriate lifestyle changes to prevent cardiovascular problems.

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ORGANIZATIONS

PXE International, 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008, (202) 362-9599, info@pxe.org, <http://www.pxe.org>

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PTSD (post-traumatic stress disorder)

Definition

PTSD (post-traumatic stress disorder) is an anxiety disorder that develops as a result of exposure to traumatic event(s). Many different types of trauma can trigger PTSD, including sexual assault or abuse, combat, witnessing violence, terrorist attacks, natural disasters, serious injury or physical harm, or the threat of harm. Symptoms include startle responses, avoidance, nightmares, and/or sleep disturbances that continue for more than a month after the event. Researchers believe that genetic factors contribute about 20% to the risk of developing PTSD after experiencing trauma. There is much interest in identifying factors that affect PTSD susceptibility and that could be used, for example, in selecting combat personnel.

Description

PTSD was first defined as a diagnostic category by the American Psychiatric Association in 1980. It entered public awareness because of large numbers of affected combat veterans; however, it can be triggered by many types of traumatic events, including child abuse, plane or car crashes, bombings, or natural disasters such as earthquakes or floods.

PTSD results from a damaged or altered “fight-or-flight” response. This is a normal reaction to the threat of harm that prepares the body to protect itself by defense or avoidance. However, people with PTSD may continue to feel the fear or stress long after the danger has passed. Although changes in areas of the brain called the amygdala and the dorsal anterior cingulate cortex (dACC) are associated with PTSD, it is unclear whether these changes are causes or consequences. The amygdala and dACC are involved in fear and appear to be overactive in people who are susceptible to PTSD. The amygdala is involved in emotion, memory, and learning, including learning to fear (fear acquisition) and fear extinction when the threat has passed. The ventromedial prefrontal cortex (PFC) of the brain stores extinction memories and dampens the original fear response. “Hyperarousal” of these brain areas may contribute to the irritability and startle response that are symptoms of PTSD. Both genetic factors and experiences appear to contribute to this heightened activity. According to one model of PTSD, although characteristics of the amygdala and dACC contribute to PTSD susceptibility, following a traumatic event, changes occur in the PFC and its interactions with the hippocampus, a structure in the brain that is involved in memory formation. The PFC is involved in fear extinction, unlinking the signal from a threat once the threat is gone, and it helps sustain long-term extinction of the fear response. Studies suggest that in PTSD, the connection between these brain areas that extinguishes fear is impaired. This impairment may contribute to two other typical PTSD symptoms—the reliving of traumatic memories and the avoidance of anything or anyone that is a reminder of the traumatic event.

The development of PTSD appears to depend not only on the circumstances of the traumatic event but also on personal factors, including genetic factors. Several different genes have been directly associated with PTSD or with increased risk for PTSD or appear to interact with a history of childhood abuse to increase the risk of PTSD. Evidence also indicates that PTSD and other stress-related disorders may be associated with dysfunction of mitochondria—the energy-generating powerhouses of cells—or with epigenetic changes—chemical modifications to genes that do not change the DNA sequence of

the genetic material. The cell danger response (CDR) is a metabolic response of cells to a variety of threats, including psychological trauma, which are sensed by mitochondria and may persist in disorders such as PTSD after the threat is gone. Mitochondria have their own DNA (mtDNA). There are multiple copies of mtDNA in cells, and they have a high rate of mutation. As a result, mtDNA sequences can vary significantly, not only within an individual but even within single cells, and this can cause mitochondrial failure, which contributes to the CDR.

Childhood abuse and trauma are strong risk factors for stress-related disorders including PTSD. Childhood mistreatment, as well as PTSD, is associated with specific epigenetic changes that affect gene expression in the brain and other tissues. Childhood trauma, head injury, or other environmental factors may also affect brain growth, increasing the risk of PTSD in response to events later in life. Finally, personality and cognitive and social factors affect susceptibility to PTSD in response to trauma.

Genetic profile

Some genetic studies of PTSD have focused on genes that produce proteins involved in creating fear memories.

- Stathmin is a protein required for forming fear memories.
- Gastrin-releasing peptide (GRP) is a brain-signaling protein that is released during emotional events.
- There is a memory-enhancing variation of the gene encoding kinase C alpha, a protein that is important for the formation of emotional memories.
- A fear-enhancing version of the *5-HTTLPR* gene controls levels of serotonin—a neurotransmitter that affects mood.
- Low levels of a specific type of serotonin receptor appear to be associated with PTSD.
- A specific variant of a serotonin-transporter gene has been associated with increased risk for PTSD in women exposed to a traumatic event.
- The *ADCYAP1* gene, which produces pituitary adenylate cyclase-activating polypeptide, appears to be involved in stress responses. Variants in the receptor for this polypeptide have been linked to PTSD in women and increase stress following exposure to violence and the startle reflex in women and children.
- Other genes encoding receptors for stress hormones and immune-system signaling proteins have been linked to PTSD.

Researchers have identified links between certain variations in mitochondrial genes and full-blown PTSD. A variation in a single DNA base—called a single-nucleotide polymorphism (SNP)—that changes a single amino acid in the *MT-ATP8* gene that encodes subunit 8 of adenosine triphosphate (ATP) synthase, as well as an SNP in the *MT-ND5* gene that encodes subunit 5 of NADH dehydrogenase, have been associated with PTSD. The risk of PTSD increases with the increasing proportion of mitochondria that contain these genetic variants. Both ATP synthase and NADH dehydrogenase are involved in regulating the production of reactive oxygen species, which can increase mutation rates and may affect brain function, particularly in the PFC.

Epigenetic changes also appear to affect PTSD susceptibility. These changes, such as methylation (attachment of a methyl group, CH₃, to a DNA building block) can activate or silence gene activity to alter a protein produced in a cell. One study found that people with PTSD who were abused as children had distinct patterns of DNA methylation and gene activity (expression). Patients who had suffered childhood abuse had up to 12 times more epigenetic markers that affect gene expression compared to patients who were not maltreated as children. Furthermore, the study found that 98% of the changes in gene expression patterns differed between PTSD patients with and without a history of childhood abuse. In particular, patients who had experienced abuse had more changes in the expression of genes involved in nervous system development and immune system regulation; those without a history of abuse had more expression changes in genes associated with growth-rate regulation and cell death. Thus, PTSD may differ among people depending on whether they suffered childhood maltreatment.

Demographics

PTSD does not develop in most people who experience traumatic events. One study found that less than 2% of people exposed to a traumatic event developed full PTSD, although 8% developed partial PTSD. Nevertheless, PTSD can affect anyone at any age, especially combat veterans and survivors of physical devastation from war, natural disasters, or injuries and survivors of sexual, physical, or emotional abuse.

- More than 60% of men and 51% of women report having experienced at least one traumatic event, and 10% of men and 6% of women report four or more traumas.
- Every year, more than 1.25 million children of all ethnic and economic backgrounds in the United States, and at

KEY TERMS

Acute stress disorder (ASD)—An anxiety disorder similar to PTSD but with symptoms occurring immediately after a traumatic event and resolving within a month.

Amygdala—Any of the four basal ganglia in each cerebral hemisphere that are involved in triggering fear.

Cell danger response (CDR)—A metabolic response of cells to various types of threats.

Cognitive-behavioral therapy (CBT)—A type of psychotherapy that teaches people to recognize and change negative patterns of thinking and behavior.

DNA methylation—The addition of methyl groups (CH₃) to nucleotide bases of DNA to regulate gene expression.

Dorsal anterior cingulate cortex (dACC)—An area of the cerebral cortex that is involved in fear, mood disorders, and PTSD.

Epigenetic—A modification outside of the actual mutation of the DNA sequence, such as the addition of a methyl group.

Hippocampus—A part of the brain that is involved in learning and memory formation.

Hyperarousal—Symptoms of traumatic stress characterized by abnormally intense reactions, such as a heightened startle response.

Mitochondria—Organelles within the cell responsible for energy production.

Mitochondrial DNA (mtDNA)—A small set of genes in the mitochondria that are maternally inherited.

Prefrontal cortex (PFC)—The anterior gray matter of the frontal lobe of the brain that regulates complex cognition, emotions, and behaviors.

Serotonin—A neurotransmitter that transmits signals between nerve cells; low levels are associated with depression and PTSD.

Single-nucleotide polymorphisms (SNPs)—Single-nucleotide variant (SNV); a variation or point mutation in a single nucleotide building block of DNA.

least 40 million children worldwide, are abused or neglected.

- An estimated 10% of women and 5% of men will experience PTSD at some point in their lives.
- At some point in their lives, about 25% of Americans are involved in motor-vehicle accidents resulting in serious

injury, and an estimated 9% of survivors develop acute stress disorder (ASD) or PTSD.

- About 30% of Vietnam War veterans, 10% of veterans of the first Gulf War, and 15% of veterans of the wars in Iraq and Afghanistan have been diagnosed with PTSD.
- Survivors and bystanders of terrorist acts appear to be at particular risk for PTSD.
- Southeast Asians, especially refugees, have high rates of PTSD.
- Victims of violent crime, abused women and children, and victims of rape and female genital mutilation are at risk for PTSD.
- Some people can develop PTSD after a loved one experiences trauma or is harmed.
- Living in a depressed urban area or on a Native American reservation is a risk factor for PTSD.
- Boys—but not girls—residing in public housing in the United States who are subsequently moved to better neighborhoods experience increased rates of PTSD.
- One study found that almost 6% of people undergoing bereavement met the criteria for PTSD, especially if a loved one's death was sudden and unexpected.
- A history of mental illness is a PTSD risk factor.
- An estimated 1–2 surgical patients per 1,000 experience “anesthesia awareness” or “intraoperative recall,” in which they awake during surgery, and up to 70% of these people experience long-term stress, including PTSD, with rates five times higher than soldiers returning from Iraq and Afghanistan.
- A 2013 study found that 25% of survivors of a transient ischemic attack (TIA) or stroke develop PTSD within a year, and one in nine chronic PTSD.

Signs and symptoms

PTSD varies from minor to severe. Symptoms of ASD occurring immediately following a traumatic event and lasting less than a month are considered normal. PTSD symptoms may not develop for weeks, months, or even years after a traumatic event, but they usually begin within three months and last more than a month. Signs and symptoms of PTSD can include the following:

- flashbacks: repeatedly reliving the trauma, including physical symptoms of stress such as sweating or a racing heart
- frightening thoughts
- nightmares
- avoidance of reminders of the traumatic experience
- emotional numbness
- depression, guilt, or one or more anxiety disorders
- loss of interest in previously enjoyable activities

- difficulty remembering the traumatic event
- ongoing symptoms of hyperarousal, such as being easily startled, tenseness, anger, sleep difficulties, poor appetite, and/or poor concentration
- substance abuse
- suicidal behaviors

Symptoms of PTSD in young children can include the following:

- bedwetting
- being unable to talk or forgetting how to talk
- acting out the frightening event in play
- clinging to a parent or other adult

PTSD symptoms in older children and teens are usually similar to those in adults, but they may include disruptive, disrespectful, or destructive behaviors or thoughts of revenge.

Diagnosis

PTSD is diagnosed by a mental-health professional, such as a psychologist or psychiatrist, who may use psychological inventories or questionnaires. Diagnosis is based on the occurrence of all of the following symptoms lasting at least one month:

- at least one symptom of reliving the experience
- at least three avoidance symptoms
- at least two hyperarousal symptoms
- symptoms that interfere with daily life, including school or work, social relationships, and accomplishing important tasks

Treatment and management

PTSD should be treated by a mental-health provider experienced in dealing with the disorder. Different patients respond differently to various treatments, so multiple types of treatment may have to be tried. Concurrent problems—such as an abusive relationship, panic disorder, depression, or substance abuse—must be treated simultaneously. Traditional PTSD treatments include the following:

- antianxiety and sleep medications and antidepressants called selective serotonin reuptake inhibitors (SSRIs)
- individual psychotherapy or “talk” therapy
- group therapy
- support groups
- couples therapy
- neurofeedback or electroencephalographic (EEG) biofeedback
- specially designed video games
- support from family and friends

QUESTIONS TO ASK YOUR DOCTOR

- Do you think I have PTSD?
- What are the diagnostic criteria for PTSD?
- What treatment(s) do you recommend?
- Are there genetic screens for susceptibility to PTSD?

Cognitive-behavioral therapy (CBT) is often effective for PTSD. Cognitive restructuring therapy aims to help people process or make sense of bad memories. Stress inoculation therapy teaches methods for reducing anxiety. Exposure therapy or cognitive-processing therapy is a relatively new and often effective treatment for PTSD arising from recent trauma. The behavioral psychologist has the patient repeatedly recall and confront the traumatic event. With each recollection, the memory is edited through memory reconsolidation, and the details gradually become uncoupled from anxiety and panic attacks by a process called habituation. Repeated sessions may lead to extinction of the memory. However, exposure therapy is only effective for recent memories.

Prognosis

The prognosis for PTSD varies. Some people recover within six months, whereas others have symptoms lasting much longer or developing into a chronic condition.

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ORGANIZATIONS

- National Center for Posttraumatic Stress Disorder, (802) 296-6300, ncptsd@va.gov, <http://www.ptsd.va.gov>
- National Human Genome Research Institute, National Institutes of Health, Bldg, 31, Rm. 4B09, 31 Center Dr., MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, (301) 402-2218, <http://www.nhgri.nih.gov>
- National Institute of Mental Health, Science Writing, Press & Dissemination Branch, 6001 Executive Blvd., Rm. 8184, MSC 9663, Bethesda, MD 20892-9663, (301) 443-4513 or (866) 615-6464, (301) 443-4279, NIMHinfo@nih.gov, <http://www.nimh.nih.gov>
- U.S. Department of Veterans Affairs, 810 Vermont Ave. NW, Washington, DC 20420, (800) 273-8255, <http://va.gov>

Margaret Alic, PhD

Pulmonary arterial hypertension

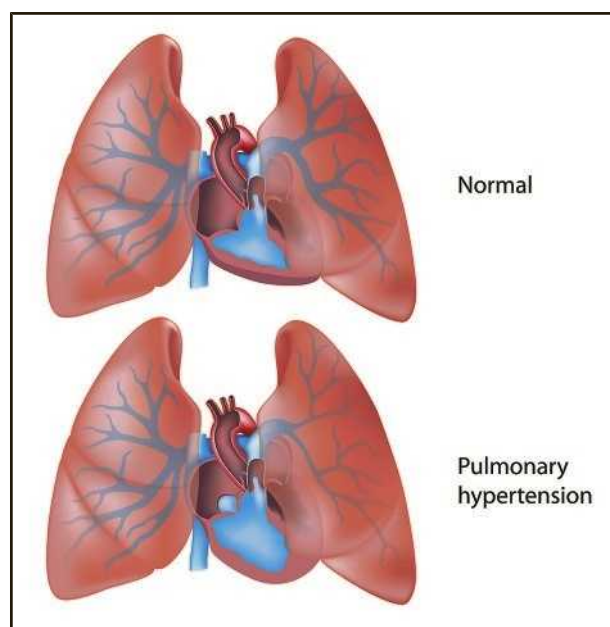
Definition

Pulmonary arterial hypertension, also known as primary pulmonary arterial hypertension or familial pulmonary arterial hypertension (FPAH) when inherited, is a progressive disorder with abnormally high blood pressure that occurs in the pulmonary artery. This is due to narrowing and thickening of small pulmonary vessels from a genetic mutation. The pulmonary artery is the main artery, or blood vessel, that carries blood from the heart to the lungs. Pathology such as this leads to a decrease in cardiac output, followed by right-side heart failure and then death.

PAH may be idiopathic, meaning the type of pulmonary hypertension that occurs in people with no known family history of the disorder. In the past, PAH often was referred to as sporadic primary pulmonary hypertension.

Description

Pathology in the lungs that lead to pulmonary artery hypertension were first described in 1891. Changes occur that cause the small blood vessels in the lungs to become



Pulmonary hypertension is a type of high blood pressure that affects arteries in the lungs and heart. (Alila Medical Media/Shutterstock)

too narrow. When the vessels narrow, blood cannot travel through the lungs. This causes the heart to work harder to try to pump blood into the lungs. Eventually, the heart muscle weakens and loses its ability to pump effectively. Eventually, the heart may fail.

David Dresdale first noticed in 1954 that people in certain families were getting this uncommon disease. After identifying a mother, her sister, and a son with the same symptoms, other physicians began identifying families with the disease. In 1984, Jim Loyd and John Newman contacted patients and their family members to identify new cases. Their work eventually led to linkage studies.

Due to mutations in the genes that code for proteins responsible for the normal growth of smooth muscle that make up the walls of arteries, these arteries do not grow properly and therefore do not function properly.

Genetic profile

The genetic change linked to most families is due to an autosomal dominant pattern of inheritance for an alteration in the *TGF- β* (transforming growth factor beta) genes, which are important in the growth and proliferation of many different types of cells. These genes include *BMPT2* and *ENG*. *BMPT2* gene is located on chromosome 2 and helps regulate cell growth in the walls of the lungs' small arteries. Individuals receive a set of genes from each parent, so each individual receives a pair of

BMPT2 protein genes. If the copy of the *BMPT2* gene received from the mother or father is mutated, the child can develop PAH. As of 2015, studies had reported additional possible mutations that may lead to earlier and/or more severe forms of PAH and other genes that may contribute to PAH. These genes include but are not limited to *CAV1*, *EIF2AK4*, and *KCNK3*.

Researchers have identified more than 140 different mutations in the *BMPT2* gene that cause FPAH. Of the total number of cases of PAH, 75% of them are said to be due to a heterozygous mutation of this gene, and the remaining 25% is a sporadic mutation (not inherited). About one-half of these mutations change how the protein receptor forms, which reduces the amount of *BMPT2* protein in the cells. Others keep the receptor from reaching the cell surface or affect its structure so that the receptor cannot receive or send signals that help pulmonary artery wall growth.

Some people with PAH have major mutations in the *BMPT2* gene that have not been identified yet through gene sequencing. The likelihood that a person who has a *BMPT2* mutation will develop PAH is about 20%, but this likelihood varies among families. It is possible that *BMPT2* mutation is associated with genetic anticipation. This is a pattern in which a familial disease worsens with each generation.

In addition to the *BMPT2* mutation, scientists have discovered that some people with *ALK1* and *ENG* mutations, which cause Rendu-Osler-Weber syndrome, also are subject to pulmonary arterial hypertension.

Demographics

As of 2015, roughly 1,000 new cases of pulmonary arterial hypertension were diagnosed in the United States each year, and about one to three cases per one million people occurred throughout the world each year. Of these, about 15% could be attributed to the familial form. Yet PAH is not common; it occurs in only 1 in 100,000 to 1 in 1 million people. Women are affected 1.7 times as often as men, and most women are diagnosed between age 20 and 40. Race does not affect risk for this disease.

Signs and symptoms

Idiopathic pulmonary artery hypertension has no known cause, but several other conditions may be associated with it. PAH has been linked to an inherited genetic change, or mutation. There also is evidence to suggest that something happens to trigger PAH in a person who has the genetic markers and is susceptible to the disorder.

The increased pressure from the narrowed arteries in the lungs causes symptoms related to the heart and lungs.

Most people with PAH experience shortness of breath during exercise or other exertion. The other most common sign of pulmonary artery hypertension is fainting. As the condition becomes worse, the person may notice dizziness, chest pain, a racing pulse, and swelling of the ankles or lower legs. Some people even notice that their lips or skin turn a bluish color and notice increased weakness and fatigue.

Diagnosis

The symptoms of PAH and idiopathic pulmonary artery hypertension are similar to other common heart and lung conditions, including asthma, pneumonia, chronic obstructive pulmonary disease, and left heart failure. Because of this, PAH may be overlooked and difficult to diagnose, especially without information on family history.

Examination

During an examination, a physician will look for the symptoms and signs of pulmonary artery hypertension. For instance, the physician will use a stethoscope to listen to the heart valves and for a particular type of heart murmur that might indicate this condition instead of other heart and lung diseases. Other possible signs noted on the physical examination include swelling of the ankles and liver enlargement. A thorough medical history that includes family history of heart and lung disease provides clues to the diagnosis.

Tests

Usually, the physician will order a blood test to check oxygen levels in the blood, kidney and liver function, and for other possible causes of the symptoms, such as thyroid problems. These tests are not final diagnostic signs but tools to help lead to a diagnosis of FPAH.

Procedures

There are a number of procedures that might help lead to a diagnosis of FPAH, including the following:

- **Electrocardiogram.** A physician might use an electrocardiogram, or ECG, to look for changes that indicate thickening in the right side of the heart. Electrodes are stuck to the skin of the chest area and a recording of the electrical impulses is made on a machine.
- **Pulmonary function test.** This test is used to measure how much air the lungs can hold and exchange. The patient is asked to breathe in and hold the breath and then breathe out fast and hard. The test can be stressful but is helpful in gaining clues about how the lungs function and what might be causing the problems with the lungs' function.

KEY TERMS

BMPR2—Bone morphogenetic protein receptor 2; it is the gene on which a mutation occurs that is most responsible for cases of familial pulmonary arterial hypertension.

Hypertension—Abnormally high blood pressure in an artery.

Mutation—A change in a gene.

Pulmonary—Relating to the lungs; the pulmonary artery carries blood from the heart to the lungs.

- **Chest radiography.** A chest x-ray may not show signs of PAH but may be the first imaging examination the physician orders to look at the lungs. Imaging gives clues, such as enlargement of the right ventricle, that help diagnose PAH. The radiograph might show clues of other lung disease, which helps physicians decide causes of symptoms. There is exposure to a small amount of radiation.
- **Echocardiogram or Doppler echocardiogram.** This form of imaging uses sound waves instead of x-rays to create an image. The sonographer places a small transducer on the patient's chest to obtain images of the heart's chambers, the thickness of the wall of the right ventricle, and the heart's structure. Doppler echocardiograms can also measure blood flow and arterial pressure. Normally, the patient lies down for an echocardiogram. But the physician may want a measure of arterial pressure during exercise. In this case, the patient is asked to ride a stationary bicycle, and measurements of pressure are obtained while the patient is exercising. Echocardiograms are noninvasive, meaning they do not puncture the skin, and the sound waves are safe.
- **Computed tomography (CT) scan.** This technology uses x-rays that rotate around the body and take images that are like slices of a small part of the body being studied. Through the use of a computer and software, the images can be reconstructed to show 3-D views. They can provide great detail on changes in the right atrium and right ventricle. CT scanning is noninvasive, although it involves use of radiation.
- **Magnetic resonance imaging (MRI).** This technology uses very powerful magnets that rotate around the body to produce images in detail, especially soft tissues. MRI can help provide enough detail to measure pulmonary artery pressure. The procedure is not invasive and does not involve radiation but is more expensive than chest x-rays or CT scanning.
- **Cardiac catheterization.** This procedure can help directly measure pulmonary artery pressures to exclude other

causes. A physician who specializes in heart disease or a specially trained radiologist will guide a catheter, or long, flexible tube, into the pulmonary artery. The physician makes a tiny incision, usually in the groin area, and guides the wire up to the right side of the heart with the help of a monitor. This is an invasive procedure, but it is relatively safe with minimal pain, bleeding, or recovery time. It is the standard test used to confirm pulmonary artery hypertension.

- Lung biopsy. In rare cases of pulmonary artery hypertension, a lung biopsy may be needed to determine the cause of a patient's symptoms.

Other tests and procedures also may be used to help a physician diagnose pulmonary arterial hypertension and to determine that the disorder is caused by an inherited genetic mutation. Diagnosing FPAH involves ruling out other causes of a patient's symptoms. A classic example is the six-minute walk test, which measures an individual's ability to breathe while exercising. The person suspected of having FPAH may be asked to walk for up to six minutes and the distance the patient can complete in that time will be recorded. The actual tests used to help diagnose PAH vary depending on a patient's symptoms, knowledge of family history, age, and other factors.

Genetic testing

If a physician suspects that a patient has PAH, the patient may have genetic testing. A blood sample will be drawn and used to search for *BMPR2* mutations. The mutation is detected in about 80% of people with PAH. Genetic testing for *BMPR2* also may be used to predict if an adult family member is at risk for developing PAH. Guidelines suggest that family members of patients with PAH receive genetic testing for the disorder and genetic counseling when available. Generally, experts do not recommend genetic testing for PAH in children. The Pulmonary Hypertension Association maintains a list of centers that offer genetic testing and professional counseling for patients with pulmonary arterial hypertension and their families.

Treatment and management

Traditional

There is no cure for PAH but there are a number of options to treat the symptoms. A physician may prescribe drugs or therapies to help reduce the workload on the heart. Patients may need oxygen therapy as their disease progresses. Genetic testing and counseling may help guide family members of individuals with the mutation or support early clinical testing in family members. People who suspect or know they have PAH should avoid using certain medications that are known to increase risk of pulmonary artery hypertension, such as certain appetite-suppressant

QUESTIONS TO ASK YOUR DOCTOR

- What new treatments are available for the disorder?
- What can I do to slow the progression of the disease?
- Whom should I tell in my family so that they can be cautious or tested?

medications. They also should avoid use of cocaine, amphetamines, and related compounds. Some studies suggest that hormone replacement therapy for women and pregnancy may increase risk of onset of PAH.

Risk factors

Although there are risk factors for pulmonary arterial hypertension, the only risk factor for the familial form is to have the disease run in one's family, that is, to have genetic predisposition to the disease. By 2000, scientists had identified the genetic marker responsible for most cases of PAH.

Drugs

Endothelin receptor antagonists can control high levels of a hormone, which helps control blood flow and cell growth in the body's blood vessels. Phosphodiesterase-5 inhibitors help to relax muscles and reduce abnormal cell growth. Prostacyclins help relax blood vessels and prevent blood clots. Calcium channel blockers, diuretics, and anticoagulants may be prescribed to help prevent complications of PAH. Nitrous oxide (NO) therapy may also be a treatment option, as NO helps increase the diameter of the vessel via vasodilation, helping to get blood and oxygen to the tissues of the body more easily. The use of prostacyclins, however, is to date the most effective therapy for PAH. Researchers conduct clinical trials on a regular basis to test new therapies especially with genome sequencing giving light to the pathogenesis of many genetic disorders such as this.

Alternative

Potassium (20 mg per day) may help improve the heart muscle's ability to contract. Antioxidants such as vitamin E and vitamin C strengthen the immune system and may help protect the heart. Acupuncture may support traditional treatment by improving circulation.

Home remedies

Steam, especially with drops of essential oils, in a humidifier, vaporizer, or atomizer can stimulate respiration and circulation.

Prognosis

The prognosis for individuals with FPAH is poor. Although in rare instances, a person can die suddenly after a diagnosis and another can live decades, most people with the disorder become worse gradually. The average survival rate after diagnosis is 2.8 years.

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ORGANIZATIONS

American Lung Association, 55 W. Wacker Dr., Suite 1150, Chicago, IL 60601, (800) 586-4872, <http://www.lungusa.org>
Pulmonary Hypertension Association, 801 Roeder Rd., Suite 1000, Silver Spring, MD 20910, (800) 748-7274, PHA@PHAssociation.org, <http://www.phassociation.org>

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Pyloric stenosis

Definition

Pyloric stenosis is caused by an enlargement of the pyloric sphincter muscle, which blocks the passage of food from the stomach to the intestines. This condition results in projectile vomiting, weight loss, and dehydration.

Description

Pyloric stenosis occurs due to enlargement of the pyloric sphincter, which is the ring of muscle at the outlet of the

KEY TERMS

Pyloric sphincter—Circular smooth muscle found at the outlet of the stomach.

Stenosis—The constricting or narrowing of an opening or passageway.

Ulcer—Inflammatory lesion of the mucous-like tissue in the stomach.

stomach that helps to control the emptying of food into the small intestine, where the digestion process continues. When the muscle cells of the pyloric sphincter become enlarged, the opening between the stomach and the small intestine (stenosis) enlarges, which blocks that passageway and causes food to be pushed back into the stomach.

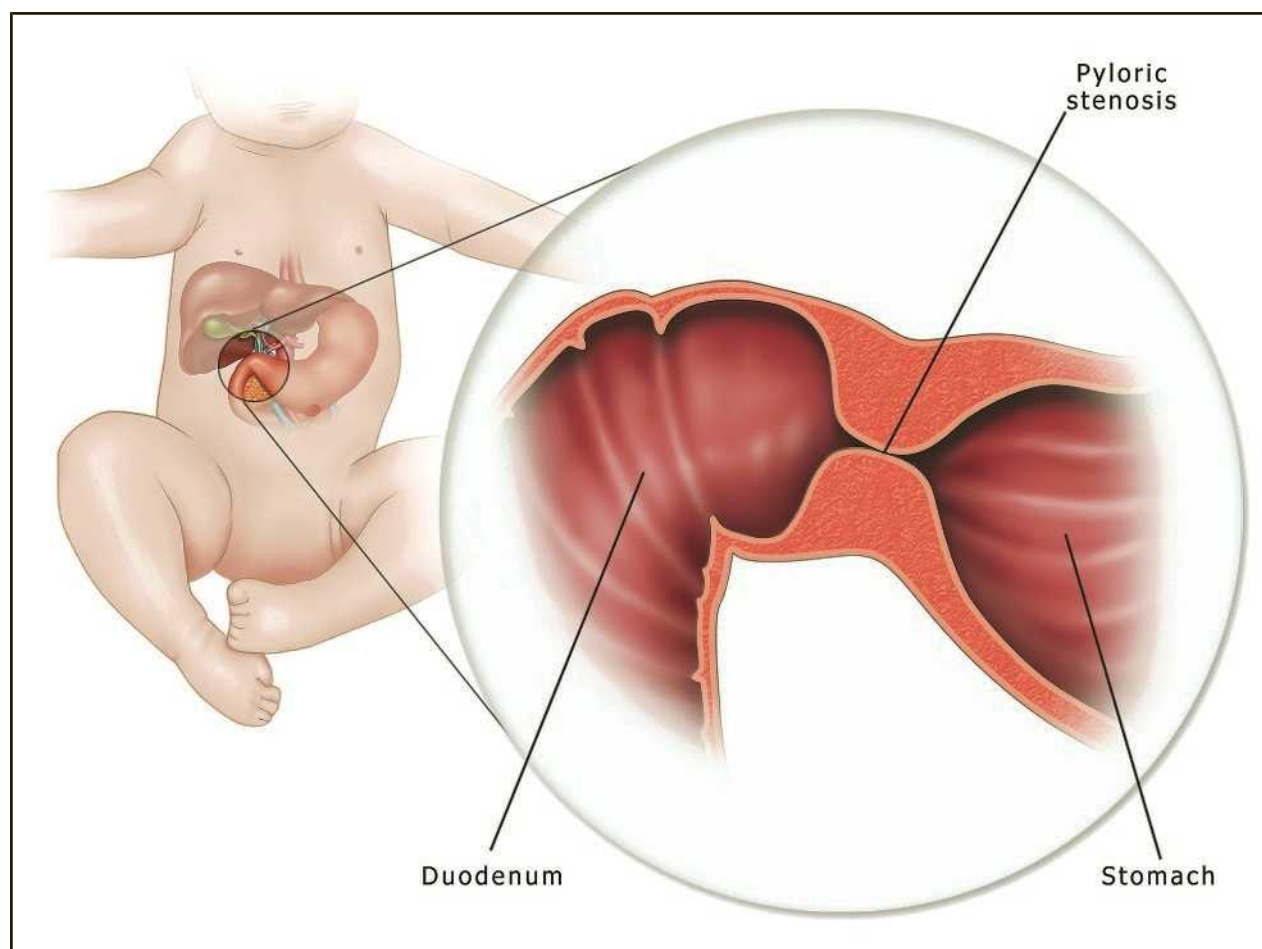
Symptoms of pyloric stenosis typically appear two to six weeks after birth. In rare cases, it occurs in older adults, and when it does, it results from scarring from a chronic ulcer or hardening of the tissue at the outlet of the stomach. Alternate names associated with the disorder are hypertrophic pyloric stenosis and infantile hypertrophic pyloric stenosis. This entry will primarily focus on infantile pyloric stenosis.

Genetic profile

The exact cause of infantile pyloric stenosis is unknown. It appears to result from both environmental and genetic factors. Pyloric stenosis aggregates in families, and both siblings in identical twin pairs are more likely to have the condition than non-identical twins. Parents with pyloric stenosis are more likely to have children with the condition. Parents with one child with the condition have a higher risk for having another child with the condition, which suggests that genetic factors may predispose a child to pyloric stenosis.

It appears that there are many different genes involved in the development of pyloric stenosis. Pyloric stenosis is found in many different genetic conditions. Genetic studies have found possible associations between many different genes and pyloric stenosis. These genes each appear to increase the risk of this condition only slightly.

There are also environmental factors that appear to increase the risk of pyloric stenosis in infants. For example, use of macroline antibiotics such as erythromycin, early in pregnancy or in young infants, significantly increases the risk of pyloric stenosis. Being first-born, cesarean section delivery, preterm birth, and being bottle fed are also associated with the development of pyloric stenosis.



The opening from the stomach to the duodenum (the first part of the small intestine) is called the pylorus. Abnormal narrowing (stenosis) of this area is called pyloric stenosis (shown in inset). This is a condition that mostly affects babies, and results in projectile vomiting. Atropine can be used to treat the condition, but surgery is often needed in a procedure known as a pyloromyotomy. (Maurizio De Angelis/Science Source)

The association of erythromycin and pyloric stenosis may be related to the function of a protein called motilin produced in the small intestine. Motilin stimulates the contraction of muscles in the gastrointestinal system (gut). It binds to the motilin receptor in order to function. Erythromycin is a motilin receptor agonist, which means that it activates the receptor, which in turn activates motilin. This activity stimulates the pyloric sphincter muscle to contract repeatedly, which can cause it to enlarge, resulting in pyloric stenosis.

Demographics

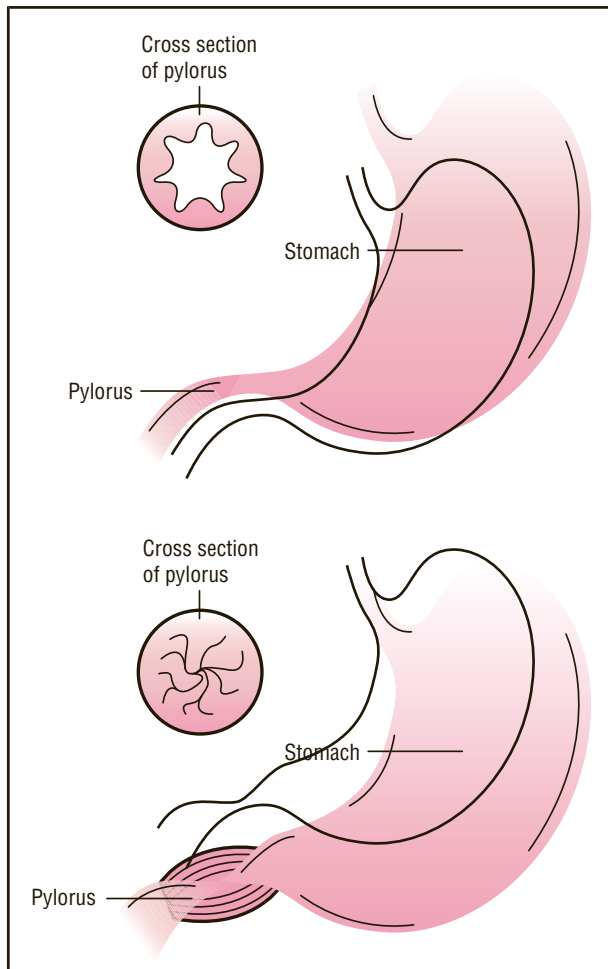
About three out of every 1,000 babies born in the United States develop pyloric stenosis. It usually appears within three to four weeks after birth and rarely appears after three months. Pyloric stenosis affects males three to four times more often than females and appears to

occur more commonly in white people of northern European ancestry. It is, also more common in the first-born child. The risk to siblings, children and cousins of females with the condition is higher than for relatives of males with the condition.

Signs and symptoms

Symptoms include the following:

- Vomiting after feeding. Vomiting may become projectile (expelled with force), and vomit may have a “coffee ground” color. Vomit does not contain stomach bile, which is acidic and a brownish-green color. Bile-colored vomit would suggest that the infant has a condition other than pyloric stenosis.
- Olive-sized abdominal mass. A mass about the size of an olive may be felt in the upper abdomen. The mass should be hard, mobile, and non-tender.



These diagrams show the cross section of a normal pylorus in relation to a stomach with pyloric stenosis where the pylorus has become extremely narrowed. Constriction of the pylorus results from enlargement of the muscle surrounding it. (Gale)

- Pylorospasm (a spasm of the pyloric muscle may occur due to increased motility)
- Persistent hunger
- Dehydration
- Constipation
- Weight loss
- Decreased urination
- Rhythmic contraction of the stomach muscle (peristalsis)
- Irritability
- Prolonged sleepiness or sluggishness

Diagnosis

Pyloric stenosis is first diagnosed through a medical history and physical assessment. A palpable mass, the

size of an olive, in the upper abdominal area usually suggests a diagnosis of pyloric stenosis. When physical findings are inconclusive, an abdominal ultrasound or barium study may be performed to confirm diagnosis. An ultrasound, the preferred method of confirmation, is a noninvasive study that uses high-frequency sound waves to view internal structures of the body. A barium study involves the ingestion of a radiographic dye. The movement of the dye through the gastrointestinal (GI) tract can be followed by fluoroscopy or x-ray studies. The upper GI series may be an effective step in confirming pyloric stenosis. This test consists of aspirating (withdrawal of fluid) and measuring gastric contents. The amount of aspirated contents is indicative of pyloric stenosis; and studies have demonstrated this method to be a reliable diagnostic tool.

In adults with symptoms of pyloric stenosis, a barium swallow study is used to diagnose the disorder. X-rays are taken of the abdominal structures after the ingestion of the barium radioisotope (a radioactive form of a chemical element).

Treatment and management

Pyloric stenosis is usually treated by a surgical pyloromyotomy. The procedure involves making an incision into the pyloric muscle and spreading the walls of the muscle apart. This allows the membrane layer of the stomach to push up through the incision and relieve the blockage.

Blood analysis should be performed before surgery and intravenous fluids should be given to correct electrolyte (e.g., sodium, potassium, calcium) imbalances and rehydrate infants. Following surgery, the infant should start on an oral electrolyte solution such as Pedialyte. Feedings will be gradually increased until the infant is tolerating 2–3 oz. (60 ml) of breast milk or formula without complications. The stomach needs time to heal; therefore, vomiting due to increased feedings is common. Infants are usually discharged 24–48 hours following surgery. It has been suggested that rapid advancement of the strength and volume of feedings is effective and may allow for quicker discharge from the hospital.

Gastric peroral endoscopic myotomy surgery (G-POEM) has recently been used to treat pyloric stenosis. It is a less-invasive surgery that takes only 14 minutes rather than the two hours that pyloromyotomy takes. G-POEM involves applying an electrical current to the pyloric sphincter muscle, which helps to increase the passage of food from the stomach to the small intestine. This surgery is guided by endoscopy, which involves inserting a flexible tube with a camera at the end through the

QUESTIONS TO ASK YOUR DOCTOR

- How does pyloric stenosis affect the physiology of a child with the disorder?
- At what age, and by what means, is this disorder diagnosed?
- What treatments are available for pyloric stenosis, and how successful do those treatments tend to be?
- What is the prognosis for a child diagnosed with pyloric stenosis?

abdomen. It only requires a small hole, as compared to surgical pyloromyotomy, which requires a large incision.

Adults being treated for pyloric stenosis usually have a stomach tube inserted into the muscle that remains in place after surgery.

Recurrence of pyloric stenosis after surgery is rare. There has been no occurrence of conditions later in life related to the occurrence of pyloric stenosis during infancy.

Prognosis

The prognosis of pyloric stenosis is very good for those who are diagnosed early and treated with surgery. Life expectancy of infants diagnosed with pyloric stenosis is the same as that of the average individual. Parents should contact a doctor if pyloric stenosis is suspected.

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Pyruvate carboxylase deficiency

Definition

Pyruvate carboxylase deficiency (PCD) is a rare non-sex-linked (autosomal) disorder that results from an insufficient amount of the enzyme pyruvate carboxylase. This disorder is inherited as a recessive trait and it is known to be caused by more than one different mutation in the same gene (allelic variants).

Description

There are two recognized types of pyruvate carboxylase deficiency: neonatal PCD (type B) and infantile-onset PCD (type A). Neonatal PCD is associated with a complete, or near complete, inability to produce pyruvate carboxylase. Infantile-onset PCD is associated with a chemical change in the pyruvate carboxylase enzyme that prevents this slightly different chemical from functioning as efficiently as the normal pyruvate carboxylase enzyme.

In order for the cells of the body to function properly, they must have energy. This energy comes in the form of the chemical ATP. ATP is primarily produced by

breaking down carbohydrates and blood sugar (glucose) molecules. To begin the process of converting glucose and carbohydrates into usable energy, these molecules are first converted into pyruvate molecules. Once pyruvate molecules have been formed, one of two things will happen: if more energy is required by the cell, the molecules will be further broken down into ATP; or, if no additional energy is needed by the cell, the pyruvate molecules will be put back together to reform a glucose molecule.

These transformations of pyruvate are accomplished primarily by two enzymes: pyruvate dehydrogenase (PDH), an enzyme that begins the breakdown of the pyruvate into ATP, and pyruvate carboxylase, an enzyme that begins the chemical process to reform glucose molecules. The reformation of glucose from pyruvate is a vital step in cellular metabolism. It allows carbohydrate molecules to be converted into a more readily usable form (glucose). Glucose is not only easier to break down into the energy required by the cells, but it is also more able to be transported through the bloodstream than most other fuel sources. This is particularly important because certain cells (primarily those of the brain and nervous system) cannot break down larger molecules; they must get their energy directly from glucose.

Pyruvate carboxylase is, in effect, part of the “off switch” for the production of ATP from pyruvate. After a cell has received the amount of ATP it requires, it is the job of pyruvate carboxylase to reconvert the excess pyruvate molecules in that cell back into glucose molecules for storage or transport to another part of the body where they may be needed. Any molecules that are not put back together will degrade into lactic acid. This lactic acid will either be released into the bloodstream or it will build up in the tissues. The build-up of lactic acid in the muscle tissues and red blood cells is normal during strenuous exercise. However, the accumulation of lactic acid in other tissues without exercise or without oxygen deprivation is symptomatic of an underlying problem in the normal metabolism of the cells.

People with PCD have either a complete inability or a severely limited ability to produce pyruvate carboxylase. Since these individuals cannot produce the amounts of this enzyme required to form glucose from pyruvate, this pyruvate is converted instead into lactic acid, which builds up in the cells. Additionally, since glucose cannot be adequately formed within the body of a pyruvate carboxylase-deficient individual, all the glucose required by the body must be ingested. This causes a glucose shortage that leads to low blood sugar (hypoglycemia) and a progressive degeneration of the tissues, with the

KEY TERMS

Allelic variants—A disease is said to have allelic variants when different mutations in the same allele result in identical, or nearly identical, symptoms. An allele is the combined locations of a gene on the two paired chromosomes that contain this gene.

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Biotin—A growth vitamin of the vitamin B complex found naturally in liver, egg yolks, and yeast.

Enzyme efficiency—The rate at which an enzyme can perform the chemical transformation that it is expected to accomplish. This is also called turnover rate. Individuals affected with type A PCD produce an enzyme that is much slower than the normal pyruvate carboxylase enzyme.

Necrotizing encephalomyelopathy—A progressive degeneration of the brain and central nervous system. This condition is fatal in nearly all individuals affected with type A pyruvate carboxylase deficiency.

Pyruvate carboxylase—The enzyme that is responsible for the first step in the conversion of pyruvate molecules into glucose molecules. Individuals with Type A PCD produce an highly inefficient form of pyruvate carboxylase. Individuals with Type B PCD either completely lack the ability to produce this enzyme, or they cannot produce it in sufficient quantities to sustain life.

most profound effects observed in the brain and central nervous system, since these tissues are the most reliant on the use of glucose for energy.

Pyruvate carboxylase is also important in the process that removes excess nitrogen from the body (the urea cycle). Since pyruvate carboxylase-deficient individuals do not have sufficient quantities of pyruvate carboxylase, they develop a build-up of nitrogen, in the form of ammonia, in the bloodstream and the tissues.

Genetic profile

The gene that is responsible for the production of pyruvate carboxylase has been localized to a small region of chromosome 11. There are at least three mutations in this gene that lead to type B PCD. There is only one known mutation that leads to type A PCD.

Both types of PCD are transmitted via a recessive trait, which means that both parents must be carriers of the mutation in order for it to occur in their children. In the case of parents with one child affected with PCD, the likelihood that a second child will be affected with PCD is 25%.

Demographics

PCD is estimated to occur in approximately 1 in every 250,000 live births, although the exact incidence of the disorder is unknown.

Type A PCD is also called North American PCD because it occurs almost exclusively in Algonquin-language-speaking Native North Americans. In the Micmac, Cree, and Ojibwa tribes of Canada, it is estimated that as many as one in ten individuals are carriers of the mutation that causes type A PCD. This suggests a founder effect in these populations. A founder effect is a genetic term that means a single individual brought a mutation into a subpopulation at a time when the subpopulation was quite small. As a result, a large majority of the members of the subpopulation carry the mutation derived through direct ancestry to this one individual.

Type B PCD is also called French PCD because it has a much higher incidence among the French than among any other subpopulation.

Signs and symptoms

Type A, or infantile-onset, PCD may be fatal prior to birth, or it may not present any symptoms until approximately three months of age. These individuals will show severe physical and mental delay. Additionally, children affected with type A PCD have a progressive degeneration of the entire brain and nervous system (necrotizing encephalomyelopathy) that eventually leads to death.

Type B, or neonatal, PCD is generally fatal prior to birth. In the rare instances of a liveborn child affected with type B PCD, severe growth delay (extremely low birth weight) and severe mental impairment are to be expected. Children born with type B PCD fail to thrive and generally do not survive past the first three months of life.

Diagnosis

PCD is diagnosed primarily through blood tests to determine the blood concentrations of lactate and pyruvate. Extremely high levels of both of these chemicals in the blood indicate that a congenital problem in cellular metabolism is most likely present. PCD is often differentiated from other cellular metabolic disorders by the

QUESTIONS TO ASK YOUR DOCTOR

- What does the term “pyruvate carboxylase” mean?
- How do type A and type B forms of this disorder differ from each other?
- What treatments are available for this disorder, and do the treatments differ for each type of the condition?
- What information can a genetic counselor provide about pyruvate carboxylase deficiency disorder?

extreme speed with which glucose levels in the blood drop during fasting (fasting hypoglycemia) and the abnormally low levels of the chemical aspartic acid in the blood.

PCD can be tested prenatally by measuring the activity of pyruvate carboxylase in chorionic villi samples.

Treatment and management

Administration of aspartic acid has been successful in decreasing the pyruvate and lactate concentrations in the blood of some PCD-affected individuals. However, this treatment does not repair the damage to the pyruvate carboxylase enzyme, so progressive degeneration of the nervous system is slowed only slightly and the outcome is still death.

Biotin (a B-complex vitamin) is a coenzyme to pyruvate carboxylase. It has been shown that type B PCD is responsive to treatment with biotin while type A is not. Therefore, in the rare instance of a liveborn child with type B PCD, life may be extended through the administration of biotin.

Prognosis

Without prenatal administration of enzyme replacement therapy (which is currently not available), in which the developing fetus is given an artificial form of pyruvate carboxylase, individuals affected with either type A or type B PCD will die either prior to birth or, generally, within the first six months of life. Without prenatal enzyme replacement therapy, most children affected with PCD are born with such brain and nervous system dysfunction that a decision has to be made about treatment to sustain life.

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ORGANIZATIONS

United Mitochondrial Disease Foundation, 8085 Saltsburg Rd., Suite 201, Pittsburgh, PA 15239, (888) 317-8633, info@umdf.org, <http://www.umdf.org>

Paul A. Johnson

Pyruvate dehydrogenase complex deficiency

Definition

Pyruvate dehydrogenase complex deficiency (PDHA) is a genetic disorder that results in a malfunctioning of the Krebs, or tricarboxylic acid (TCA), cycle. It is sex-linked and appears to be a dominant trait.

Description

PDHA is one of the most common of the genetic disorders that cause abnormalities of mitochondrial metabolism. The mitochondria are the organelles inside cells that are responsible for energy production and respiration at the cellular level. One of the most important processes in the mitochondria is the TCA cycle (also known as the Krebs cycle). The TCA cycle produces the majority of the ATP (chemical energy) necessary for maintenance (homeostasis) of the cell. The production of this ATP is accomplished by chemically converting molecules of the chemical pyruvate into carbon dioxide, water, and ATP. After a blood sugar (glucose) molecule has been broken

down into two pyruvate molecules, one of two things will occur: if energy is required by the cell, the molecules will be further broken down into ATP, carbon dioxide, and water; or, if energy is not needed by the cell, the pyruvate molecules will be put back together to reform a glucose molecule. These transformations of pyruvate are accomplished primarily by two enzymes: pyruvate carboxylase, an enzyme that converts pyruvate molecules into oxaloacetate molecules in preparation to reform glucose molecules; and pyruvate dehydrogenase (PDH), an enzyme that begins the breakdown of the pyruvate into the eventual products of carbon dioxide, water, and ATP. To break down the pyruvate, PDH gets some help from two other enzymes: dihydrolipoyl transacetylase and dihydrolipoyl dehydrogenase. These three enzymes and the five coenzymes (CoA, NAD⁺, FAD⁺, lipoic acid, and TPP) that assist these enzymes are collectively known as the pyruvate dehydrogenase complex (PDH complex).

Individuals affected with PDHA have deficiencies in one or more of the three enzymes within the PDH complex. Most have a deficiency of the PDH enzyme itself. Tissues that require the greatest amounts of oxygen (highly aerobic tissues), such as those of the brain and the rest of the central nervous system, are most sensitive to deficiencies in the PDH complex.

People with PDHA have either a complete inability or a severely limited ability to produce PDH. Since these individuals cannot produce the amounts of PDH required to break down pyruvate, the cells cannot produce enough energy, in the form of ATP, to maintain themselves. This causes a progressive degeneration of the tissues, with the most profound effects observed in the brain and central nervous system.

PDH is an enzyme. An enzyme is a chemical that facilitates (catalyzes) the chemical reaction of another chemical or of other chemicals; it is neither a reactant nor a product in the chemical reaction that it facilitates (catalyzes). As a result, enzymes are not used up in chemical reactions; they are recycled. One molecule of an enzyme may be used to facilitate (catalyze) the same chemical reaction over and over again several hundreds of thousands of times. All the enzymes necessary for catalyzing the various reactions of human life are produced within the body by genes. Genetic enzyme deficiency disorders, such as PDHA, result from only one cause: the affected individual cannot produce enough of the necessary enzyme because the gene designed to make the enzyme is faulty. Enzymes are not used up in chemical reactions, but they do eventually wear out or accidentally get expelled. Also, as an individual grows, they may require greater quantities of an enzyme. Therefore, most enzyme deficiency disorders will have a time component

to them. Individuals with no ability to produce a particular enzyme may show effects of this deficiency at birth or shortly thereafter. Individuals with only a partial ability to produce a particular enzyme may not show the effects of this deficiency until their need for the enzyme, because of growth or maturation, has outpaced their ability to produce it.

The level of ability of the pyruvate dehydrogenase complex deficiency-affected individual to produce PDH, or his or her ability to sustain existing levels of PDH, are the sole determinants of the severity of the observed symptoms in that individual and the age of onset of these symptoms.

PDHA is the most common cause of non-exercise-related build-up of lactic acid in the tissues (primary lactic acidosis). When a tissue requires more energy than it can gain from aerobic processing (TCA cycle), it begins to break down carbohydrates, via an anaerobic process, in order to gain the necessary energy. Lactic acid is the by-product of carbohydrate metabolism. The build-up of lactic acid in the muscle tissues and red blood cells is normal during strenuous exercise. However, the accumulation of lactic acid in other tissues without exercise or without oxygen deprivation is symptomatic of an underlying problem in the normal aerobic process (TCA cycle).

Genetic profile

The gene responsible for PDHA has been mapped to Xp22.2-p22.1. This gene is now termed the *PDHA1* gene. At least 50 different mutations of this gene resulting in varying symptoms of PDHA have been identified. Because the gene for PDHA is on the X chromosome, it is called a sex-linked disease. PDHA shows a dominant inheritance pattern: therefore, females with only one affected X chromosome also exhibit symptoms of the disease.

Demographics

While the actual prevalence remains unknown, almost equal numbers of males and females have been identified as being affected with PDHA. Even though PDHA is known to be transmitted as a sex-linked dominant trait on the X chromosome, it is not necessarily lethal in affected males (who possess only a single X chromosome), because the symptoms of PDHA are quite different depending on the precise mutation responsible for the symptoms in each individual. The genetic mutations are linked to the sex of the affected individual. Affected live-born males tend to have minor (missense/nonsense-type) mutations, while affected females tend to have more major (insertion/deletion-type) mutations. The almost unobserved insertion/deletion-type mutations in males with PDHA suggests that these mutations are fatal to males with

KEY TERMS

ATP—Adenosine triphosphate. The chemical used by the cells of the body for energy.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Highly aerobic tissues—Tissue that requires the greatest amount of oxygen to thrive.

Hypotonia—Reduced or diminished muscle tone.

Lactic acid—The major by-product of anaerobic (without oxygen) metabolism.

Mitochondria—Organelles within the cell responsible for energy production.

Pyruvate dehydrogenase complex—A series of enzymes and co-factors that allow pyruvate to be converted into a chemical that can enter the TCA cycle.

TCA cycle—Formerly known as the Krebs cycle, this is the process by which glucose and other chemicals are broken down into forms that are directly useable as energy in the cells.

only a single X chromosome (homozygous males). Females with two X chromosomes, only one of which contains an insertion/deletion-type mutation (heterozygous females), and males with an extra X chromosome (XXY males) with this type of mutation on only one chromosome (heterozygous males) are affected with nonlethal forms of PDHA.

A fixed sequence difference between African and non-African samples of the *PDHA1* gene has been identified. That is, those of African descent carry a different version of the *PDHA1* gene than those of non-African descent. It has been established that these differences in the subpopulations arose more than 200,000 years ago, which predates the earliest known modern human fossils. This genetic evidence is interesting in that it suggests that the modern human emerged from already genetically divided subpopulations.

Signs and symptoms

PDHA affects primarily the brain and central nervous system. In individuals with extreme deficiencies of PDH, the brain may fail to reach normal size during fetal development, leading to a small brain and skull (microcephaly). Abnormal development of the cerebrum, cerebellum, and brain stem are the most common brain dysfunctions associated with PDHA. The normal hollow cavities (ventricles) within the brain are usually much

larger than normal (dilated) in individuals affected with PDHA. The connection between the left and right hemispheres of the brain (corpus callosum) is generally underdeveloped or completely absent as well.

A condition in which the normal insulating layer (myelin) that surrounds the neurons is either absent or insufficient (leukodystrophy) is observed in many individuals affected with PDHA. Some PDHA-affected individuals also have periods of brain malfunctioning in which the neurons within the cerebellum temporarily lose the ability to act in a coordinated fashion (cerebellar ataxia). These attacks of cerebellar ataxia generally last from a few days to a few weeks and reoccur every three to six months throughout life with decreasing severity after puberty. Lactic acid accumulation in the brain may also lead to breathing (respiratory) and kidney (renal) problems.

Some individuals affected with PDHA experience increased muscle tone in both legs (spastic diplegia) or in all four limbs (spastic tetraplegia) similar to that seen in the classic case of cerebral palsy. Seizures occur in almost all individuals affected with PDHA. A seizure is the result of sudden abnormal electrical activity in the brain. This electrical activity can result in a wide variety of clinical symptoms including muscle twitches; tongue biting; fixed, staring eyes; a loss of bladder control resulting in involuntary urination; total body shaking (convulsions); and/or loss of consciousness.

Unusual, or dysmorphic, facial features are sometimes associated with PDHA. These include a broad or upturned nose; low-set ears; downward-slanted eyes, drooping eyelids; and a staring or squinting appearance. Other physical symptoms of PDHA include short fingers and arms, urogenital malformations, low muscle tone (hypotonia), and feeding difficulties. Mental impairment is present in some cases. Delayed physical and motor development can also occur.

Diagnosis

Improper brain development in individuals with PDHA is observable in the womb via ultrasound or via MRI after birth, although brain malformations may result from any number of other factors. Babies born with PDHA may exhibit low birth weight, a weak suck, failure to thrive, lack of muscle tone, and unusual appearance of the head, face, and limbs. Convulsions, developmental delay, and eye problems may develop a few months after birth. A diagnosis of PDHA is generally confirmed with a blood test for severe lactic acidosis, an observance of deficient PDH activity in sampled or cultured fibroblasts, or by an observance of elevated amounts of lactate and pyruvate in the cerebrospinal fluid drawn in a spinal tap.

QUESTIONS TO ASK YOUR DOCTOR

- How is the normal biochemistry of a person with pyruvate dehydrogenase complex deficiency disrupted by the disease?
- Is gene replacement therapy a cure for this disease, and, if so, what are the risks involved?
- Are there prenatal tests for pyruvate dehydrogenase complex deficiency, and why would they be recommended or not recommended?
- Are there Internet sources from which I can get additional information about pyruvate dehydrogenase complex deficiency?

Treatment and management

Treatment of PDHA is on a case-by-case basis depending on the observed symptoms. These treatments may include early and continuing intervention programs for developmental delays and intellectual disability, anticonvulsants to control seizures, muscle relaxants to control spasticity, and/or surgery to release the permanent muscle, tendon, and ligament tightening (contracture) at the joints that is characteristic of longer-term spasticity.

A high-fat diet including beer as an alternative source of the chemical acetyl-CoA that is not produced in high enough supply because of the deficiency of PDH enzyme is often recommended for those individuals affected with PDHA. Dietary supplements of thiamine, lipoic acid, and L-carnitine have also proven beneficial in some cases.

Prognosis

The prognosis for PDHA-affected individuals varies widely with the severity of the symptoms. Until gene or enzyme replacement therapy becomes available, the most seriously affected individuals are not likely to receive relief from their symptoms and many will die at early ages. For those less seriously affected, several treatments are available to improve quality of life. Many less severely affected individuals live normal lifespan with their abilities and quality of life only limited by the degree of mental impairment and muscle spasticity that is present.

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ORGANIZATIONS

Children's Mitochondrial Disease Network, Mayfield House, 30 Heber Walk, Chester Way, Northwich, Cheshire UK CW9 5JB, +44(0) 01606 43946, <http://www.emdn-mitonet.co.uk>

United Mitochondrial Disease Foundation, 8085 Saltsburg Rd., Suite 201, Pittsburgh, PA 15239, (888) 317-8633, info@umdf.org, <http://www.umdf.org>

Paul A. Johnson

Pyruvate kinase deficiency

Definition

Pyruvate kinase deficiency (PKD) is part of a group of disorders called hereditary nonspherocytic hemolytic anemias. Hereditary nonspherocytic anemias are rare genetic conditions that affect the red blood cells. PKD is caused by a deficiency in the enzyme pyruvate kinase.

Description

In PKD, there is a functional abnormality with the enzyme pyruvate kinase. Usually, pyruvate kinase acts as a catalyst in the glycolysis pathway and is considered an essential component in this pathway. Glycolysis is the method by which cells produce their own energy. A problem with any of the key components in glycolysis can alter the amount of energy produced. In the red blood cells, glycolysis is the only method available to produce energy. Without the proper amount of energy, the red blood cells do not function normally. Since pyruvate kinase is one of the key components in glycolysis, when there is a problem with this enzyme in the red blood cells,

there is a problem with the production of energy, causing the red blood cells to not function properly.

There are four different forms of the pyruvate kinase enzyme in the human body. These forms, called isozymes, all perform the same function, but each isozyme of pyruvate kinase is structurally different and works in different tissues and organs. The four isozymes of pyruvate kinase are labeled M1, M2, L, and R. The isozyme M1 is found in the skeletal muscle and brain, isozyme M2 can be found in most fetal and adult tissues, isozyme L works in the liver, and isozyme R works in the red blood cells. In PKD, only the pyruvate kinase isozyme found in red blood cells, called PKR, is abnormal. Therefore, PKD affects only the red blood cells and does not directly affect the energy production in the other organs and tissues of the body.

Genetic profile

There are two PK genes and each gene produces two of the four isozymes of pyruvate kinase. The M1 and M2 isozymes are produced by the pyruvate kinase gene called *PKM2* and pyruvate kinase isozymes, L and R, are products of the pyruvate kinase gene, *PKLR*. The *PKLR* gene is located on chromosome 1, on the q arm (the top half of the chromosome), in region 21 (written as 1q21). There have been over 125 different mutations described in the *PKLR* gene that have been detected in individuals with PKD.

PKD is mainly inherited in an autosomal recessive manner. There have been a few families where it appeared that PKD was inherited in either an autosomal dominant manner or where the carriers of PKD exhibited mild problems with their red blood cells. As with all autosomal recessive conditions, affected individuals have a mutation in both pairs of genes. Most individuals with PKD are compound heterozygotes, meaning that each *PKLR* gene in a pair contains a different mutation. There are individuals who have the same mutation on each *PKLR* gene, but these individuals tend to be children of parents who are related to each other.

There are three mutations in the *PKLR* gene—*1529A*, *1456T*, and *1468T*—that are seen more frequently in individuals with PKD than the other mutations. The mutation *1529A* is most frequently seen in Caucasians of northern and central European descent and is the most common mutation seen in PKD. The mutation *1456T* is more common in individuals of southern European descent and the mutation *1468T* is more common in individuals of Asian descent.

For most of the mutations seen in the *PKLR* gene, no correlation between the specific mutation and the severity of the disorder has been observed. However, for two of

the mutations, there has been speculation on their effect on the severity of PKD. When the mutation *1456T* has been seen in the homozygous state (when both *PKLR* genes contain the same mutation), those rare individuals experienced very mild symptoms of PKD. Also, there have been individuals who were homozygous for the *1529A* mutation. These individuals had a very severe form of PKD. Therefore, it is thought that the *1456T* mutation is associated with a milder form of the disease and the *1529A* mutation is associated with a more severe form of the disease. It is not known how these mutations affect the severity of PKD when paired with different mutations.

Demographics

PKD is the most common of the hereditary non-spherocytic anemias, with 500 families documented as suffering from the disorder. It occurs worldwide, but most cases have been reported in northern Europe, Japan, and the United States. In general, PKD does not appear to affect one gender more than another or be more common in certain regions. However, there are studies of an Amish group in Pennsylvania where a severe form of PKD is more common. The three mutations found in the *PKLR* gene have been linked to individuals of specific descents. Caucasians of northern and central European descent are more likely to have the *1529A* mutations, individuals of southern European descent usually have the *1456T* mutation, and individuals of Asian descent are more likely to have the *1468T* mutation. The prevalence of PKD in people of European descent is 1 in 20,000.

Signs and symptoms

In general, the more severe the PKD, the earlier in life symptoms tend to be detected. Individuals with the more severe form of PKD often show symptoms soon after birth, but most individuals with PKD begin to exhibit symptoms during infancy or childhood. In individuals with the more mild form of PKD, the condition is sometimes not diagnosed until late adulthood, after an acute illness, or during a pregnancy evaluation.

Symptoms of PKD are similar to those symptoms seen in individuals who have long-term hemolytic anemia. The more common symptoms include variable degrees of jaundice (a yellowish pigment of the skin), slightly to moderately enlarged spleen (splenomegaly), and increased incidence of gallstones. Other physical effects of PKD can include smaller head size and the forehead appearing prominent and rounded (called frontal bossing). If a child with PKD has their spleen removed, their growth tends to improve. Even within the same

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Catalyst—A substance that changes the rate of a chemical reaction but is not physically changed by the process.

Compound heterozygotes—Having two different mutated versions of a gene.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Glycolysis—The pathway in which a cell breaks down glucose into energy.

Hemolytic anemia—Anemia that results from premature destruction and decreased numbers of red blood cells.

Heterozygote—Having two different versions of the same gene.

Homozygote—Having two identical copies of a gene or chromosome.

Isozyme/Isoenzyme—A group of enzymes that perform the same function, but are different from one another in their structure or how they move.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Nonspherocytic—Literally means not sphere-shaped. Refers to the shape of red blood cells in nonspherocytic hemolytic anemia.

family, individuals can have different symptoms and severity of PKD.

In individuals with PKD, the red blood cells are taken out of their circulation earlier than normal (shorter lifespan). Because of this, individuals with PKD have hemolytic anemia. Additionally, the anemia or other symptoms of PKD may worsen during a sudden illness or pregnancy.

Diagnosis

A diagnosis of PKD can be made by measuring the amount of pyruvate kinase in red blood cells. Individuals with PKD tend to have 5%–25% of the normal amount of pyruvate kinase. Carriers of PKD also can have less

QUESTIONS TO ASK YOUR DOCTOR

- What is the long-term prognosis of pyruvate kinase deficiency?
- What is the likelihood that I may have the same condition as my sibling?
- What kinds of treatments are used to treat pyruvate kinase deficiency?
- Are my children likely to inherit this condition from me?

pyruvate kinase in their red blood cells, approximately 40%–60% of the normal value. However, there is an overlap between the normal range of pyruvate kinase and the ranges seen with carriers of PKD. Therefore, measuring the amount of pyruvate kinase in the red blood cells is not a good method of detecting carriers of PKD. If the mutations causing PKD in a family are known, it may be possible to perform mutation analysis to determine carrier status of an individual and to help diagnose individuals with PKD.

Treatment and management

In the severest cases, individuals with PKD will require multiple blood transfusions. In some of those cases, the spleen may be removed (splenectomy). Red blood cells are normally removed from circulation by the spleen. By removing an individual's spleen (usually a child), the red blood cells are allowed to stay in circulation longer than normal, thereby reducing the severity of the anemia. After a splenectomy, or once an individual with PKD is older, the number of transfusions tends to decrease.

Prognosis

The prognosis of PKD is extremely variable. Early intervention and treatment of symptoms frequently improve the individual's health. Without treatment, individuals may experience severe complications that could become fatal. Individuals with a mild form of PKD may appear to have no symptoms at all.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, <http://www.rarediseases.org>

Office of Rare Diseases Research (ORDR), 6701 Democracy Blvd., Suite 1001, MSC 4874, Bethesda, MD 20892, (301) 402-4336, ordr@od.nih.gov, <http://rarediseases.info.nih.gov>

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R

Race and genetics

Understanding race

Race, based on appearance and sometimes family history, is a highly subjective and socially defined way that cultures classify individuals into groups. For years, many people have mistakenly believed that there is a biological or genetic basis for race and that differences in characteristics such as health, intelligence, and athletic ability are the result of genetic differences. This is simply not true. There are no “biological races”: Racial identity is not contained in the DNA of an individual or group, nor is it explained by any portion of the human genome.

Assigning people to different races does not explain or define human genetic variation. The characteristics and attributes mistakenly ascribed to race are more likely related to a population’s geographic location, which is called “geographic ancestry,” and does relate to genetics but is not the same as race. People who live in the same region are likely to be similar genetically. Genetic variation is related to geographic distance; the farther apart people are from one another, and the longer they have lived far from one another, the more likely they are to have genetic differences. Other differences often attributed to race result from differences in how people live, such as diet and nutrition, physical activity levels, and access to medical care. For people of color many of these differences in lifestyle, such as limited access to healthy food and medical care and living or working in unsafe environments, result from systemic and structural racism, not from any biological or genetic differences.

A brief overview of the history of race

The history of race is inextricably bound to the history of racism. Many historians assert that the concept of race originated as a way to force millions of dark skinned Africans to the Americas between 1525 and 1866. Europeans and later Americans rationalized this action, maligning and debasing their captives and

declaring them inferior based on the color of their skin. To justify this economic exploitation, they developed quasi-scientific explanations of race. Some asserted that dark skin was the result of vapors in the skin or darkened sperm; others claimed that heat and air darkened the skin.

In the mid 1700s, the notion of “degeneration” gained favor. Degeneration proposed that the original, superior race was white and that as this race migrated, climate induced mutations increased the pigment in skin. This notion is the opposite of our current understanding of skin color as the result of natural selection and the adaptation that occurred with each successive migration from Africa.

Early physicians bolstered this racist notion and attempted to develop a scientific rationale for it. They described dark skin as damaged by living in a tropical climate, and European physicians erroneously claimed that Black Africans suffered from a host of physical and mental disabilities such as limited intelligence and laziness. In 1851 Samuel A. Cartwright (1793–1863), a physician who practiced in Mississippi and Louisiana, published a “Report on the Diseases and Physical Peculiarities of the Negro Race” that described a mental illness called drapetomania, which was believed to cause slaves to run away, and dysaesthesia aethiopica, a form of lethargy that supposedly afflicted Africans who were not enslaved or watched over by whites.

European physicians and naturalists persisted in advancing the belief that race was a way to distinguish humans from one another. German physician, naturalist, physiologist, and anthropologist Johann Friedrich Blumenbach (1752–1840) introduced the term “Caucasian” to describe white Europeans because he believed that the “white race” originated in the Caucasus region, which includes parts of Asia and Europe between the Black Sea and the Caspian Sea and is home to Armenia, Azerbaijan, Georgia, and parts of Southern Russia. Unlike many of his naturalist colleagues who contended that Africans were an entirely different species, Blumenbach believed that anatomical variations among humans did not

represent differences between human species; instead he posited that race distinguished subspecies of humans. Based on his detailed studies of skulls and human anatomy, Blumenbach concluded that there were five distinct races of humans: Caucasian, Mongolian, Malayan, Ethiopian, and American. Although he incorrectly described and designated distinct races, he argued strongly against the use of anthropology as a means to promote discrimination.

Although abolitionists and others sought to debunk these racist ideas and spoke out against unscientific racial claims, they nonetheless took hold in the United States, largely because they appeared to support slavery. Many historians and observers feel that these incorrect and discriminatory ideas are deeply rooted in American history and persist in the 21st century. They argue that although the U.S. Civil War formally ended the institution of slavery, it didn't end racism, and the small, slow, uneven progress in ending race-based prejudice and discrimination drags on.

The 1950s and 1960s saw a robust campaign to end racial segregation and discrimination. The August 1963 March on Washington, in which more than 200,000 people of all races gathered in Washington, DC, to advocate for civil rights legislation and job equality is one of the best known events of the civil rights movement. The peaceful demonstration was attended by civil rights leaders and it is where Martin Luther King, Jr. (1929–1968) made his famous and oft-quoted speech, “I Have a Dream.” King and other civil rights leaders witnessed the signing of the Civil Rights Act of 1964, which guaranteed equal employment, limited the use of literacy tests for voters, and enabled federal authorities to ensure that public facilities were integrated.

On March 7, 1965, 600 demonstrators marched in Alabama from Selma to Montgomery to protest the killing of civil rights activist Jimmie Lee Jackson (1938–1965) by a white police officer and express their support for the 15th amendment, which was ratified in 1870 and prohibited the federal and state governments from denying citizens the right to vote based on race, color, or previous condition of servitude. When the peaceful demonstrators approached the Edmund Pettus Bridge, they were blocked from crossing it by state and local police, and as they attempted to cross the bridge they were brutally beaten and teargassed by the police. The events on the bridge were widely televised and became known as “Bloody Sunday.”

Systemic racism persisted in the United States, and in May 2020 efforts to recognize, expose, and eliminate it were reignited after Minnesota police murdered an African American man named George Floyd (1973–

2020) because a store clerk suggested that he may have used a counterfeit \$20 bill to pay for his purchases. Officer Derek Chauvin (1976–), one of four police officers at the scene, knelt on Floyd's neck and back for 9 minutes and 29 seconds as Floyd begged for his life. Chauvin was convicted of second-degree unintentional murder, third-degree murder, and second-degree manslaughter, and was sentenced to 22-and-a-half years in prison. Floyd's murder and previous acts of police brutality and high-profile police killings and racially motivated violence restarted the “Black Lives Matter movement,” which was founded in 2013 to “eradicate white supremacy and build local power to intervene in violence inflicted on Black communities by the state and vigilantes.” The movement prompted many American institutions and individuals to engage in a racial reckoning. Books, broadcasts, speeches, and demonstrations catapulted race to the forefront of Americans' consciousness and corporations pledged billions of dollars to address injustice. Although many remain hopeful that a national reflection on racism might catalyze efforts to overcome systemic injustice, national polls found that by June 2021, interest in, and enthusiasm for, the movement had waned among white Americans.

Genetics and five races

Even as knowledge, appreciation, and enthusiasm for genetics research increased in the 21st century, misperceptions about race persisted. Completion of the Human Genome Project in 2003 enabled scientists and researchers to trace human ancestry using genetics. Consumers also eagerly sought clues to their past in readily accessible, affordable, convenient, at-home genetic testing. These popular tests purport to accurately determine an individual's geographic origins based on a genetic analysis. But these direct-to-consumer tests that estimate ancestral composition are still based on the old, misguided premise that DNA can be used to assign people to one of five distinct races: European, African, Asian, Oceania, or Native American. This antiquated and rigid view of race assumes that each race has a uniform genetic identity and that the variation between races is great.

It is now known that there is no uniform identity, and that genetic variation within a single region is large. It is also true that while human populations do vary based on geographic regions of origin, the genetic variation between different regions is very small. So, while the five races do offer a way to describe the geographic distribution of populations, variation between them is smaller, a scant 0.1%, and blurrier than popular genetic tests suggest.

A 2002 landmark study conducted by Stanford University researchers that considered the genotypes of more

than 1,000 people found that within-population differences among individuals accounted for 93% to 95% of genetic variation, while differences between major groups accounted for just 3% to 5%. The researchers identified six main genetic clusters; five of these corresponded to major geographic regions. They found no evidence that the populations typically termed races have distinct genetic identities, and they found substantial genetic variation within groups termed races. In fact, there is so much variation within races that two people of African descent may be more genetically similar to a European than to one another.

Race is a social construct

Today, most scientists concur that race is a social construct, not a biological characteristic. Humans invented the classification of people into races as a way to distinguish physical differences; there are no genes common to all people who are white, black, or Asian. Even though race has served in the past as a way to characterize human genetic diversity, it is a very weak stand-in for diversity. At best, race is a poorly defined marker of diversity and an inexact stand-in for the relationship between ancestry and genetics. From the standpoint of biology and genetics, it is much more useful to describe populations and individuals based on their ancestry, which is the geographical origins of their predecessors.

Genetic disorders

If race is not related to genetics, then why do some genetic disorders disproportionately affect people from particular racial and ethnic groups? This is because some genetic disorders occur more frequently among people who come from a specific geographic area. People from the same geographic area share certain versions of genes, called gene variants that they have inherited from their ancestors. When one of these gene variants contains a disease-causing mutation, then the disease will occur more frequently in the racial or ethnic group. Advanced genotyping methods are beginning to elucidate patterns for genetic diseases and disorders within specific populations; these patterns are increasingly described according to their biogeographical ancestry rather than according to race.

Examples of genetic disorders that appear more frequently in particular racial or ethnic groups include sickle cell disease, which is more common in people of African, African American, or Mediterranean heritage; and Tay-Sachs disease, which occurs more frequently among Jewish people with eastern and central European heritage and people with French Canadian ancestry. Other genetic

disorders such as cystic fibrosis primarily affect white people.

Health disparities

Other diseases that are not strictly considered genetic disorders, even though specific genetic variants may increase susceptibility or risk of developing these conditions, disproportionately affect African-Americans. These include:

- **Asthma.** African Americans are three times as likely as white Americans to die from asthma.
- **Cancer.** African American men are 40% more likely to die from cancer than their white peers and African American women are 20% more likely to die than white women. African American men are 50% more likely than white men to develop lung cancer, even though they have less exposure to tobacco.
- **Diabetes.** African Americans suffer from diabetes 60% more than do white Americans and are much more likely to suffer the consequences of untreated or inadequately treated diabetes.
- **Hypertension (high blood pressure).** African Americans develop hypertension more frequently and at younger ages than do whites. More than 40% of African Americans age 20 and older have hypertension, which is a risk factor for heart disease and stroke.
- **Stroke.** African Americans have nearly twice the risk of first stroke than do whites and strokes claim the lives of four times as many African Americans ages 35 to 54 compared to whites.
- **Sarcoidosis,** an inflammatory disease that affects many organs, but mostly scars the lungs, occurs 16 times more frequently among African Americans than whites.

Although these and other conditions disproportionately affect African Americans, it is not because of their race. Race is a proxy for other structural barriers to health including socioeconomic status, which not only affects lifestyle issues related to health—such as diet and nutrition, physical activity, safe housing and workplaces, and stable employment—but also access to quality medical care. Access to health care is a key determinant of health and even people of color with access to health-care services may find those services mired in institutionalized racism. The concerns of African American patients may not be taken seriously, their complaints may be dismissed, and they may be diagnosed later, when treatment may be less effective.

Health equity in genetic testing

In addition to health disparities resulting from racism and income inequality, medical research has failed to

KEY TERMS

Phenotype—An individual's observable traits, such as height, eye color, and blood type. The genetic contribution to the phenotype is called the genotype. Some traits are largely determined by the genotype, while other traits are largely determined by environmental factors.

Racial disparities—Inequities and inconsistencies in the way people are treated based on the color of their skin, in terms of socioeconomic status, education, access to health care, housing, and other aspects of life.

Social determinants of health—Conditions in the places where people live, learn, work, and play that affect a wide range of health and quality-of-life issue for individuals and groups.

Systemic racism—Also known as institutional racism, this is racism written into the laws, regulations, and practices of institutions, organizations, and groups. Systemic racism results in discrimination in education, housing, employment, health care, the criminal justice system and other aspects of life.

include diverse populations. This inequity is especially glaring in genetics research; most data are collected from white study subjects rather than diverse populations. Further, in 2021, some published genetics research still identified racial categories as biological variables. By overlooking and omitting information from diverse populations, some researchers, physicians, and public health professionals are ill-equipped to meet the needs of diverse populations and populations that are disproportionately underserved.

Polygenic risk scores, which estimate the effect of multiple genetic variants on a person's phenotype, are an example of a technology designed to improve risk management and treatment of people with heart disease, cancer, and diabetes—diseases that disproportionately affect people of color. But the majority of data used to develop these risk scores were obtained from whites of European ancestry; they do not reflect the patients of color who, in many cases, stand to benefit most from them.

Today, clinical genetic testing is still inadequate because it does not include or address the majority of the world's population, which is of non-European ancestry. It remains a challenge for all health-care systems to reduce inequities and to offer all populations the

opportunity to obtain accurate genetic information to inform their medical decision-making, enabling clinicians and researchers to meet the health-care needs of all people.

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ORGANIZATIONS

American Society of Human Genetics, 9650 Rockville Pike, Bethesda, MD 20814-3998, (301) 634-7300, (301) 634-7079, society@ashg.org, <http://www.ashg.org>

BlackInGenetics. <http://www.blackingenetics.com>

Genetics Society of America, 6120 Executive Boulevard Suite 550, Rockville, MD 20852, (240) 880-2000, <https://genetics-gsa.org>

Barbara Wexler, MPH

Rapp-Hodgkin syndrome see **Ectodermal dysplasia**

Raynaud's disease

Definition

Raynaud's disease is a disorder in which the fingers or toes (digits) suddenly experience decreased blood circulation. It is characterized by repeated episodes of color changes of the skin of digits during cold exposure or emotional stress.

Description

Raynaud's disease can be classified as one of two types: primary (or idiopathic) and secondary (also called Raynaud's phenomenon). Primary Raynaud's disease has no predisposing factor, is milder, and causes fewer complications. About half of all cases of Raynaud's disease are of this type. Women are seven times more likely than men to develop primary Raynaud's disease. The average age of diagnosis is between 20 and 40 years. Approximately 3 out of 10 people with primary Raynaud's disease eventually progress to secondary Raynaud's disease after diagnosis. About 15% of individuals improve.

Secondary Raynaud's disease is the same as primary Raynaud's disease but occurs in individuals with a predisposing factor, usually a form of collagen vascular disease. What is typically identified as primary Raynaud's may be later identified as secondary once a predisposing disease is diagnosed. This occurs in approximately 30% of patients. As a result of the predisposing disease, the secondary type is often more complicated and severe, and is more likely to worsen.

Several related conditions that predispose persons to secondary Raynaud's disease include scleroderma, lupus erythematosus, rheumatoid arthritis, and polymyositis. Pulmonary hypertension and some nervous system disorders such as herniated discs and tumors within the spinal column, strokes, and polio can progress to Raynaud's disease. Finally, injuries due to mechanical trauma caused by vibration (such as that associated with chain saws and jackhammers), repetitive motion (carpal tunnel syndrome), electrical shock, and exposure to extreme cold

can lead to the development of Raynaud's disease. Some drugs used to control high blood pressure or migraine headaches have been known to cause Raynaud's disease.

Genetic profile

There is significant familial aggregation of primary Raynaud's disease. However, no causative gene had been identified.

Risk factors for Raynaud's disease differ between males and females. Age and smoking seem to be associated with the disease only in men, while the associations of marital status and alcohol use with Raynaud's disease are usually only observed in women. These findings suggest that different mechanisms influence the expression of Raynaud's disease in men and women.

Demographics

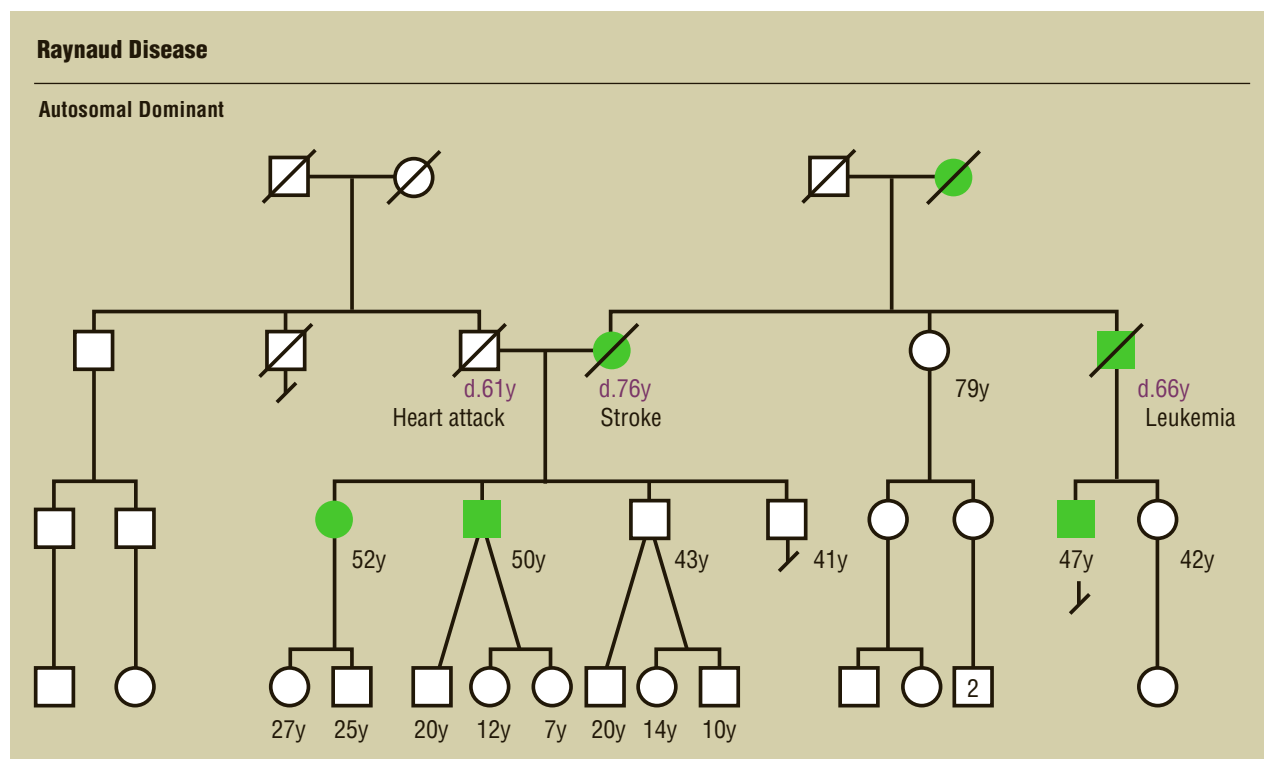
The prevalence of Raynaud's phenomena in the general population varies from 4%–15%. Females are seven times more likely to develop Raynaud's diseases than are men. The problem has not been correlated with coffee consumption, dietary habits, occupational history (excepting exposure to vibration), or exposure to most drugs. An association between Raynaud's disease and migraine headaches has been reported. Secondary Raynaud's disease is common among individuals with systemic lupus erythematosus in tropical countries.

Signs and symptoms

Both primary and secondary Raynaud's disease signs and symptoms are thought to be due to arterioles overreacting to stimuli. Cold normally causes the tiny muscles in the walls of arteries to contract, thus reducing the amount of blood that can flow through them. In people



A woman's hands affected by Raynaud's disease, where blood flow is being restricted to the fingers. (Graham Dunn/Alamy)



Raynaud's Disease: pedigree analysis chart (Gale)

with Raynaud's disease, the extent of constriction is extreme, thus severely restricting blood flow. Attacks or their effects may be brought on or worsened by anxiety or emotional distress.

There are three distinct phases to an episode of Raynaud's disease. When first exposed to cold, small arteries respond with intense contractions (vasoconstriction). The affected fingers or toes (in rare instances, the tip of the nose or tongue) become pale and white because they are deprived of blood and, thus, oxygen. In response, capillaries and veins expand (dilate). Because these vessels are carrying deoxygenated blood, the affected area then becomes blue in color. The area often feels cold and tingly, or numb. After the area begins to warm up, the arteries dilate. Blood flow is significantly increased. This changes the color of the area to a bright red. During this phase, persons often describe the affected area as feeling warm and throbbing painfully.

Raynaud's disease may initially affect only the tips of fingers or toes. As the disease progresses, it may eventually involve all of one or two digits. Ultimately, all the fingers or toes may be affected. About 1 person in 10 will experience a complication called sclerodactyly. In sclerodactyly, the skin over the involved digits becomes tight, white, thick, smooth, and shiny. In approximately 1% of cases of Raynaud's disease, deep sores (ulcers) may

develop in the skin. In rare cases of frequent, repetitive bouts of severe ischemia (decreased supply of oxygenated blood to tissues or organs), tissue loss, or gangrene, may result and amputation may be required.

Diagnosis

Primary Raynaud's disease is diagnosed following the four components of the Allen-Brown criteria. The certainty of the diagnosis and severity of the disease increase as more criteria are met. The first is that at least two of the three color changes must occur during attacks provoked by cold and/or stress. The second is that episodes must occur periodically for at least two years. The third is that attacks must occur in both the hands and the feet in the absence of vascular occlusive disease. The last is that there is no other identifiable cause for the Raynaud's episodes.

A cold stimulation test may also be performed to help to confirm a diagnosis of Raynaud's disease. The temperature of affected fingers or toes is taken. The hand or foot is then placed completely into a container of ice water for 20 seconds. After removal from the water, the temperature of the affected digits is immediately recorded. The temperature is taken every 5 minutes until it returns to the pre-immersion level. Most individuals recover normal temperature within 15 minutes. People

KEY TERMS

Arteriole—The smallest type of artery.

Artery—A blood vessel that carries blood away from the heart to peripheral tissues.

Gangrene—Death of a tissue, usually caused by insufficient blood supply and followed by bacterial infection of the tissue.

Idiopathic—Of unknown origin.

Lupus erythematosus—A chronic inflammatory disease that affects many tissues and parts of the body including the skin.

Polymyositis—An inflammation of many muscles.

Pulmonary hypertension—A severe form of high blood pressure caused by diseased arteries in the lung.

Rheumatoid arthritis—A chronic autoimmune disease marked by inflammation of the membranes surrounding joints.

Scleroderma—A relatively rare autoimmune disease affecting blood vessels and connective tissue that makes skin appear thickened.

with Raynaud's disease may require 20 minutes or more to reach their pre-immersion temperature.

Laboratory testing is performed frequently. However, these results are often inconclusive for several reasons. Provocative testing such as the ice immersion just described is difficult to interpret because there is considerable overlap between normal and abnormal results. The antinuclear antibody test of blood is usually negative in Raynaud's disease. Capillary beds under fingernails usually appear normal. Erythrocyte sedimentation rates are often abnormal in people with connective tissue diseases. Unfortunately, this finding is not consistent in people with Raynaud's disease.

Treatment and management

There is no known way to prevent the development of Raynaud's disease. Furthermore, there is no known cure for this condition. Therefore, avoidance of the trigger is the best supportive management available. Most cases of primary Raynaud's disease can be controlled with proper medical care and avoidance.

Many people are able to find relief by simply adjusting their lifestyles. Affected individuals need to stay warm and keep their hands and feet well covered in cold weather. Layered clothing, scarves, heavy coats, heavy

socks, and mittens over gloves are suggested because gloves alone allow heat to escape. It is also recommended that patients cover or close the space between their sleeves and mittens. Indoors, they should wear socks and comfortable shoes. Excessive emotional stress should be avoided. Smokers should quit, as nicotine worsens the problem. The use of vibrating tools should be avoided as well.

Biofeedback has been used with some success in treating primary Raynaud's. This involves teaching people to "think" their fingers and toes to be warm by willing blood to flow through affected arterioles. A patient is given continuous information on the temperature of his or her digits and then taught to voluntarily control this temperature. Biofeedback has had only limited success. Occasionally, medications such as calcium-channel blockers, reserpine, or nitroglycerin may be prescribed to relax artery walls and improve blood flow.

Because episodes of Raynaud's disease have also been associated with stress and emotional upset, the condition may be improved by learning to manage stress. Regular exercise is known to decrease stress and lower anxiety. Hypnosis, relaxation techniques, and visualization are also useful methods to help control emotions.

Some alternative practitioners believe that certain dietary supplements and herbs may be helpful in decreasing the vessel spasm of Raynaud's disease. Suggested supplements include vitamin E (found in fruits, vegetables, seeds, and nuts), magnesium (found in seeds, nuts, fish, beans, and dark green vegetables), and fish oils. The circulatory herbs cayenne, ginger, and prickly ash may help enhance circulation to affected areas.

Prognosis

The prognosis for most people with Raynaud's disease is very good. In general, primary Raynaud's disease has the best prognosis, with a relatively small chance (1%) of serious complications. Approximately half of all affected individuals do well by taking simple precautions and never require medication. The prognosis for people with secondary Raynaud's disease (or phenomenon) is less predictable. This prognosis depends greatly on the severity of other associated conditions such as scleroderma, lupus, or Sjögren's syndrome. A long-term case study of over 30 years concluded in 2015 that among Caucasians with a diagnosis of Raynaud's phenomenon there was a high correlation with cardiovascular disease and cardiovascular-related death. This study went on to hypothesize that Raynaud's phenomenon may be an indicator of a more serious underlying vascular disease, which is important to note for management of the condition.

QUESTIONS TO ASK YOUR DOCTOR

- How do the two types of Raynaud's disease differ from each other?
- What are the most serious medical complications associated with Raynaud's disease?
- How is Raynaud's disease diagnosed?
- What support groups or nonprofit organizations can provide me with additional information about Raynaud's disease?
- How often should I be screened for other autoimmune or vascular diseases?

Resources

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ORGANIZATIONS

American Heart Association, 7272 Greenville Ave., Dallas, TX 75231, (800) 242-8721, <http://www.heart.org>

National Heart, Lung, and Blood Institute, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, nhlbiinfo@nhlbi.nih.gov, <http://www.nhlbi.nih.gov>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203)

798-2291, <http://www.rarediseases.org>

Raynaud's Association, 11 Topstone Rd., Redding, CT 06896, (800) 280-8055, info@raynauds.org, <http://www.raynauds.org>

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Recurrence risk counseling

Definition

Recurrence risk is a statistic estimating the chance that a genetic disorder that has appeared in one or more members of a family will reappear in the present or future generations. It can be expressed as a probability (a proportion between 0 and 1, with 0 indicating that an event cannot occur, and 1 indicating that it must occur); as a percentage; as odds; or as chance. For example, if a genetic disorder has a probability of 0.5 recurrence in a family, it is equally likely to recur or not recur. The same probability can be expressed as a 50% likelihood, or as 1 chance in 2 that the disorder will recur in the family.

Recurrence risk counseling is therefore a specialized form of genetic counseling that requires numerical calculations to estimate the probability of recurrence following the collection of information from the family and obtaining a diagnosis of the specific genetic disorder. While such calculations are relatively straightforward when Mendelian or single-gene disorders affecting one set of parents and their immediate children are involved, they can become extremely complex when the genetic disorder in question does not follow Mendelian patterns of inheritance or when second- or third-degree relatives are brought into the discussion.

Purpose

Recurrence risk counseling has several goals:

- Gathering information about the family of the proband (i.e., the person who is being evaluated for the presence of a genetic disorder or the risk of developing one). Other members of a family may have the disorder in question, but the person who seeks medical attention for the disorder is designated the proband.
- Establishing the correct diagnosis of the genetic disorder in question. In the past, genetic testing was most often done for one gene at a time. More recently, multigene or panel testing has become widely available. Last, a growing number of people have taken direct-to-consumer (DTC) genetic tests, which require confirmation by a clinical

laboratory. Whichever test was used, accurate identification of the genetic disorder is essential to recurrence risk counseling.

- Building rapport with the proband and his or her family. People vary widely in their ability to understand medical information and their ability to cope with the emotional stress aroused by finding out that a genetic disorder runs in one's family. Recurrence risk counseling requires an ability to convey genetic information in nontechnical language, patience, and a willingness to repeat or reword the information as often as needed.
- Offering ongoing support to the family. Recurrence risk counseling is nondirective in that the proband and other family members are not told what to do with the information provided to them but are encouraged to learn about their options and discuss the implications and possible outcomes of these options among themselves.

Description

Recurrence risk counseling for any genetic disorder begins with the construction of a pedigree, which is a visual chart of the proband's family. The pedigree begins with the proband, whose sex is indicated by a circle if female, or a square if male. The parents are then added, siblings (if any) in order of birth (beginning with the oldest at left and moving rightward with younger siblings), then uncles, aunts, grandparents, and cousins. Those who have died are identified with a diagonal line through their circle or square, with age at death and cause of death noted. Relatives whose sex is unknown are represented by a diamond.

Generations are numbered with Roman numerals, with I for the oldest generation on the chart. The pedigree should include ethnic identifications and as many relatives unaffected by the disorder as possible. Each specific person on the pedigree is identified with their generation number, any diagnoses received along with age at onset, current age if known, and an asterisk indicating whether they are willing to participate in the study. Examples of pedigree constructions can be found throughout this book, and for more information on the subject, please see the entry on "Pedigree analysis."

Mendelian disorders

Mendelian (single-gene) disorders are the simplest to calculate risk recurrence, because they follow the basic rules of inheritance discovered by the German botanist Gregor Mendel (1822–1884) in the mid-nineteenth century. In many cases, the risk can be illustrated by using a Punnett square, which is a grid that predicts the probability of an offspring having a particular genotype when maternal alleles for a single trait are crossed with

paternal alleles. Capital letters are used for dominant alleles, and lowercase letters for recessive alleles. For example, brown eye color is dominant (B) in humans, and blue eye color is a recessive trait (b). If two parents who are heterozygous for brown eyes have a child, a Punnett square will show that the child has a 25% chance of being homozygous for brown eyes (BB); a 50% chance of being heterozygous for brown eyes (Bb); and a 25% chance of having blue eyes (bb).

AUTOSOMAL DOMINANT. An autosomal dominant disorder is one in which one altered copy of a gene is sufficient for a single-gene disorder to appear in the offspring. Autosomal dominant disorders can affect either sex, and they can be transmitted from father to son. The pathogenic variant (disease-causing mutation) may be inherited from either parent, or it may be a new mutation. Examples of autosomal dominant disorders include Marfan syndrome, polycystic kidney syndrome, myotonic muscular dystrophy, and Huntington's disease.

AUTOSOMAL RECESSIVE. An autosomal recessive disorder is one in which a person must have inherited two copies of the variant gene, one from each parent. The parents typically do not show any signs of the disorder, and the disorder often skips generations in an affected family. Examples of autosomal recessive disorders include cystic fibrosis, sickle cell disease, and phenylketonuria.

X-LINKED DOMINANT. X-linked disorders are those caused by variant genes on the X chromosome, one of two sex chromosomes. A dominant variant gene on the X chromosome will cause the disorder in male offspring (who have only one X chromosome) and in female offspring (who have two X chromosomes). However, females typically have less severe symptoms than males. In addition, fathers cannot pass x-linked disorders to their sons. Aicardi syndrome is an example of an X-linked dominant disorder.

X-LINKED RECESSIVE. X-linked recessive disorders are also caused by variant genes on the X chromosome. In males, who have only one X chromosome, one variant recessive gene is sufficient to cause the disorder. Females must inherit the variant gene from both parents to have the disorder. Because the likelihood of inheriting two copies of the variant gene is relatively small, X-linked recessive disorders appear much more often in males than in females. Females are, however, likely to be carriers of the variant gene. Examples of X-linked recessive disorders include hemophilia A and Duchenne muscular dystrophy.

Y-LINKED. Y-linked genetic disorders are caused by variant genes on the Y chromosome, which are present only in males. Y-linked disorders can only be passed from father to son. Most of these disorders are rare but usually result in reduced fertility.

KEY TERMS

Allele—One of two (or more) forms of the same gene at the same place on a chromosome.

Autosome—Any chromosome that is not a sex chromosome. The human genome has 22 pairs of autosomes.

Bayes' theorem—A theorem that estimates the probability of an event, based on knowledge of prior conditions that may be related to the event. It is named for Thomas Bayes (c. 1701–1761), an English Presbyterian minister and Fellow of the Royal Society. Bayes' theorem is used in genetic risk assessment for non-Mendelian disorders.

Carrier—In genetics, a person who has a genetic mutation associated with a disease and is capable of passing it on. A carrier may or may not display the symptoms of the disease.

Cascade testing—A term that refers to performing genetic counseling and testing in blood relatives of a person identified as having a specific genetic mutation. It is most commonly recommended for the relatives of patients carrying a genetic mutation linked to cancer.

Empirical—Relying on, or derived from, observations gained through the senses or by experimentation.

Genotype—The complete set of an organism's genetic material. The term is sometimes used to refer to the genes or set of genes for a single trait, such as height or eye color.

Heterozygous—Referring to the genetic condition of having inherited two different forms (alleles) of a particular gene from each of a person's two parents.

Homozygous—Referring to genetic condition of having inherited the same allele for a specific gene from both parents.

Imprinting—A condition in which the expression of a gene depends upon the sex of the parent who passed on the gene to the child.

Klinefelter syndrome—A genetic disorder characterized by one or more extra X chromosomes in a male, with a 47,XXY, 48,XXX, or 49,XXXXY karyotype. Most men with this syndrome are infertile or have reduced fertility. The syndrome is named for Harry Klinefelter (1912–1990), an American endocrinologist who first described it in 1942.

Mendelian disease—A disease caused by a single mutated gene; also called a single-gene disease. These diseases are named for Gregor Mendel (1822–1884), an Austrian monk who discovered the basic

Non-Mendelian inheritance patterns

Non-Mendelian genetic disorders do not follow the inheritance patterns outlined by Mendel for single-gene disorders. They may have one or more of the following characteristics:

- **Codominance.** In codominant inheritance, both alleles for a trait are equally expressed in the phenotype of the offspring. In humans, the most common example of codominance is the A and B blood types; a person who inherits the A allele from one parent and the B allele from the other will have AB type blood. (Type O is recessive to both A and B.)
- **Reduced penetrance.** Penetrance refers to the proportion of people with a variant gene who exhibit the symptoms of a genetic disorder. If there are people with the variant who do not develop such symptoms, the disorder is said to have reduced penetrance. Many familial cancer syndromes, including those associated with mutations in the *BRCA1* and *BRCA2* genes, have reduced penetrance. This characteristic complicates risk-assessment counseling for these disorders.
- **Variable expressivity.** Variable expressivity is a term that refers to differences in the type and severity of symptoms that appear in persons with the disorder in question. For example, some people with Marfan syndrome have very long fingers and are unusually tall but are otherwise healthy, while others have life-threatening cardiovascular complications.
- **Imprinting.** Imprinting is seen in genetic disorders in which the expression of a gene depends on the sex of the parent who contributed it to the offspring. The best-known example in humans concerns a chromosome deletion at 15q11-13. If the deletion occurs on the copy of the chromosome inherited from the father, the child will develop Prader-Willi syndrome; if it occurs on the copy inherited from the mother, the child will develop Angelman syndrome.
- **Mitochondrial disorders.** Mitochondrial disorders are a group of disorders caused by mutations in either mitochondrial DNA or in the genes in the cell nucleus that code for mitochondria. Mitochondrial DNA (mtDNA) is inherited only from the mother; however,

principles of inheritance of single-gene traits through experimentation with plants in his garden.

Mitochondria (singular, mitochondrion)—Organelles in the cytoplasm of cells that contain genetic material and enzymes responsible for converting food to usable energy.

Mitochondrial disease—Any of several hundred inherited conditions caused by functional failure of the mitochondria within cells.

Monogenic disease—Another term for a single-gene disorder.

Mosaicism—A condition in which two or more genetically different sets of cells occur in the same individual.

Multifactorial disorders—A general term for polygenic disorders complicated by the effects of environmental factors. Multifactorial disorders do not have clear patterns of inheritance. They are sometimes called complex diseases or disorders.

Pedigree—A genetic diagram of a family tree that shows the appearance of a trait or disorder across several generations.

Penetrance—The frequency with which the characteristics transmitted by a gene appear in individuals possessing that gene. In medical genetics, the

penetrance of a disease-causing mutation is the proportion of persons with the mutation who display clinical symptoms of the disease.

Phenotype—The set of observable characteristics or traits of an organism. It includes physical form and structure, development, metabolic processes, movement, and behavior.

Polygenic—Referring to an inherited disorder or trait whose phenotype is influenced by more than one gene.

Proband—The specific person being reported on in a genetic investigation. In most cases, the proband is the first member of a family to bring the disorder to medical attention.

Punnett square—A grid used to determine the probability that the offspring of two parents with a single-gene trait being crossed will have a particular genotype. The square is named for Reginald Punnett, a British geneticist who first devised it in 1905.

Turner syndrome—A chromosomal disorder with a 45,X or 45,X0 karyotype that affects only females, in which one of the X chromosomes is either partially or completely missing. Most women with Turner syndrome are infertile because of a lack of ovarian function.

both males and females can develop mitochondrial disorders. In addition, the 37 genes in human mitochondrial DNA show new mutations more frequently than the genes in the cell nucleus.

- **Polygenic inheritance.** Many human characteristics are determined by a combination of a number of different genes, such as height, intelligence, and skin color. Many disorders are polygenic as well, including autism spectrum disorders, hypertension, diabetes, and coronary heart disease. In a polygenic disorder, each variant gene contributes a small additive effect to the eventual outcome.
- **Multifactorial disorders.** Multifactorial disorders are those that represent interactions between a person's heredity and his or her environment, which includes such factors as nutrition, climate, sun exposure, and personal behaviors like smoking, heavy drinking, or drug consumption. Multifactorial disorders are sometimes called complex disorders. These have a tendency to run in families but at much lower levels than single-gene disorders that follow Mendelian patterns of inheritance.

The likelihood that a given individual will exhibit the phenotype of a multifactorial disorder depends on the number of genes that contribute to the disorder plus exposure to the environmental factors that favor the emergence of the disorder. Only individuals with enough multiple genes who are in the presence of certain environmental factors will exhibit the phenotype. The threshold is the point at which these factors combine sufficiently for affected individuals to exhibit the phenotype.

- **Disorders with delayed age of onset.** Genetic disorders whose symptoms do not appear until adult life are among the most difficult for assessing the risk of recurrence in a family. For example, in Huntington's disease, symptoms might not appear before age 30, and sometimes not until age 50.
- **Mosaicism.** Mosaicism is a condition in which a person has more than one genetic line of cells as a result of a mutation. It can be found in some women with Turner syndrome and some men with Klinefelter syndrome.

QUESTIONS TO ASK YOUR DOCTOR

- Have you ever referred a patient for recurrence risk genetic counseling?
- Have you ever attempted recurrence risk counseling yourself?
- What is your opinion of the increasing use of Bayes' theorem in genetic risk assessment?
- Have you ever recommended cascade testing to a patient with a hereditary cancer syndrome?

Calculating recurrence risk in non-Mendelian disorders

DATA COLLECTION AND EMPIRICAL OBSERVATIONS.

Calculating recurrence risk for non-Mendelian disorders is usually done by using a combination of data from population studies and empirical observations. The most widely used database for identifying the frequency of a disease-causing gene variation worldwide is the Frequency of Inherited Disorders Database or FINDbase, which was started by a group of Greek researchers in 2006 and has been updated several times since. Empirical observations about recurrence include the following:

- Recurrence risk is higher in first-degree relationships (parents, children, siblings), because these relatives share 50% of their genetic material, compared to 25% for second-degree relatives (grandparents, aunts, uncles, nieces, and nephews) and 12.5% for third-degree relatives (first cousins). The recurrence risk to first-degree relatives of the proband is the square root of the general population risk.
- If the genetic defect is more common in one sex than in the other, the recurrence risk is higher if the proband belongs to the less commonly affected sex.
- Recurrence risk is higher when the proband is more severely affected. For example, if the proband has a bilateral cleft lip and palate, a future sibling has a recurrence risk of 6%. If the cleft lip is on one side only, that risk for a future sibling drops to 2%.
- Recurrence risk is higher if more than one child in the family has already been diagnosed with the genetic disorder in question.
- In hereditary cancer syndromes, the recurrence risk is higher if the proband developed cancer at an unusually early age, if the proband developed more than one type of primary cancer, if there is a cluster of the same type of cancer in close relatives (mother, daughter, and sisters), if the proband has a rare type of cancer (male breast

cancer), or if the proband belongs to an ethnic group known to be at high risk of hereditary cancers. Many genetic counselors recommend cascade testing in hereditary cancer syndromes.

BAYES' THEOREM. Bayes' theorem is a theorem used to calculate probabilities in genetic risk assessments, including risk recurrence. The initial probability of each event is known as its prior probability and is based on anterior family information contained in the pedigree. The observations that modify these prior probabilities allow the geneticist to determine conditional probabilities. In genetic counseling, these observations are usually based on numbers of offspring and/or the results of genetic tests. This type of information is posterior information. The resulting probability for each event or outcome is known as its joint probability. The final probability for each event is known as its posterior or relative probability and is obtained by dividing the joint probability for that event by the sum of all the joint probabilities.

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ORGANIZATIONS

American College of Medical Genetics and Genomics (ACMG), 7101 Wisconsin Avenue, Suite 1101, Bethesda, MD 20814, (301) 718-9603, (301) 718-9604, acmg@acmg.net, <https://www.acmg.net/>

American College of Obstetricians and Gynecologists (ACOG), 409 12th Street SW, Washington, DC 20024-2188, (800) 673-8444, (202) 638-5577, <https://www.acog.org/>

FINDbase: Genome Variation Allele Frequencies Worldwide, University of Patras School of Health Sciences, Department of Pharmacy, University Campus, Rion, Patras, Greece GR-265 04, permed@upatras.gr, <https://www.findbase.org/#/>

National Cancer Institute (NCI), 9609 Medical Center Drive, Rockville, MD 20850, (800) 422-6237, (301) 435-3848, NCInfo@nih.gov, <https://www.cancer.gov/>

National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, <https://www.genome.gov/about-nhgri/Contact>, <https://www.genome.gov/>

National Society of Genetic Counselors (NSGC), 330 North Wabash Avenue, Suite 2000, Chicago, IL 60611, (312) 321-6834, nsgc@nsgc.org, <https://www.nsgc.org>

Rebecca J. Frey, PhD

Recurrent polyserositis see **Familial Mediterranean fever**

Refsum disease

Definition

Refsum disease is an inherited disorder in which the enzyme responsible for processing phytanic acid is defective. Accumulation of phytanic acid in the tissues and the blood leads to damage of the brain, nerves, eyes, skin, and bones.

Description

Refsum disease was first characterized by the Norwegian physician Sigvald Refsum in the 1940s and is known by other names, such as classical Refsum disease, adult Refsum disease, phytanic acid alpha-hydroxylase deficiency, phytanic acid storage disease, hypertrophic neuropathy of Refsum, hereditary ataxia polyneuritis, and hereditary motor and sensory neuropathy IV. Refsum disease should not be confused with infantile Refsum disease, which was once thought to be a variant of the disorder but is now known to be a genetically and biochemically distinct entity. Sometimes infantile Refsum disease is simply referred to as “Refsum disease,” furthering the confusion.

Living bodies are made up of millions of individual cells that are specifically adapted to carry out particular functions. Within cells are even smaller structures, called organelles, that perform jobs and enable the cell to serve its ultimate purpose. One type of organelle is the peroxisome, whose main function is to break down waste materials or to process materials that, if allowed to accumulate, would prove toxic to the cells.

Phytanic acid is a substance found in foods, such as dairy products, beef, lamb, and some fish. Normally, phytanic acid is processed by a set of enzymes within the cell to convert it to another form. In the past, scientists were unsure where in the cell this process took place, hypothesizing that it may occur in the peroxisome or another

organelle, called the mitochondrion. However, recent research has definitively determined that the enzymes responsible for processing phytanic acid are located in the peroxisome.

Refsum disease is an inherited disorder in which one of the peroxisomal enzymes, phytanic acid hydroxylase (also called phytanic acid oxidase, or phytanyl CoA hydroxylase), is defective, resulting in unprocessed phytanic acid. Consequently, high levels of phytanic acid build up in the tissues of the body and the bloodstream, causing damage to different organ systems.

Genetic profile

Refsum disease is a genetic condition and can be inherited or passed on in a family. The genetic defect for the disorder is inherited as an autosomal recessive trait, meaning that two abnormal genes are needed to display the disease. A person who carries one abnormal gene does not display the disease and is called a carrier. A carrier has a 50% chance of transmitting the gene to his or her children. A child must inherit the same abnormal gene from each parent to display the disease.

Refsum disease is caused by a deficiency in an enzyme, phytanic acid hydroxylase. The gene encoding for this enzyme, called *PAHX* or *PHYH*, was identified in 1997 and mapped to human chromosome 10 (locus: 10pter-p11.2). Several common mutations have been identified in the gene that result in Refsum disease.

Demographics

Refsum disease is rare, but the exact incidence and prevalence of the disorder in the general population is not known. Refsum disease may not be distributed equally among geographical areas or different ethnic groups, as most of the diagnosed cases have been found in children and young adults of Scandinavian heritage.

Signs and symptoms

Patients with Refsum disease generally do not show obvious defects at birth, and growth and development initially appears normal. The onset of clinical symptoms varies from early childhood to age 50, but symptoms usually appear before 20 years of age. The manifestations of Refsum disease primarily involve the nervous system, the eye, the skin, the bones, and, in rare cases, the heart and kidneys.

Phytanic acid deposits in the fatty sheaths surrounding nerves, causing damage and resulting in peripheral neuropathy in 90% of patients with Refsum disease. “Peripheral neuropathy” is the term for dysfunction of the nerves outside of the spinal cord, causing loss of

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Cerebellar ataxia—Unsteadiness and lack of coordination caused by a progressive degeneration of the part of the brain known as the cerebellum.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Ichthyosis—Rough, dry, scaly skin that forms as a result of a defect in skin formation.

Mutant—A change in the genetic material that may alter a trait or characteristic of an individual or manifest as disease.

Organelle—Small, subcellular structures that carry out different functions necessary for cellular survival and proper cellular functioning.

Peripheral neuropathy—Any disease of the nerves outside of the spinal cord, usually resulting in weakness and/or numbness.

Peroxisome—A cellular organelle containing different enzymes responsible for the breakdown of waste or other products.

Phytanic acid—A substance found in various foods that, if allowed to accumulate, is toxic to various tissues. It is metabolized in the peroxisome by phytanic acid hydroxylase.

Phytanic acid hydroxylase—A peroxisomal enzyme responsible for processing phytanic acid. It is defective in Refsum disease.

Plasmapheresis—A procedure in which the fluid component of blood is removed from the bloodstream and sometimes replaced with other fluids or plasma.

Retinitis pigmentosa—Progressive deterioration of the retina, often leading to vision loss and blindness.

sensation, muscle weakness, pain, and loss of reflexes. Nerves leading to the nose and ears can also be affected, resulting in anosmia (loss of the sense of smell) in 35% of patients and hearing loss or deafness in 50% of patients. Finally, Refsum disease results in cerebellar

ataxia in 75% of patients. Cerebellar ataxia is a defect in a specific part of the brain (the cerebellum), resulting in loss of coordination and unsteadiness. In contrast to infantile Refsum disease, people with Refsum disease do not show intellectual disability and generally have normal intelligence.

Accumulation of phytanic acid also results in disorders of the eye. The most common finding is retinitis pigmentosa, a degeneration of the retina resulting in poor nighttime vision and sometimes blindness. Disorders of pupil movement and nystagmus (uncontrollable movements of the eye) may also be present due to related nervous system damage. Other eye manifestations of Refsum disease may include glaucoma (abnormally high pressure in the eye, leading to vision loss) and cataracts (clouding of the lens of the eye).

People with Refsum disease often develop dry, rough, scaly skin. These skin changes, called ichthyosis, can occur over the entire body, but sometimes will appear only on the palms and soles of the feet. In addition to these skin abnormalities, 60% of affected people may experience abnormal bone growth, manifesting as shortened limbs or fingers, or abnormal curvatures of the spine.

Patients with Refsum disease usually first present to a physician complaining of weakness in the arms and legs, physical unsteadiness, and/or night blindness or failing vision. The symptoms associated with Refsum disease are progressive and, if untreated, will become more numerous and severe as the patient ages. For reasons that are not completely understood, clinical deterioration can sometimes be interrupted by periods of good health without symptoms.

Diagnosis

Refsum disease is diagnosed through a combination of consistent medical history, physical exam findings, and laboratory and genetic testing. When patients with Refsum disease present to their physicians complaining of visual problems or muscle weakness, physical signs of retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, or skin and bone changes (as discussed above) are often noted. These findings raise suspicion for a genetic syndrome or metabolic disorder, and further tests are conducted.

Laboratory tests reveal several abnormalities. Normally, phytanic acid levels are essentially undetectable in the plasma. Thus, the presence of high levels of phytanic acid in the bloodstream is highly indicative of Refsum disease. If necessary, a small portion of the patient's connective tissue can be sampled and grown in a laboratory and tested to demonstrate a failure to

QUESTIONS TO ASK YOUR DOCTOR

- What is the role of phytanic acid in Refsum disease?
- What treatments are available to control the progress of Refsum disease?
- How does a physician determine the prognosis for a child with Refsum disease?
- Can you recommend a website that will provide additional information on Refsum disease?

process phytanic acid appropriately. Other associated laboratory abnormalities include the presence of high amounts of protein in the fluid that bathes the spinal cord, or abnormal electrical responses recorded from the brain, muscles, heart, ears, retina, and various nerves as a result of nervous system damage.

Genetic testing can also be performed. When a diagnosis of Refsum disease is made in a child, genetic testing of the *PAHX/PHYH* gene can be offered to determine if a specific gene change can be identified. If a specific change is identified, carrier testing can be offered to relatives. In families where the parents have been identified to be carriers of the abnormal gene, diagnosis of Refsum disease before birth is possible. Prenatal diagnosis is performed on cells obtained by amniocentesis (withdrawal of the fluid surrounding a fetus in the womb using a needle) at about 16–18 weeks of pregnancy or from the chorionic villi (a part of the placenta) at 10–12 weeks of pregnancy.

Treatment and management

There is no cure for Refsum disease, thus treatment focuses on reducing levels of phytanic acid in the bloodstream to prevent the progression of tissue damage. Phytanic acid is not made in the human body and comes exclusively from the diet. Restriction of phytanic acid-containing foods can slow progress of the disease or reverse some of the symptoms. Patients are advised to maintain consumption of phytanic acid below 10 mg/day (the normal intake is approximately 100 mg/day). Sources of high levels of phytanic acid to be avoided include meats (beef, lamb, goat), dairy products (cream, milk, butter, cheese), and some fish (tuna, cod, haddock). Plasma levels of phytanic acid can be monitored periodically by a physician to investigate the effectiveness of the restricted diet and determine if changes are required. As a result of dietary restriction, nutritional deficiencies may

result. Consultation with a nutritionist is recommended to ensure proper amounts of calories, protein, and vitamins are obtained through the diet, and nutritional supplements may be required.

Because phytanic acid is stored in fat deposits within the body, it is important for patients with Refsum disease to have regular eating patterns; with even brief periods of fasting, fat stores are converted to energy, resulting in the release of stored phytanic acid into the blood stream. Thus, unless a patient assumes a regular eating pattern, repeated and periodic liberation of phytanic acid stores results in greater tissue damage and symptom development. For these same reasons, intentional weight loss through calorie-restricted diets or vigorous exercise is discouraged.

Another useful adjunct to dietary treatment is plasmapheresis. Plasmapheresis is a procedure by which determined amounts of plasma (the fluid component of blood that contains phytanic acid) are removed from the blood and replaced with fluids or plasma that does not contain phytanic acid. Regular utilization of this technique allows people who fail to follow a restricted diet to maintain lower phytanic acid levels and experience less tissue damage and symptoms.

Patients with Refsum disease should be seen regularly by a multidisciplinary team of healthcare providers, including a pediatrician, neurologist, ophthalmologist, cardiologist, medical geneticist specializing in metabolic disease, nutritionist, and physical/occupational therapist. People with Refsum disease, or those who are carriers of the abnormal gene or who have a relative with the disorder, can be referred for genetic counseling to assist in making reproductive decisions.

Prognosis

The prognosis of Refsum disease varies dramatically. The disorder is slowly progressive and, if left untreated, severe symptoms will develop with considerably shortened life expectancy. However, if diagnosed early, strict adherence to a phytanic acid-free dietary regimen can prevent progression of the disease and reverse skin disease and some of the symptoms of peripheral neuropathy. Unfortunately, treatment cannot undo existing damage to vision and hearing.

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ORGANIZATIONS

- Genetic Disease Foundation, 1425 Madison Ave., Box 1498, New York, NY 10029, (212) 659-6704, <http://www.geneticdiseasefoundation.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Oren Traub, MD, PhD

Reis-Pucklers corneal dystrophy see **Corneal dystrophy**

Renal agenesis

Definition

Renal agenesis is the failure of kidney formation during fetal development. Renal agenesis can be unilateral, with one kidney present, or bilateral, with no kidneys or very little kidney present. The two types of renal agenesis have very different clinical courses, with unilateral agenesis being more favorable.

Description

Kidneys perform many important bodily functions. Having at least one kidney is necessary for life. Kidneys filter waste and extra fluid from the blood; keep a healthy blood level of electrolytes and minerals, such as sodium, phosphorus, calcium, and potassium; help to maintain healthy blood pressure; and release hormones that are important for bodily functions. Normally, there are two fist-sized kidneys present, one on each side of the spinal column at the back just below the ribcage. Each kidney contains microscopic filter lobules called nephrons that transfer bodily waste products from the bloodstream to the urinary system. Functional nephrons are critical for maintaining bodily functions and for eliminating the buildup of waste products that can be life threatening.

Unilateral renal agenesis

Unilateral renal agenesis results from defects in fetal development that cause only one kidney to form. Having a solitary kidney instead of two is not necessarily life-threatening. The solitary kidney usually enlarges, and is able to perform most bodily functions to a degree sufficient for life. When a solitary kidney does negatively affect health, it is through very subtle and gradual changes that may not be noticed initially. Over long periods of time, changes, such as an increase in blood pressure, may require specific preventive measures or treatments. Having a solitary kidney also means that if injury or disease leads to renal failure, there is no backup kidney to take over. In this circumstance, the consequences of a diseased unilateral kidney can be life threatening.

Bilateral renal agenesis

Bilateral renal agenesis is a genetic disorder involving the failure of both kidneys to form during fetal development. Fetal kidney development begins between five and seven weeks of gestation. During development, the fetus is cushioned, protected, and maintained at constant temperature in a substance known as amniotic fluid. Fetal urine production begins in early gestation and is responsible for the majority of the amniotic fluid present in the second and third trimesters of pregnancy. The fetus continuously swallows amniotic fluid, which is reabsorbed in the fetal gastrointestinal tract and excreted back into the amniotic cavity by the kidneys. Because amniotic fluid is maintained by fetal urine, a fetus with no kidneys has little amniotic fluid to surround and protect it in the amniotic sac. This condition is known as oligohydramnios, and results in physical compression of the fetus in the womb. Bilateral renal agenesis causes a set of physical complications known as Potter syndrome. While bilateral renal agenesis is not the only cause of Potter syndrome, the lack of both kidneys naturally results in Potter syndrome symptoms. Only 20% of all Potter syndrome cases are caused by bilateral renal agenesis. The amniotic membrane sticking to the fetus, and the compression, cause further physical malformations, including the squashed facial features characteristic of Potter syndrome.

Compression and lack of amniotic fluid also lead to a serious defect in lung development. The fetal urine is critical for proper lung development. Fetal urine helps to expand the airways and supplies the amino acid proline, a critical amino acid for lung development. Upon leaving the womb, an infant must rely on the lungs and on breathing air to receive oxygen for life. Alveoli are the many small sacs deep in the lungs that are responsible for exchanging oxygen with the blood. If the alveoli are underdeveloped (pulmonary hypoplasia) at birth, the infant cannot breathe properly and will go into respiratory

distress. In most cases, the condition is fatal within the first few months of postnatal life. The cause of death is pulmonary hypoplasia, with consequent respiratory insufficiency. There are rare cases in which a portion of one kidney has formed and some lung development occurs. These cases are also often fatal. If sufficient lung development is present, an infant with bilateral renal agenesis may be rescued through dialysis and eventual kidney transplant.

Genetic profile

Bilateral renal agenesis (BRA) is a rare condition thought to occur in sporadic and autosomal recessive forms. Sporadic forms of BRA have an unknown cause that may or may not be genetic. It is thought that BRA can be inherited in an autosomal recessive form, caused by the inheritance of two defective copies of a gene. Each parent contributes one copy of a gene. In autosomal recessive inheritance, if both copies are defective, the result is disease. If only one defective copy is present, the disease does not occur, but the defective gene can still be passed on to subsequent generations. If both parents are carrying a defective gene, each offspring has a one in four (25%) chance of inheriting the disease. Populations with a high frequency of healthy individuals carrying defective genes will also have higher prevalence of offspring with the disease.

BRA is also more common when a parent has a distinct kidney malformation, especially unilateral renal agenesis. Research has demonstrated that unilateral renal agenesis and bilateral renal agenesis are genetically related. For this reason, when bilateral renal agenesis is detected in an infant, an ultrasound is performed on the kidneys of parents and siblings. Approximately 9% of first-degree relatives of infants with bilateral renal agenesis have some type of asymptomatic renal malformation.

The exact genetic causes of both unilateral and bilateral renal agenesis were unknown. It is speculated that both conditions are caused by mutations in the genes involved in fetal kidney development. Normal fetal kidney development involves an essential interaction between the forming kidney buds (ureteric bud) and a tissue known as the metanephric mesenchyme. The interaction of the ureteric bud with the metanephric mesenchyme is necessary for kidney formation. The interaction is controlled by a combination of genes, cellular-signaling molecules that control gene expression (transcription factors), and cellular-signaling molecules that control cell growth (growth factors). Animal studies have identified several of the factors that can be mutated to cause renal agenesis. Research is ongoing to determine the cause in humans.

In 2014, researchers D. Y. Hwang et al. in China studied 650 families with congenital anomalies of the kidney and urinary tract (CAKUT), a condition that is present in approximately 50% of children with renal failure. CAKUT involves a spectrum of kidney anomalies including renal agenesis. They discovered mutations in the following genes: *BMP7*, *CDC5L*, *CHD1L*, *EYA1*, *GATA3*, *HNF1B*, *PAX2*, *RET*, *ROBO2*, *SALL1*, *SIX2*, and *SIX5* were associated with CAKUT in 41 of the 650 families. In another study of 590 families with CAKUT in China, researchers identified recessive genetic mutations in *FRAS1*, *FREM2*, *GRIPI*, *FREM1*, *ITGA8*, and *GREM1* associated with isolated CAKUT in 15 of the 590 families. Specifically, they identified recessive biallelic missense mutations in these six genes. Additional research has suggested that the vast majority of cases of renal agenesis showed a lack of obvious differences at the genome level and nongenetic factors are most likely involved in the pathogenesis of renal agenesis.

Demographics

Unilateral kidney agenesis is fairly common, occurring in approximately 1 per 1,000 live births in the United States. Bilateral renal agenesis occurs in 1 per 3,000 live births. There is no association of renal agenesis with race. Males have a higher rate of developing Potter syndrome than females. Individuals with bilateral renal agenesis present with the condition as neonates, whereas individuals with unilateral renal agenesis may not be aware of their condition even as adults. Unilateral renal agenesis is usually discovered in an adult undergoing tests for some other condition.

Signs and symptoms

Unilateral renal agenesis

Most people born with a solitary kidney do not experience any noticeable signs or symptoms that would indicate they have unilateral renal agenesis. A solitary kidney is usually discovered when the individual is having ultrasound imaging or surgery for some other problem. However, having unilateral renal agenesis can cause gradual changes in bodily functions that lead to unhealthy clinical conditions. A potential complication of a solitary kidney is high blood pressure.

Kidneys normally contribute to maintaining a healthy blood pressure in two ways. Kidneys regulate how much fluid flows through the bloodstream and how much fluid is excreted from the body. The more fluid that flows through the bloodstream, the more the blood pressure increases. Kidneys also release a hormone called renin that works as part of a team of hormones to expand or contract blood vessels. The more contraction of blood vessels there is, the higher the blood pressure. Many

individuals who are born with a solitary kidney eventually develop slightly higher blood pressure.

In addition, one kidney doing the work of two kidneys can cause more wear and tear than normally would occur. A solitary kidney may eventually be slightly damaged, causing excessive protein to be excreted from the body through the urine. This condition is known as proteinuria, and is a sign of kidney damage. Another potential complication of having a solitary kidney is reduced efficiency at removing waste from the bloodstream. The portion of the kidney that acts as a filter is the glomerulus. A reduced ability to filter the blood is known as a reduced glomerular filtration rate (GFR), a potential complication of unilateral renal agenesis. As long as these complications are controlled, individuals with a solitary kidney often experience no actual symptoms.

Bilateral renal agenesis

There are many signs of bilateral renal agenesis during neonatal (first six weeks of life) care. Potter facies are facial features associated with Potter syndrome from bilateral renal agenesis. The facies include a squashed facial appearance, flattened nose, recessed chin, prominent epicanthal folds (fold of skin from root of nose to eyebrow), and low-set abnormal ears. A poor or absent urine output during the first 48 hours of life, respiratory distress, and poorly developed lungs are all indicative signs. The degree of lung development corresponds with the extent and duration of the oligohydramnios. Respiratory distress is often the cause of death.

Diagnosis

Unilateral renal agenesis

A diagnosis of unilateral renal agenesis can be made using various imaging techniques such as an ultrasound, or directly through surgery. Diagnosis of unilateral renal agenesis is usually made in asymptomatic adults, while they are investigating some other condition. Complications of unilateral renal agenesis may include proteinuria and reduced GFR. A diagnosis of proteinuria is made through urinalysis. High levels of protein in the urine indicate kidney damage. Highly sensitive urinalysis tests are also performed to diagnose proteinuria. These tests calculate the protein-to-creatinine ratio. A high protein-to-creatinine ratio in urine indicates that the kidney is leaking protein that should be kept in the blood, and indicates kidney damage. The GFR can be measured by injecting a contrast medium into the bloodstream. The injection is followed by a 24-hour period of urine collection to determine how much of the medium was filtered through the kidney. A more recent method of determining GFR is by measuring blood creatinine levels and performing

KEY TERMS

Amniotic sample—Sample of amniotic fluid, the protective fluid surrounding a fetus in the womb.

Anemia—Condition in which there are low levels of red blood cells.

Asymptomatic—Without symptoms.

Biallelic—Pertaining to both pair of genes or alleles in a set.

Creatinine—A normal component of blood kept in low levels in urine by functioning kidneys.

Dialysis—Filtering of blood to remove waste products that the kidneys would normally remove if they were present and functioning.

DNA—Deoxyribonucleic acid, inheritable material that constitutes the building blocks of life.

Gastrointestinal tract—The food intake and waste export system that runs from the mouth, through the esophagus, stomach, and intestines, to the rectum and anus.

Growth factors—Cellular-signaling components that stimulate cell division or other cell processes.

Missense—A portion of mRNA in which the coding is changed because of an abnormal change in the protein base sequence.

Neonate—A newborn infant up to six weeks of age.

Oligohydramnios—An abnormally small amount of amniotic fluid.

Pulmonary hypoplasia—Underdevelopment of the lungs.

RNA—Ribonucleic acid, the intermediate step between DNA and its final expression product. DNA is transcribed into RNA and RNA is translated into protein.

Transcription—The process by which DNA is changed into RNA.

Transcription factors—Cellular-signaling components that cause the transcription of a gene.

calculations that involve weight, age, and values assigned for sex and race. If GFR remains consistently below 60, a diagnosis of chronic kidney disease is made.

Bilateral renal agenesis

Bilateral renal agenesis is investigated if there is a history of oligohydramnios, prenatal sonograms depicting renal agenesis, or unilateral renal agenesis in the family. If

an infant has bilateral renal agenesis, blood tests will show altered levels of electrolytes and minerals that the kidney typically filters and normalizes. Renal function and GFR can be assessed through measuring blood levels of creatinine. Urinalysis, if any urine is present, is used to detect proteinuria. Ultrasound imaging can reveal renal agenesis both before and after birth, but the prenatal condition is not as easily visualized. Chest x-rays, although undesirable in an infant, can be used to assess lung development. In neonates who die from this condition, an autopsy is recommended to confirm the diagnosis.

Treatment and management

Unilateral renal agenesis

No treatment is necessary for unilateral renal agenesis other than controlling complications if they arise. Kidney function is monitored by regular physical examinations that check blood pressure and blood and urine tests. These tests are usually done once a year, and are designed to assess whether the unilateral kidney is functioning properly. Regular monitoring is critical because if the solitary kidney becomes diseased or damaged, there is no backup kidney available to maintain life.

Normal blood pressure is defined as a measurement of 120/80 or lower. High blood pressure is defined as a measurement of 140/90 or higher. Individuals with unilateral renal agenesis are advised to maintain blood pressure levels below 130/80 to prevent kidney damage. If medication is required to control blood pressure, individuals with unilateral renal agenesis may need blood pressure medications that also protect kidney functions. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are two classes of blood pressure medication that can also protect kidney function and reduce proteinuria. Diuretics may also be used to help lower blood pressure by removing excess fluid from the body.

Individuals with unilateral renal agenesis do not need to follow a special diet, but should limit daily sodium intake to avoid developing high blood pressure. While a special diet is not required, some methods of dieting are contraindicated. High-protein diets are not advised for individuals with unilateral renal agenesis. Because protein breakdown products add stress to the kidneys as they remove waste from the bloodstream, excessive protein intake puts an extra burden on the solitary kidney. Normal, moderate amounts of protein intake are recommended in unilateral renal agenesis. Alcohol and caffeine intake should also be limited. Individuals with unilateral renal agenesis are often advised to avoid contact sports unless protective gear is worn. Damage to the single functional kidney could quickly become life threatening.

Bilateral renal agenesis

Neonates born with bilateral renal agenesis are immediately placed in the neonatal intensive care unit. The level of renal and respiratory function is immediately assessed. Evaluation is also made of any other malformations in bodily systems. Once the long-term prognosis of survival is determined, a treatment plan can be addressed. If a neonate with bilateral renal agenesis has severe respiratory distress from severe pulmonary hypoplasia, no further treatment may be the decided course of action. If lung development is sufficient to respond to treatment, mechanical ventilation can supply respiratory support. Management of renal failure involves a complex course of action taken to address all the consequent complications. Adequate nutrition with restricted sodium and fluid intake may be achieved through a nasogastric feeding tube. Medications and vitamin supplementation can be used to address electrolyte imbalances from lack of kidney function. Because the kidney is responsible for vitamin D formation, vitamin D therapy is important. Calcium carbonate is also supplemented because the kidneys are not present to regulate calcium levels in the blood.

Children with chronic renal failure often have poor growth and require supplemental human growth hormone (Genotropin, Humatrope, Nutropin). Human growth hormone stimulates the growth of bone, skeletal muscle, and organs. Human growth hormone acts in conjunction with another medication, erythropoietin, to increase the number of red blood cells and address the additional complication of anemia. Anemia occurs because the kidneys are not present to produce erythropoietin, which is responsible for the stimulation of red blood cell production in the bone marrow. Epoetin alfa (Epogen, Procrit) is a synthetic form of erythropoietin used in the treatment of bilateral renal agenesis. Anemia is also treated with iron supplements, which can be given orally or administered through an injection.

Renal failure causes hypertension; infants with bilateral renal agenesis may require hypertension medications in addition to restricted sodium and fluids. In renal failure, hypertension is caused by fluid overload. To treat the hypertension associated with bilateral renal agenesis, diuretic agents (Lasix) are used. Diuretic agents promote the excretion of water and electrolytes from the body. They decrease blood pressure by decreasing the amount of fluid present in the blood vessels. Other hypertensive medications may also be used, as is appropriate for the patient's age. Dialysis is required to function as a blood filter replacement for the kidney. Frequent dialysis treatments remain necessary until the infant is old enough to receive a kidney transplant.

Prognosis

In the absence of kidney injury or disease, the prognosis for unilateral renal agenesis is excellent. Individuals

with unilateral renal agenesis usually lead normal, healthy lives. Avoidance of injury and basic health practices are important to maintain this quality of life.

Bilateral renal agenesis has a very poor prognosis. It is usually fatal in the first few days of life. The usual cause of death is respiratory failure and acute renal failure during the neonatal period. If survival progresses to early childhood, patients may have chronic lung disease or chronic renal failure. If the lungs have sufficient development, a kidney transplant is necessary for survival. After a kidney transplant, the prognosis is improved.

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ORGANIZATIONS

- National Kidney Foundation, 30 E. 33rd St., New York, NY 10016, (800) 622-9010, info@kidney.org, <https://www.kidney.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

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Renal failure due to hypertension

Definition

Renal failure (kidney failure) is caused primarily by chronic high blood pressure (hypertension) over many years. Hypertension is the second major cause, after diabetes, of end-stage renal disease (ESRD) and is

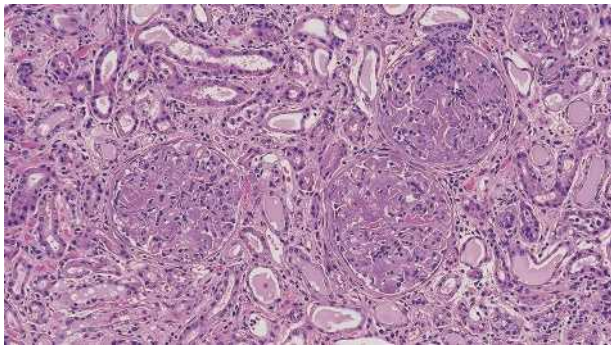
responsible for 25%–30% of all reported cases. In addition, many people with diabetes also have hypertension, thus high blood pressure plays an even larger role in kidney failure. Renal failure due to hypertension in its inherited form is also known as familial nephropathy.

Description

Hypertension is a chronic, persistent increase in blood pressure that can be due to many factors such as diet, lifestyle, and a genetic predisposition. Chronic hypertension causes a physiological change in the arteries of the body, decreasing their ability to pump blood correctly. The kidney may be seriously affected by hypertension if the structures of the renal arteries are compromised due to hypertension. If the arteries are not functioning correctly, the organ will not function properly either, possibly leading to renal failure. Diabetic nephropathy and hypertensive nephropathy are the two most common causes of end-stage renal failure. There is still controversy regarding the genetic component of renal failure due to hypertension, but with the recent advances in genome sequencing, more studies can be performed to determine the exact cause.

Genetic profile

It is believed that most cases of hypertension leading to kidney failure have a genetic element. Finding a genetic link is complicated by the fact that nearly half of all people with renal failure have three or more serious disorders, such as diabetes. Animal studies have been done to find genetic linkages to hypertension and kidney failure, but genetic studies on humans are in their infancy. A recent breakthrough came in a study of African American subjects with hypertensive end-stage renal disease. Researchers found a significant association between severe hypertension and mutations on the *HSD11B2* gene located at position 16q22.1. This is a



Light micrograph of a kidney displaying hypertrophy (enlargement) of its walls because of high blood pressure (hypertension). (Voisin/Phanie/Science Source)

KEY TERMS

Dialysis—Process by which special equipment purifies the blood of a patient whose kidneys have failed.

Nephropathy—Kidney disease.

Proteinuria—Excess protein in the urine.

Serum creatinine—A chemical in the urine of kidney patients used to determine kidney disease and failure. Elevated levels of serum creatinine are an early marker for severe kidney disease or failure.

Transplantation—The implanting of an organ from either a deceased person (cadaver) or from a live donor to a person whose organ has failed.

gene that plays a role in sodium retention and the inter-conversion between cortisol and cortisone. The mutation of this gene is typically inherited in an autosomal dominant pattern.

In another study, researchers studied an Israeli family of Iraqi-Jewish origin whose members suffered from hypertension and renal failure. The researchers found a genetic locus at 1q21 that was autosomal dominant. They also hypothesized that the gene encoding *atrial natriuretic peptide receptor 1 (NPR1)* was the disease gene that led to the hypertension/renal failure.

Other families with high rates of hypertension have also been studied. For example, researchers observed a family of Old Order Amish in Lancaster, Pennsylvania, and found a genetic link for hypertension to chromosome 2q31-34. The subjects were not experiencing kidney failure, thus, further study would be needed to determine if the identified genetic locus also coded for ESRD.

Animal models are also indicating that genes associated with the coding of *HNF1*, a transcription factor related to disorders such as renal cell carcinoma and diabetes mellitus, may be associated with hypertension affecting the kidney.

Demographics

People of all ages, races, and both sexes may develop kidney failure due to hypertension. However, some groups are at much greater risk than others. African Americans are at particularly high risk for both hypertension and renal failure, and have three and a half times the number of ESRD cases as Caucasians. They also experience kidney failure at a younger age, with an onset at about age 56 compared to an onset at age 62 for Caucasians. African Americans also have a higher rate of

diabetes than non-African Americans, another reason for their increased risk for kidney failures. Native Americans and Alaskan Natives are also at high risk for ESRD. There are about the same number of males and females with newly diagnosed ESRD.

In 2012, there were 636,905 prevalent cases of ESRD due to hypertension in the United States, up 3.7% from the previous year. The risk increases with age, with environmental factors, and in combination with other disorders such as diabetes and other metabolic disorders.

Signs and symptoms

Universal symptoms of ESRD are severe fatigue, fluid retention (edema), and elevated blood pressure readings. Other symptoms include a failure to eat (anorexia) and skin color changes such as a change to a yellow-brown skin color. Urea from perspiration may appear on the skin as whitish crystals, similar to frost. Pruritus (severe itching of the skin) is common. Patients may have muscle cramps and convulsions. Many have malnutrition from anorexia and vomiting. Gastric ulcers are common, as are cardiac symptoms stemming from the retention of sodium and water. Anemia (low levels of iron in the blood) is also common.

Diagnosis

Diagnosis is based on the results of a physical examination and laboratory blood and urine tests. A patient who has end-stage renal disease looks very ill and has obvious fluid retention and clear indicators of severe disease. Anemia is common. Blood pressure is elevated, and even patients who did not have hypertension prior to the onset of ESRD will develop hypertension. Patients also usually have massive amounts of protein in the urine and high levels of serum creatinine. Urea levels are also raised.

Treatment and management

Once physicians diagnose end-stage renal disease, they must make a plan for dialysis. In addition, patients may be placed on restricted fluids. Anemia is treated and transfusions are given if anemia is severe. ACE inhibitor drugs may be prescribed at low doses to treat cardiac symptoms. Diuretics may be prescribed to reduce fluid retention. Multivitamins may be recommended because of food restrictions.

All patients with kidney failure, despite the cause of the failure, must receive kidney dialysis or kidney transplantation. Eventually, those on dialysis will require transplantation of a kidney, either from a recently deceased person or a live donor. (Each person has two

QUESTIONS TO ASK YOUR DOCTOR

- What are the characteristics of end-stage renal disease, and how is that condition related to hypertension?
- What evidence is there for the hypothesis that hypertension is at least partially a genetic disorder?
- Can hypertension be diagnosed prenatally or in newborn infants?
- What lifestyle choices can a person make to help control the progress of hypertension?

kidneys and can live normally with only one kidney.) About 13,000 kidney transplants are performed in the United States each year and about 47,000 people wait for a donated kidney each year.

There are two types of dialysis. The most common type of treatment is “hemodialysis,” a procedure that uses a machine called a dialyzer to clean and filter the blood, since the kidneys can no longer perform that function. A connection from the machine is made to the patient’s bloodstream and the blood travels through the dialyzer where it is cleaned for 2–4 hours. This procedure is generally performed three times a week. Patients must also change their diets to carefully limit the amount of salt, potassium, and fluids that are consumed, among other dietary restrictions that are given.

Peritoneal dialysis is another option for patients with kidney failure. In this procedure, the patient’s own abdominal lining (the peritoneal membrane) is used to help clean the blood. Rather than the patient’s own blood traveling to a machine, as with a dialyzer, a cleansing solution is transferred through a special tube (catheter) directly into the body. The catheter remains in the body. The number of treatments and time to perform the cleansing procedures varies.

Prognosis

Most patients will eventually need a transplanted kidney to continue to live. The survival rate for those on kidney dialysis after 1 year is about 80% and after 2 years, about 66%. However, the 5-year survival rate with dialysis is 29%, and the 10-year survival rate is only 8%.

In contrast, the survival rate for those who receive a transplanted kidney from a deceased person is 94% after 1 year, 92% after 2 years, and 80% after 5 years. The 10-year survival rate with a cadaver transplantation is

57%. The survival rates are higher when the kidney is from a live donor; for example, the survival rate after 5 years with a live donor kidney is 89% and about 77% after 10 years.

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ORGANIZATIONS

American Association of Kidney Patients, 2701 N. Rocky Point Dr., Suite 150, Tampa, FL 33607, (800) 749-2257, <http://www.aakp.org>

American Kidney Fund, 11921 Rockville Pike, Suite 300, Rockville, MD 20852, (899) 638-8299, <http://www.kidneyfund.org>

National Kidney Foundation, 30 E. 33rd St., New York, NY 10016, (800) 622-9010, info@kidney.org, <http://www.kidney.org>

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Renal-hepatic ciliopathy

Definition

Renal-hepatic ciliopathy refers to the ciliopathic disorders affecting the kidneys and liver. Ciliopathies are genetic disorders that stem from mutations in genes associated with primary cilia-cellular organelles that are required for sensing the environment and controlling molecular signaling pathways. Recent findings have shown that a number of genetic disorders that were not previously thought to be related may be linked by root causes in cilia-dependent dysfunctions.

Description

Nephronophthisis-related ciliopathies (NPHP-RC) are a group of rare autosomal recessive cystic kidney

KEY TERMS

Ciliopathy—A range of genetic disorders caused by mutations in cellular cilia, basal bodies, or by changes in ciliary function.

Cilium—A slender protuberance from a larger cellular body. Required for sensing environmental and chemical stimuli, controlling signaling and developmental pathways. Plural: cilia.

Hepatic—Pertaining to the liver.

Nephronophthisis—An autosomal recessive genetic disorder of the kidneys that usually affects children.

Renal—Pertaining to the kidneys.

Wnt Signaling—A signal transduction pathway that functions to pass signals from the outside of the cell to the inside of the cell. Signals are transduced through the binding of proteins to receptors on the plasma membranes of cells. The receptor then transfers the signal to additional signaling proteins that function inside the cell. Wnt signaling pathways regulate cell shape and growth, cell polarity, and cell-cell communication, among other required cellular mechanisms.

disorders. Most NPHP affect children, and while rare among the general population, they are the most common cause of kidney failure in children. It is expected that only 0.9 in a million people in the United States have NPHP. NPHP-RC include diseases such as Senior-Loken syndrome, which is a ciliopathy that can affect the eyes as well as the kidneys; Joubert syndrome, which affects the development of the cerebellum; and Meckel-Gruber syndrome, a multi-organ ciliopathy that is characterized by renal cystic dysplasia, polydactyly, central nervous system deformities, and hepatic developmental defects. NPHP is the most common genetic cause of end-stage renal failure and is characterized by many histological abnormalities as well as organ function problems.

Because primary cilia play such a diverse role in many different tissue types, ciliopathic diseases can have a wide range of symptoms and affect otherwise seemingly unrelated organs.

Genetic profile

Ciliopathies are most commonly autosomal recessive and can affect males and females equally. The majority of cases results from a family history of

disease, but about 5%–10% can occur from spontaneous *de novo* mutations.

Renal ciliopathies are the most common of the childhood-onset ciliopathies, occurring in 1 out of 20,000 live births. While most renal ciliopathic disorders are recessive, there are some cases where they can be autosomal dominant, especially if the mutation occurs in germ-line cells. Even in these cases, renal cysts only form in about 5% of cells that acquire a second mutation.

Hepatic ciliopathies show similar prevalence in both men and women, but cysts tend to be exaggerated in female patients, particularly if the woman has had multiple births or has used oral contraception. The majority of liver disorders are caused by mutations in ciliary proteins.

Demographics

Ciliopathy has been recorded in all ethnicities and generally affects men and women alike.

Signs and symptoms

In the cases of ciliopathies that affect the liver and kidneys, common symptoms include decreased urine concentration and the formation of cysts on the organs; this may or may not affect organ function and can often cause discomfort or abdominal pain. Because important cellular signaling is disrupted in ciliopathies, flaws in cell development alter how organs grow and function. It is also characteristic for multiple organs to be affected in ciliopathic disorders.

In patients with NPHP, approximately 15% exhibit renal failure or dysfunction, liver malformation, retinal dystrophy, or cerebellar hypoplasia. All these symptoms are due to the incomplete or incorrect development of organs because of mutations in proteins that localize to primary cilia and are required for cell differentiation and development.

Diagnosis

Congenital symptoms are associated with renal-hepatic ciliopathies and can include brain defects, extra fingers, and retinal degeneration. These characteristics can usually be seen early in life, if not prenatally. For those who know ciliopathic disorders run in their family, a family history can be developed, and potential inheritance probabilities can be calculated. Those who are born with or develop renal-hepatic disorders rely on palliative treatment to maintain organ function and for pain management.

Due to recent findings that many genetic disorders are related to mutations in ciliopathic proteins, there has

QUESTIONS TO ASK YOUR DOCTOR

- Relatives in my family have a ciliopathic disease. Is it possible that I could be a carrier?
- My child has been diagnosed with kidney disease; what form of the disease do they have and is there a course of treatment?
- I have a ciliopathic disease; can I pass it on to my children?
- What other disorders might be linked to the ciliopathic disease I have been diagnosed with?

been a developing interest in identifying not only more of the genes related to ciliopathies but also in the identification of their functions. To date, over 90 genes are associated with recessive mutations that cause ciliopathies; a better understanding of what roles the encoded proteins play in development could lead to more specialized treatments for ciliopathic disorders.

In one such study of 1,056 members of a family with NPHP-RC, 50% of the cases were due to a mutation in a gene whose function is unknown. Homozygosity mapping and sequencing were used to ID more genes that are associated with NPHP. The gene *DCDC2* was identified as one such gene that causes a renal-hepatic variant of NPHP-RC. *DCDC2* localizes with other NPHP-RC genes in primary cilia and interacts with DVL (Disheveled), a mediator of Wnt signaling. It is thought that *DCDC2* regulates cell division through its direct interaction with the Wnt signaling pathway. These results show that defects in Wnt signaling play a central role in NPHP-RC, and this identification opens the door to potential specialized treatment of the disease.

Treatment and management

Treatment is limited to dialysis or transplant for those whose kidneys fail due to ciliopathic disease. In some cases of hepatic ciliopathy the liver functions properly, but cyst development can affect quality of life. Cysts can be removed surgically but often grow back.

Some ciliopathies affect brain development, which can lead to learning and physical disabilities depending on the area of the brain that is most affected. In such cases, physical and educational therapies can be utilized to mediate or improve the patient's quality of life.

Prognosis

Because the symptoms and severity of ciliopathic diseases can vary so much, the prognosis can be unique to each individual case.

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- "Ciliopathy." ScienceDirect. <https://www.sciencedirect.com/topics/neuroscience/ciliopathy> (accessed June 18, 2021).

ORGANIZATIONS

- Ciliopathy Alliance, 91 Royal College St., London, UK NW1 0SE, <http://www.ciliopathyalliance.org>

Emily R. Larson, PhD

Renpenning syndrome

Definition

Renpenning syndrome is an inherited X-linked disorder that manifests itself in males. It is characterized by intellectual disability, short stature, a smaller than normal head circumference (microcephaly), and small testes. Hans Renpenning first described the syndrome in 1962 in a large Mennonite family living in Manitoba, Canada. The term "Renpenning syndrome" came to be used as a general designation for X-linked intellectual disability. However, as the syndrome has been mapped to Xp11.2-p11.4, the term "Renpenning syndrome" should be limited to the condition that maps to this region and is characterized by severe intellectual disability, microcephaly, short stature, and small testes. Its prevalence is unknown.

Description

Renpenning syndrome is among the group of genetic disorders known as X-linked intellectual disability (XLMR) syndromes. Developmental delay is present early, with males learning to walk at age 18–24 months



Renpenning syndrome is a form of intellectual disability linked to a gene abnormality on the X-chromosome. (Creations/Shutterstock)

KEY TERMS

Microcephaly—An abnormally small head.

Renpenning syndrome—X-linked intellectual disability with short stature and microcephaly not associated with the fragile X chromosome and occurring more frequently in males, although some females may also be affected.

Short stature—Shorter than normal height, can include dwarfism.

Small testes—Refers to the size of the male reproductive glands, located in the cavity of the scrotum.

X-linked intellectual disability—Subaverage general intellectual functioning that originates during the developmental period and is associated with impairment in adaptive behavior. Pertains to genes on the X chromosome.

and able to say simple words at age 3–4 years. Although an affected male may appear physically normal, his head circumference and height will be at the lower limits of normal. After puberty, testes will be smaller than normal. Diagnosis is very difficult, especially if there is only one male with intellectual disability in a family. The diagnosis is exclusively based on evidence of inheritance of the above clinical findings in an X-linked manner and localization to the short arm (Xp11.1-p11.4) of the X chromosome.

Genetic profile

Renpenning syndrome is caused by an alteration in the *PQBPI* gene located on the short arm (Xp11.2-p11.4) of the X chromosome and encodes the protein polyglutamine-binding protein 1. The function of polyglutamine-binding protein 1 is not well defined but is thought to be important in RNA processing and transport. Most of the mutations in *PQBPI* in cases of Renpenning syndrome produce a truncated protein that does not function properly or has partial function that interferes with the normal protein.

The altered gene in affected males is inherited from their mother, if she is a carrier for the mutation. Since males have only one X chromosome, a gene mutation on the X is fully expressed in males. Carrier females, with one normal X chromosome and one affected X chromosome, do not have any of the phenotype associated with Renpenning syndrome.

Female carriers have a 50% chance of transmitting the altered gene to a daughter or a son. A son inheriting the altered gene will have Renpenning syndrome and will likely not reproduce.

Demographics

Only males are affected with Renpenning syndrome. Carrier females do not express any of the signs or symptoms. Renpenning syndrome is a rare disorder and its prevalence across race and nationality is unknown. In the 15 families where it has been observed, more than 60 individuals have been identified.

Signs and symptoms

Manifestations of Renpenning syndrome may be present at birth. One male was reported to have global developmental delay at birth. All affected males had delay in reaching developmental milestones—walking at age 18–24 months and having little or no speech by age 3.

Affected males have a small head circumference (microcephaly), are of short stature, and have small testes. Facial features may include central balding, an upward slant to the eyes, and a short distance between the nose and the upper lip. Other clinical findings present in some of the affected males are blindness, seizures, and diabetes mellitus.

Mental impairment is severe, with IQ ranging from 15 to 40.

Diagnosis

The diagnosis of Renpenning can tentatively be made on the basis of the clinical findings, including an analysis of the family history for evidence of X-linked inheritance. Linkage or segregation analysis using DNA markers could possibly rule out other X-linked intellectual disability syndromes. Unfortunately, there are no laboratory or radiographic changes that are specific for Renpenning syndrome.

Sutherland-Haas syndrome, another X-linked intellectual disability syndrome, also has microcephaly, short stature, small testes, and upslanting of the eye openings. Furthermore, this syndrome is localized from Xp11.3 to Xq12, which overlaps with the localization of Renpenning syndrome. However, males with Sutherland-Haas also have spasticity, brachycephaly (disproportionate shortness of the head), and a thin appearance. It is possible these two syndromes have different mutations in the same gene.

The mutation that causes Chudley-Lowry syndrome, which also has microcephaly, short stature, and small testes, has yet to be identified. However, males have distinct

QUESTIONS TO ASK YOUR DOCTOR

- What does it mean to say that Renpenning syndrome is an “X-linked” genetic disorder?
- What physical and mental characteristics are typically associated with Renpenning syndrome?
- Do carriers for Renpenning syndrome exhibit any signs or symptoms related to the disorder?
- What treatments are available for the disease or related medical conditions?
- If Renpenning syndrome occurs in my family and I am a woman, how likely is it that I am a carrier?

facial features similar to those observed in XLMR-hypotonic faces, and obesity. As this syndrome has not been mapped it is possible that Chudley-Lowry syndrome results from a mutation in the same unknown gene responsible for Renpenning syndrome.

Three other X-linked intellectual disability syndromes (Borjeson-Forssman-Lehman, X-linked hereditary bullous dystrophy, and XLMR-hypotonic facies) have microcephaly, short stature, and small testes. However, these conditions are located in different regions on the X chromosome and can be ruled out if DNA marker analysis is done in the family.

Treatment and management

Treatment for Renpenning syndrome is supportive. Early educational intervention may prove to be of some benefit for affected males. Some males have been reported to have seizures or diabetes mellitus; medication to control these conditions may be required at some point. In more severe cases, individuals with the syndrome may eventually have to live in facilities outside the home.

Prognosis

Life-threatening or other health concerns have not been associated with Renpenning syndrome. However, the presence of severe mental impairment likely will result in some affected males living in a more controlled environment outside the home.

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ORGANIZATIONS

The Arc, 1825 K St. NW, Suite 1200, Washington, DC 20006, (202) 534-3731 or (800) 433-5255, (202) 534-3731, <http://www.thearc.org>

Charles E. Schwartz, PhD
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Retinitis pigmentosa

Definition

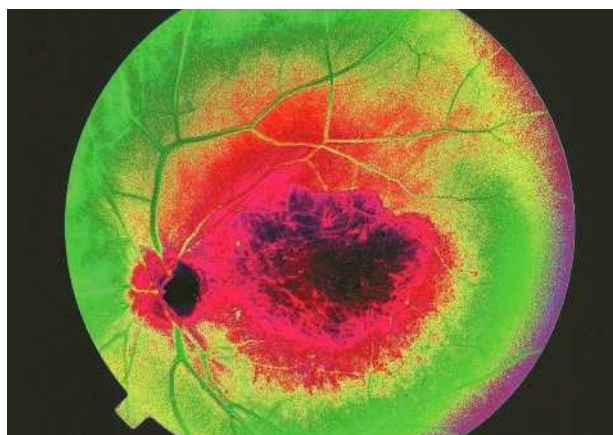
Retinitis pigmentosa (RP) refers to a group of inherited disorders that slowly lead to blindness due to abnormalities of the photoreceptors (primarily the rods) in the retina.

Description

The retina lines the interior surface of the back of the eye. The retina is made up of several layers. One layer contains two types of photoreceptor cells referred to as the rods and cones. The cones are responsible for sharp central vision, distinguishing and recognizing colors, and seeing fine details. The cones are primarily located in a small area of the retina called the fovea.

The area surrounding the fovea and on the perimeter of the retina contains the rods, which are necessary for vision on the sides, as well as vision in dark and dimly lit conditions. The number of rods increases in the periphery.

The rod and cone photoreceptors normally convert light that enters the eye into electrical impulses; these



A retinal photograph showing retinitis pigmentosa. The disorder first affects night vision and peripheral vision. (J. Cavallini/Custom Medical Stock)

impulses are sent to the brain along the optic nerve at the back of the eye and an image is recognized by the brain. Another layer of the retina is called the retinal pigmented epithelium (RPE).

In RP, the photoreceptors begin to break down and lose their ability to function. The rods are primarily affected, and as a result it becomes difficult to see in dim light and in the peripheral areas. The ability to see color is also lost in some cases. In the late stages of the disease, only a small area of central vision remains and this can also be lost.

There are many forms of retinitis pigmentosa and all of them are genetic. Sometimes the disorder is classified by the age of onset or by the inheritance pattern. RP can also be part of a medical syndrome, in which other medical problems are present. This entry focuses on nonsyndromic RP, the type that is not associated with other medical complications.

Genetic profile

RP is an inherited disease associated with different inheritance patterns. It is felt that as many as 100 genes can cause the various types of the condition. The RP may be a familial condition, in which multiple family members are affected. It may also be isolated (or simplex), in which there is only one person with RP in the family. People with isolated RP represent 10%–40% of all cases. Some of these may be the result of new gene changes (or mutations). Other isolated cases are those in which the person has a relative with a gene mutation, but that relative has no obvious signs of RP.

RP is most commonly inherited as an autosomal dominant, autosomal recessive, or sex-linked condition

in a family. Autosomal dominant RP (ADRP) occurs in about 15%–25% of affected individuals. At least 14 different genes have been identified as causing ADRP, with significant ones called the *RHO*, *RP1*, *RDS*, and *ROM1* genes. People with ADRP often have an affected parent and other relatives in multiple generations. Someone with ADRP has a 50% chance to have a son or daughter with the same type of RP.

Autosomal recessive RP (ARRP) occurs in about 5%–20% of affected individuals. At least 22 genes have been identified that cause this type of RP, including significant ones called *RPE65*, *PDE6A*, and *PDE6B*. In ARRP, each parent of the affected person is a carrier of a gene mutation that causes ARRP. Neither of these parents has symptoms of ARRP, and they have a 25% chance to have an affected son or daughter in every pregnancy together. All of the children of someone with ARRP would be a carrier for the condition.

Five to fifteen percent of people with RP have the sex-linked form of recessive RP, which is most often X-linked recessive RP (XLRP). At least five genes have been identified with XLRP, with the most significant called *RP2* and *RP3*. Males are usually more affected than females with XLRP and females carry an XLRP mutation on their X chromosome. Carrier females may not have signs of XLRP or they may have mild symptoms. In some cases, carriers have serious vision loss associated with XLRP. A female carrier's sons have a 50% chance of being affected, and her daughters have a 50% chance to be carriers. For a male with XLRP, his daughters would all be carriers, but none of his sons would be affected. RP is rarely inherited in an X-linked dominant manner. The risks to family members are very similar to XLRP, but females typically have some symptoms of RP instead. The family history pattern can be very similar to ADRP, and the difference may only be the gene mutation causing the RP in the family.

Rarely, RP is inherited by gene mutations in the *MTTS2* gene. This gene is located in the cell's mitochondria, as opposed to the cell's nucleus like all of the other genes. When the *MTTS2* gene is involved, only a female's sons and daughters would be at risk for RP. If a male has RP caused by the *MTTS2* gene, his children would not be at risk for RP.

Also very rarely, RP is caused by the involvement of both the *RDS* gene and the *ROM1* gene in the same family. An individual with RP may have a mutation in each of these genes. The risks to family members would be similar to those found in ADRP.

KEY TERMS

Amniocentesis—A procedure involving removal of a small amniotic fluid sample during pregnancy to obtain fetal genetic results.

Choroid—Layer of tissue underneath the retina.

Fundus—The interior back wall of the eyeball.

Melanin—Colored pigment that is naturally present in the eye.

Mitochondria—Structures within the cell responsible for making energy; contain their own genetic material, which is inherited through females.

Nucleus—Structure within the cell that contains most of a person's genetic material.

Ophthalmoscope—An instrument with special lighting, designed to view structures in the back of the eye.

Optic nerve—Nerve at the back of the eye that connects the retina to the brain.

Photoreceptor—Cells at the back of the eye that process the light that hits them; examples are cone and rod cells.

Demographics

RP is the most common form of blindness in people between the ages of 20 and 60 years old. It is thought to affect about 1.5 million men and women worldwide and approximately 1 out of every 3,500 to 4,000 people in the United States and Europe. For other parts of the world, there are no published data on exact prevalence, but RP is seen in all ethnic groups.

Signs and symptoms

The first symptoms are typically difficulties seeing in dimly lit conditions or night blindness. People may notice that they are uncomfortable with an oncoming car's bright headlights when driving at night, or they may have a hard time finding their seat in a darkened movie theater. People may begin to notice this as young as in childhood, adolescence, or later on in adulthood. In general, the earlier one notices this the more severe their RP may be over time. XLRP is usually associated with a more severe progression of symptoms than other forms of RP.

Eventually, people with RP experience a loss of peripheral vision and this may first start in childhood or early adolescence. This peripheral visual field loss typically progresses to tunnel vision, akin to seeing the world through two narrow straws. Prior to complete constriction

of their visual fields, people with undiagnosed RP may be considered clumsy by those who know them, because they may not see the things that are in the normal visual field.

People with RP usually maintain crisp central vision for a very long time, because the cones are not usually involved until the later stages of the condition. Once the cones become involved, people may have their central vision affected, with difficulty distinguishing colors. Occasionally, the loss of the ability to see color occurs before the loss of peripheral vision. Additionally, RP sometimes significantly affects one's visual acuity; men with XLRP may have a visual acuity less than or equal to that of legal blindness.

Specific changes in the eye are consistent with RP. In the early stages of RP, visual testing indicates abnormal rod functioning, but there may be no physical changes in the retina. People may see occasional flickering or small lights flashing in their eyes. Over time this can progress. There may be narrowing to the blood vessels in the retina, fine dust-like coloring within the retina, and floating in the eye's natural liquid. There is often loss of pigment from the layer of tissue underneath the retina. As the rods break down, clumps of dark-colored melanin cause a bone spicule formation along the retina's periphery. These are very characteristic of RP. Eventually, the optic nerve and retinal blood vessels can become pale in color. Others may have white dots deep in the retina, and other abnormalities of the optic nerve.

Those with RP often develop a specific type of cataracts, known as a posterior subcapsular cataract (PSC). These are different than the cataracts found in the general population. PSCs have a yellowish crystal-like appearance in the eye's lens, and this looks different than typical cataracts seen in those without RP. These cataracts may be removed by an ophthalmologist, but this does not help tunnel vision or night blindness.

People with RP usually have these changes in both of their eyes. However, some only have them in one section or one-half of an eye. This is called sector RP. People with this usually have no problems with night blindness, though visual testing can identify abnormal rod and cone functioning. Sector RP usually is inherited in a dominant manner, but is also seen in some female carriers of XLRP.

Diagnosis

A diagnosis of RP is usually made based on analysis of a person's symptoms, visual test results, and family history. Genetic testing is available for some types of RP.

When a person complains of problems with night vision, an ophthalmologist or optometrist usually

performs a careful eye examination, including pupil dilation, to determine if there are physical changes to the retina and back of the eye that are suggestive of RP. Other retinal problems can cause night blindness and must be ruled out. However, these may not have the retinal changes that are typical of RP. A careful eye examination can also determine one's visual acuity and color vision.

An electroretinogram (ERG) tests how well the photoreceptors in the retina are functioning. Specifically for RP, this test is very good at identifying how well the rod cells are working. It can also show how well the cone cells are working. A dark adaptation curve (DAC) test can document the exact amount of time one's eyes take to adjust to darkness.

Testing of the visual fields can determine how much is being seen from left to right, and up and down. The full field of vision is studied to identify any blind spots or clarify whether the central vision is affected.

Fluorescein angiography (FA) can be helpful to determine whether blood flow is normal throughout the back of the eye. These detailed photographs of the eye's blood vessels can help identify any circulatory problems at the back of the eye, as well as changes in the retina's structure.

Fundus photographs can be taken to document changes in the eye structure, shape, and color.

A consensus conference documented by Marmor et al. in 1983 established criteria to diagnose RP. They are:

- Rod dysfunction as measured by DAC or ERG
- Progressive loss in photoreceptor function
- Loss of peripheral vision
- Involvement of both eyes

Other eye conditions can mimic RP but do not have the specific eye changes and visual test results of RP. Gyrate atrophy of the choroid and retina, a recessive disorder, may seem like RP in its symptoms. However, it may be associated with round patches affecting the choroids and retina, which occur in the middle of the retina. Choroideremia, an X-linked recessive disorder, causes progressive blindness. However, it usually causes fine dark lines and patches on the choroids, which progress into pale yellow areas.

Leber congenital amaurosis is a group of recessive retinal abnormalities that cause serious vision problems or blindness that appear at or shortly after birth. Children affected with this condition usually have roving eye movements. Cone-rod dystrophy is a retinal problem in which the rods function well, but the cones progressively

QUESTIONS TO ASK YOUR DOCTOR

- What tests will you have to conduct to determine whether or not my child has retinitis pigmentosa?
- Does this genetic condition inevitably lead to blindness?
- What factors affect the rate at which this disorder progresses?
- What information can a genetic counselor provide about retinitis pigmentosa?

worsen. The symptoms may be similar to RP, but occur in the reverse order.

There are a few syndromes that involve RP. These include Usher syndrome and Bardet-Biedl syndrome. Usher syndrome is a group of recessive conditions that combine RP with deafness of varying degrees. Bardet-Biedl syndrome is a group of recessive conditions that combine RP with extra fingers and toes, mental delays, obesity, genital abnormalities, kidney abnormalities, and other medical complications. Genetic blood testing is available for some forms of Usher and Bardet-Biedl syndromes.

Genetic testing from a blood sample is available for some types of nonsyndromic RP on a clinical basis. In these cases, an abnormal result would identify a mutation (or mutations) in the gene causing RP for that individual. Other at-risk family members can sometimes be offered genetic testing once a mutation is identified in a family. In some cases, prenatal testing is available through an amniocentesis procedure. All genetic testing should be accompanied by careful genetic counseling.

Treatment and management

There is no cure for RP, or known way to stop the disease progression altogether. However, some things can help maintain good retinal function and health.

It is felt that a diet rich in leafy green vegetables and fish may be good for the retina. In addition, certain fish contain omega-3 fatty acids, such as docosahexaenoic acid (DHA) that is naturally found in the retina in very high concentrations. Eating a diet of fish like salmon, tuna, mackerel, or whitefish twice a week should naturally provide good DHA levels. Otherwise, good fish oil capsules containing DHA and other omega fatty acids can be obtained with a prescription or purchased at specialty health stores.

Multivitamins containing vitamins A, E, and C may be useful. These have antioxidant properties, which may be protective for the eyes. However, large doses of certain vitamins may be toxic, and affected individuals should speak to their doctors before taking supplements.

Protecting the eyes from harmful ultraviolet rays is essential to cone cell health. People with RP should wear good sunglasses outdoors and especially when over water or near snow on a bright, sunny day.

Smoking has been associated with deteriorating retinal health. Even quitting smoking late in life can make a positive impact on eye health.

PSCs do not usually severely impact the vision of those with RP. However, in some cases an ophthalmologist can remove the eye's lens and replace it with an artificial one to remove the cataract.

Low vision aids can be helpful for those in school or at work. Binocular lens and magnifying screens, large-print reading materials, closed-circuit television, special eyeglass lenses, and other tools can be helpful and are often available from organizations supporting those with vision loss.

Living with a chronic vision problem makes a significant impact on a person's life and family. It is often helpful for families to have a social worker connect them to helpful resources. Others may find genetic counseling, psychotherapy, or meeting other individuals with RP through support groups helpful.

Prognosis

Life expectancy is normal in RP. It eventually leads to serious visual impairment or blindness. The more severe forms will lead to blindness sooner than the milder forms, but each person's experience with the condition is unique and impossible to predict. Research and future treatments continue to offer hope for those with RP.

Resources

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"Retinitis Pigmentosa." National Eye Institute. <https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/retinitis-pigmentosa> (accessed July 9, 2021).

ORGANIZATIONS

American Association of the Deaf-Blind, PO Box 8064, Silver Spring, MD 20907-8064, (301) 563-9064, aadb-info@aadb.org, <http://www.aadb.org>

Foundation Fighting Blindness, 7168 Columbia Gateway Dr., Suite 100, Columbia, MD 21046, (800) 683-5555, info@FightBlindness.org, <http://www.blindness.org>

Foundation of the American Academy of Ophthalmology, PO Box 7424, San Francisco, CA 94120-7424, (415) 561-8500, <http://www.aao.org>

Retinitis Pigmentosa International, PO Box 900, Woodland Hills, CA 91365, (800) 344-4877, info@rpinternational.org, <http://www.rpinternational.org>

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Amy Vance, MS
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Retinoblastoma

Definition

Retinoblastoma is a rare cancer affecting the retina of one or both eyes. It occurs mainly in children under the age of five. The retina is the part of the eye that captures the images of the outside world and transfers these images to the brain. Most cases of retinoblastoma result when both copies of the RB1 gene, or less commonly the MYCN gene, have a pathogenic variant (mutation).



Retinoblastoma is a rare cancer affecting one or both eyes, most often in young children. (Custom Medical Stock)

In some case *RB1* gene variants can be passed down in families.

Description

Retinoblastoma accounts for about 4% of all cancers in children younger than age 15. Sixty percent of people with retinoblastoma have unilateral retinoblastoma, which affects only one eye. Unilateral retinoblastoma is usually diagnosed at age two. Forty percent of cases are bilateral, affecting both eyes, and these are usually diagnosed at 15 months.

Many of the early symptoms of retinoblastoma, such as intermittent pain of the eye, inflammation of the eye, and poor vision, are often overlooked. It is often a parent who first notices a whitish-appearing pupil (leukocoria), which leads to the diagnosis of retinoblastoma. If retinoblastoma is detected early enough, treatment such as surgery or radiation can result in a 95% cure and survival rate. If left untreated, retinoblastoma cancer cells can spread to other areas of the body, including the bone marrow.

Genetic profile

In order for cancer to develop, multiple genes in a retinal cell need to change (mutate). In some cases, the change produces a variant (mutation) in a tumor-suppressor gene. A tumor suppressor contains instructions for a protein that normally helps stop cancer from starting. Tumor suppressor proteins work by regulating cell growth and preventing cells from dividing too quickly or abnormally. In other cases, the variant activates a gene that causes the cell to grow out of control (oncogene). Variants in these genes cause the cells in

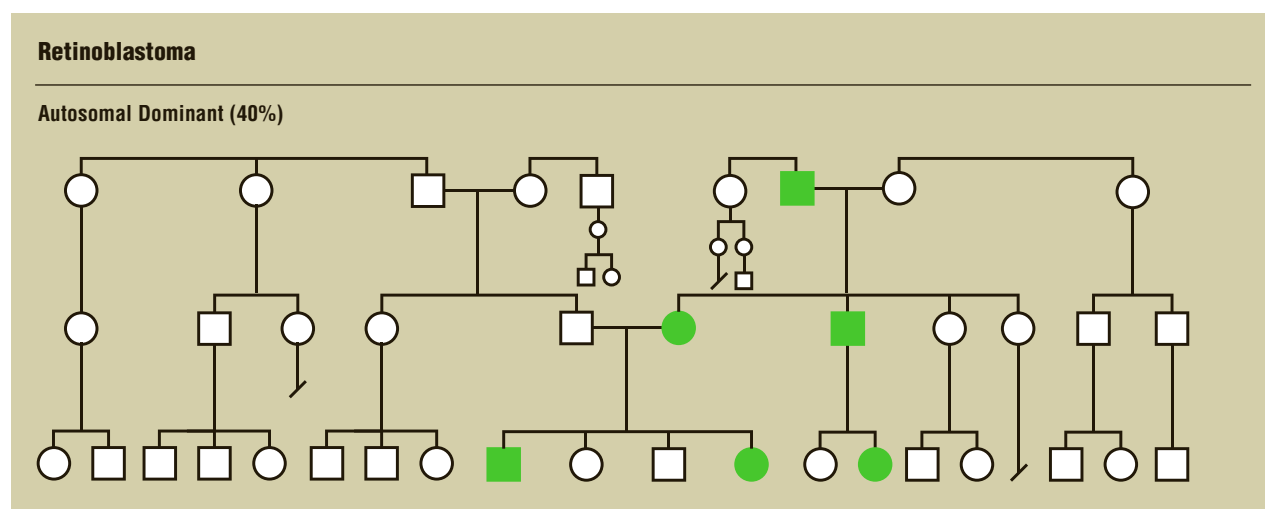
the retina to divide uncontrollably and form cancerous tumors.

The most important gene that is involved in retinoblastoma is *RB1*, which is a tumor suppressor gene. For most people with this condition, the retinoblastoma starts only if both copies of the *RB1* gene have variants in at least one cell. In 1.5% of individuals with isolated unilateral retinoblastoma, there are no variants in their *RB1* gene. Instead, they have variants in both copies of their *MYCN* oncogene.

About one in three people with retinoblastoma are born with a variant in the *RB1* gene in every cell of their body. This is called germline retinoblastoma. People with germline retinoblastoma have a 50% chance of passing it on to their children. For three out of four (75%) children, this germline variant happened early in fetal development (de novo). The other one out of four (25%) inherited it from one of their parents.

Having germline retinoblastoma increases the risk of cancer, because a variant only has to happen in the other *RB1* gene in one cell for cancer to develop. What causes a variant in the other copy of the gene is not known, but in some cases, DNA-damaging agents, such as radiation, tobacco, or UV light, might be responsible.

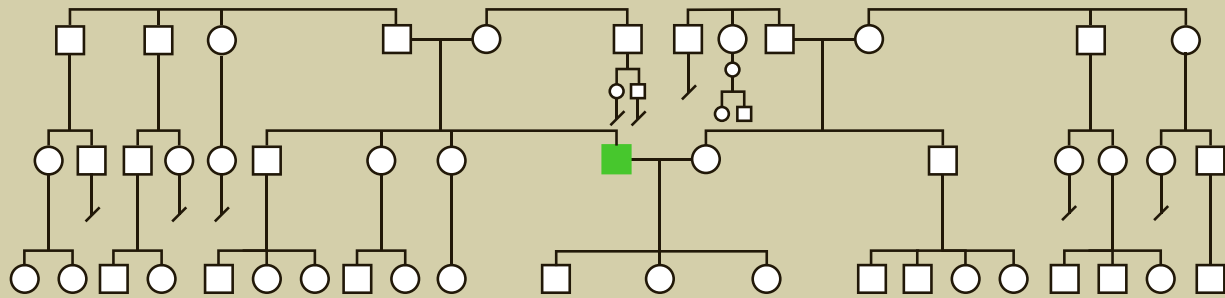
In some cases, the variant can look de novo but actually have come from a variant that was in the sperm or egg. This is called germline mosaicism. In those cases, some of the eggs from the mother or some of the sperm from the father have a variant in one copy of their *RB1* gene. A person with germline mosaicism has less than a 1% chance (approximately 0.08%) of having another child with retinoblastoma. Although a low risk, this is



Retinoblastoma: pedigree analysis chart (Gale)

Retinoblastoma

Sporadic



Retinoblastoma: pedigree analysis chart (Gale)

still 200 to 500 times higher than the general population's risk. If the germline variation is inherited from a parent who also has a germline variant, then the risk to other siblings is 50%

In germline retinoblastoma, the *RB1* gene variant is inherited in an autosomal dominant pattern, which means that a variant in only one copy of the *RB1* gene is sufficient to increase cancer risk. The retinal cancer does not happen unless the other copy acquires a variant in at least one retinal cell, which usually happens after the child is born. A person with bilateral retinoblastoma usually has germline retinoblastoma. But individuals with germline retinoblastoma can also have unilateral cancer. Those with germline retinoblastoma are also at an increased risk for other types of cancer.

The chance that someone with germline retinoblastoma will develop retinal cancer depends on the type of variant that they have. Most people with germline retinoblastoma have a null variant that produces no normal protein. They have a greater than 99% chance of developing retinal cancer. Fewer than one in ten (10%) people with germline retinoblastoma have a variant where their risk of cancer is only about 25(10%). In some rare cases, the risk of getting developing cancer is higher if the variant comes from the father rather than the mother.

Retinoblastoma can also be sporadic, which means that the child is born with two normal copies of the *RB1* gene and the *MYCN* gene. In sporadic retinoblastoma, both copies of either the *RB1* or *MYCN* gene acquire variants. What causes these variants is not known, although in some cases DNA-damaging agents such as radiation, tobacco, or UV light might be responsible. Retinoblastoma caused by variants in the *MYCN* gene are always sporadic. In sporadic retinoblastoma,

usually only one eye is affected. Genetic testing can usually determine whether the retinoblastoma is germline or sporadic.

Some people have mosaic retinoblastoma, meaning that they have a variant in their *RB1* gene in only some of the cells of their body, which can increase their risk of retinoblastoma. The degree of risk depends on how many cells have the variant. It can be difficult to diagnose mosaic retinoblastoma.

Approximately 5% to 8% of people with retinoblastoma have a piece missing (deletion) of chromosome 13 that contains the *RB1* gene. Because this chromosomal deletion includes other genes, affected children usually display other symptoms, such as intellectual disability, slow growth, and distinctive abnormal facial features.

Demographics

Retinoblastoma is the most common type of eye cancer in children. It accounts for about 4% of all cancers in children younger than age 15. It occurs worldwide in approximately one in 15,000–20,000 births. Approximately 250–300 children and adolescents are diagnosed with retinoblastomas each year in the United States. Most retinoblastoma cases occur among young children, with almost 63% of all retinoblastomas occurring before the age of two, and 95% occurring before the age of five. Rates of retinoblastoma are essentially equal among males and females and among different races and ethnicities.

Signs and symptoms

Since the successful management of retinoblastoma depends on detecting it early, recognition of the

signs and symptoms of the condition is critical, especially for primary care physicians, who are often the first medical personnel to see infants or children with retinoblastoma.

There are many ways that retinoblastoma can present itself in infants and children. More than half of all patients with the condition will have a white pupil reflex called leukocoria. In healthy infants and children, their pupils will appear black or, when photographed, red. However, patients with retinoblastoma will often have a pupil that appears gray or white.

The second most commonly presenting sign of retinoblastoma, occurring about 25% of the time, is a crossed eye, a medical condition referred to as strabismus. The child's eye may appear to be looking out toward the ear, called *exotropia*, or inward toward the nose, called *esotropia*. It should be noted that 3% to 4% of all American children present with some form of strabismus, but not all of these children have retinoblastoma. However, since 25% of children with retinoblastoma have strabismus, any child with this condition should have a detailed eye exam to rule out retinoblastoma.

While leukocoria and strabismus are the two most commonly presenting signs of retinoblastoma, there are other ways the condition may present itself. Other symptoms may include a red, painful eye, poor vision, orbital cellulitis (inflammation of the skin and tissue around the eye), and amblyopia, or "lazy eye." Heterochromia, a difference in coloration of the irises (the colored part in the

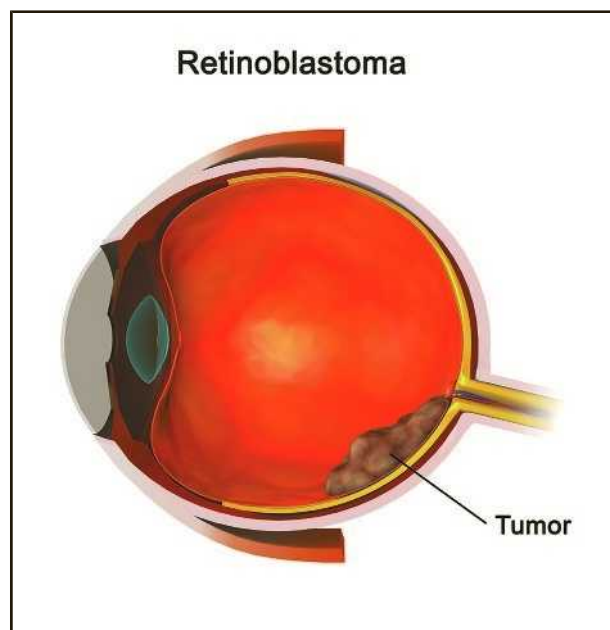


Illustration of a retinoblastoma, a rare cancerous tumor in the retina of eye. (Stocktrek Images/Science Source)

KEY TERMS

Esotropia—A form of strabismus in which one or both eyes turns inward.

Exotropia—A form of strabismus where the eyes are deviated outward.

Germline retinoblastoma—A type of retinoblastoma where all cells of the body have a variant in one copy of the *RB1* gene. This can be inherited or result early in the development of the embryo.

Leukocoria—An abnormal white reflection from the retina.

Mosaic retinoblastoma—A type of retinoblastoma where a variant in one copy of the *RB1* gene is found in only some cells of the body.

Pathogenic variant—A variation in a gene that causes problems with the protein the gene produces.

Retina—Multilayered sensory tissue that lines the back of the eye. It contains millions of photoreceptors that capture light rays and convert them into electrical impulses. These impulses travel along the optic nerve to the brain, where they are turned into images.

Sporadic retinoblastoma—A type of retinoblastoma where the cancer-causing gene variants happen in a retinal cell after birth and are not inherited.

Strabismus—A condition in which the eyes are not properly aligned with each other.

center of the eye surrounding the pupil), may also be the first sign of retinoblastoma.

Other Symptoms of Germline Retinoblastoma

People with germline retinoblastoma are at increased risk for benign (non-cancerous) retinal tumors called retinomas. Retinomas sometimes develop into cancer, but other times they stay benign. These individuals are at slightly increased risk for tumors in retinal-like tissue in the pineal gland of the brain. These tumors are rare and usually fatal.

People with germline retinoblastoma are also at increased risk for tumors in other parts of the body, such as the bone, muscles, and skin. These tumors usually develop in adolescence or adulthood. The chance of developing one of these tumors is 50% in people with germline retinoblastoma who also have had radiation

therapy. Even those who have not had radiation treatment have a high lifetime risk of cancer.

Diagnosis

The diagnosis of retinoblastoma is frequently made by the parents of an infant or child with the condition. Often, the parents will tell the physician that they have noticed that their child's eye looks "white," or that the child's eye or eyes seem to drift to one side or the other.

When a child is born into a family with a history of retinoblastoma, diagnosis of the condition can often be made before the baby leaves the hospital, by an ophthalmologist. If there is no family history, and the initial diagnosis is made by the parents or family physician, then the child can be sent to an ophthalmologist for a more thorough eye exam.

To examine a child for retinoblastoma, dilating drops are placed in both eyes to dilate (enlarge) the pupils and allow the ophthalmologist to view the retina. If a tumor is seen or suspected, an ultrasound examination, which uses sound waves to penetrate and outline structures in the eye, is used to confirm the presence of a tumor. Computed tomography (CT) scans use computers to take very detailed pictures of the inside of the body and can be used to see whether there are tumors in other parts of the body.

Genetic Testing

Since the gene responsible for retinoblastoma has been identified, genetic testing is available. Individuals who are most likely to have germline retinoblastoma are those with bilateral retinoblastoma, retinoblastoma in the family, or those with unilateral retinoblastoma with multiple tumors. They should all have blood testing for variants in the *RB1* gene.

People with unilateral retinoblastoma who have only one tumor and no family history of the disease can first have testing of their tumor tissue. If an *RB1* variant is found, then a blood test looking for this variant should be done. If no tumor tissue is available, then they should have blood testing for *RB1* variants.

Treatment and management

Treatment options for retinoblastoma have significantly increased over the past twenty years. The earliest form of treatment for retinoblastoma was *enucleation*, the removal of the major portion of the affected eye. This procedure led to total loss of vision in that eye. While enucleation is still used, especially when the tumor is very large, newer and more sophisticated treatments have emerged that offer the chance to save at least some vision in the affected eye.

QUESTIONS TO ASK YOUR DOCTOR

- My child has just been diagnosed with unilateral retinoblastoma. What is the long-term prognosis for the disorder likely to be?
- What kind of ongoing treatment does my child need to deal with this disorder?
- What are the differences in symptoms and prognosis between unilateral and bilateral retinoblastoma?
- Are there surgical treatments for retinoblastoma?

Lasers can be used in a treatment known as photocoagulation. This treatment is best used when the tumor is small and confined to the retina. The laser is actually used to burn and destroy blood vessels that feed the tumor rather than directly on the tumor itself. The treatment can be repeated once or twice, and in some studies complete remission of the retinoblastoma has been achieved in 70% of patients.

Another treatment that works well with tumors that are confined to the retina is cryotherapy. It may be used as either the primary mode of treatment or in conjunction with other treatment modalities. Like photocoagulation, cryotherapy has its highest success rates with smaller tumors. Unlike photocoagulation, cryotherapy uses extreme cold to destroy the tumor itself.

Thermotherapy uses heat generated from ultrasound or microwaves to destroy the retinoblastoma tumor. While thermotherapy works well on its own with small tumors, it is even more effective when used with chemotherapy or radiation therapy, which are thought to make the tumor more susceptible to the heat generated by thermotherapy.

The use of radiation treatment is not recommended, as it can increase the risk of future tumors. Of patients who receive external beam radiation, 35% develop another retinoblastoma within a 30-year time frame. It is, therefore, only used if treatment, such as cryotherapy or photocoagulation, fails or cannot be used due to large tumor size. While radiation is applied directly to the tumor, with careful application, the eye itself can be saved from destruction in about 75% of patients.

Probably the most significant advancement in the treatment and management of retinoblastoma has come about in the use of chemotherapy. While in the past, chemotherapy was only used to treat patients whose tumors had spread outside the eye, newer chemotherapy agents,

such as carboplatin and etoposide, along with older agents such as vincristine, are being used with significant success to treat tumors that are confined to the eye. Using these chemotherapeutic agents, it has been shown that tumors typically decrease in size 30% to 45% of the time. This then allows more conservative and eye-sparing therapy, such as cryotherapy and photocoagulation, to be used much more effectively. New chemotherapies that precisely target the tumor, while sparing vision and reducing side effects, are being developed. New criteria such as the RB-RECIST criteria will help to better evaluate the efficacy of chemotherapeutic agents targeting retinoblastoma in clinical trials.

Monitoring

Children with germline RB1 variants should have eye examinations under anesthesia every three to four weeks until they are six months old, and then every three to six months until age three. After that, they should have yearly exams until age seven, and then exams every two years for the rest of their life. DNA-damaging agents such as radiation, tobacco, and UV light should be avoided when possible.

Even people who do not appear to have germline retinoblastoma, should have regular clinical examination of the eyes, including ultrasound. This is because they could have mosaic retinoblastoma.

Prognosis

The prognosis for the vast majority of patients with retinoblastoma is excellent. In the United States, over 95% of children with retinoblastoma survive and lead healthy, productive lives.

Children who have unilateral retinoblastoma have at least one normal eye and can lead normal childhood lives, and even drive cars as they get older. The majority of children with bilateral retinoblastoma retain some vision in one eye, and sometimes in both eyes. However, all children who are affected with bilateral retinoblastoma and 15% of children with familial unilateral retinoblastoma have a higher risk of developing other cancers throughout their lives. Therefore, children in these categories need to have regular medical checkups throughout their lives to watch for any signs of secondary cancers in areas such as bone, muscle, skin, and brain.

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American Cancer Society (ACS), 250 Williams Street, NW, Atlanta, GA 30303, (800) 227-2345, <http://www.cancer.org>

The Foundation of the American Academy of Ophthalmology, P.O. Box 7424, San Francisco, CA 94120-7424, (415) 561-8500, <http://www.aao.org>

National Cancer Institute (NCI), BG 9609 MSC 9760, 9609 Medical Center Drive, Bethesda, MD 20892-9760, (800) 422-6237, <http://cancer.gov>

National Eye Institute (NEI) Information Office, 31 Center Drive MSC 2510, Bethesda, MD 20892-2510, (301) 496-5248, 2020@nei.nih.gov, <http://www.nei.nih.gov>

Retinoblastoma International, 18030 Brookhurst Street, P.O. Box 408, Fountain Valley, CA 92708, info@retinoblastoma.net, <http://www.retinoblastoma.net>

Edward R. Rosick, DO, MPH, MS
Revised by Lisa M. Andres, MS, CGC

Retinoic acid embryopathy see **Accutane embryopathy**

Rett syndrome

Definition

Rett syndrome is a progressive neurological disorder seen almost exclusively in females. The most common symptoms are decreased speech, intellectual disability, severe lack of coordination, small head size, and unusual hand movements.

Description

Dr. Andreas Rett first reported females with the symptoms of Rett syndrome in 1966. Females with this X-linked dominant genetic condition are healthy and of average size at birth. During infancy, head growth is abnormally slow and microcephaly (small head size) develops. Babies with Rett syndrome initially have normal development. At approximately one year of age, development slows and eventually stops. Patients with Rett syndrome develop autistic features. Involuntary hand movements are a classic feature of Rett syndrome.

Females with Rett syndrome may also develop seizures, curvature of the spine (scoliosis), irregular breathing patterns, swallowing problems, constipation, and

difficulties walking. Some females with Rett syndrome are unable to walk. There is currently no cure for Rett syndrome. Most girls with Rett syndrome live until adulthood. The gene responsible for Rett syndrome has been identified and genetic testing is available.

Genetic profile

Rett syndrome is an X-linked condition. This means that the mutation (genetic change) responsible for Rett syndrome affects a gene located on the X chromosome. The affected gene is the methyl CpG-binding protein 2 (*MECP2*) gene. This gene makes a protein that regulates other genes. When there is a mutation in *MECP2*, the protein it makes does not work properly. This is thought to prevent normal neuron (nerve cell) development.

Rett syndrome is considered to be X-linked dominant in nature. Males have one X chromosome and one Y chromosome. Females have two X chromosomes. Males with a mutation in their *MECP2* gene typically die as infants or are miscarried before birth. Rett syndrome is usually considered fatal in males because the Y



Maryjane Luntz, a child with Rett syndrome, works on her hand-eye coordination by trying to pop bubbles. The disorder leads to developmental reversals. (ZUMA Press, Inc./Alamy)

chromosome cannot compensate for the *MECP2* mutation on the X chromosome. Females with a mutation in the *MECP2* gene develop Rett syndrome, but the presence of the second X chromosome in females carrying a normal *MECP2* gene enables them to survive.

The severity of the syndrome in females is related to the type of mutation in the *MECP2* gene and the activity of the X chromosomes. Normally, both X chromosomes have the same activity. However, the activity can be unequal. If the X chromosome with the mutation in the *MECP2* gene is more active than the X chromosome without the mutation, the female is more severely affected. The reverse is also true. If the X chromosome without the mutation is more active than the X chromosome with the mutation, the female is less severely affected.

If a woman has a mutation in her *MECP2* gene, she has a 50% risk with any pregnancy to pass on her X chromosome with the mutation. However, it is uncommon for women with Rett syndrome to have children due to the severity of the disorder.

Demographics

The incidence of Rett syndrome is estimated to be 1 in 8,500 females. It is seen almost exclusively in females. The vast majority of cases of Rett syndrome are sporadic in nature. Therefore, the risk of a family having more than one affected daughter is typically very low.

Signs and symptoms

Infants with Rett syndrome typically have normal size at birth. They develop normally until approximately 6–18 months of age. Development then slows, eventually stops, and soon regresses. Affected individuals are unable to do things they were once able to do. Girls with Rett syndrome lose the ability to speak, become uninterested in interacting with others, and stop voluntarily using their hands. The loss of language and eye contact causes girls with Rett syndrome to appear to be autistic. Between one and three years of age, girls with Rett syndrome develop the unusual hand movements that are associated with the disease. Patients wring their hands, clap their hands, and put their hands in their mouth involuntarily. Some patients with Rett syndrome also lose the ability to walk. If the ability to walk is maintained, the gait is very ataxic (uncoordinated, clumsy).

By preschool age, the developmental deterioration of girls with Rett syndrome stops, but they continue to have lack of speech, inability to understand language, poor eye contact, intellectual disability, ataxia, and apraxia (inability to make purposeful movements). Other common symptoms associated with Rett syndrome include

KEY TERMS

Apraxia—Impairment of the ability to make purposeful movements, but not paralysis or loss of sensation.

Ataxia—A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

Autism—A syndrome characterized by a lack of responsiveness to other people or outside stimulus. Often in conjunction with a severe impairment of verbal and nonverbal communication skills.

Microcephaly—An abnormally small head.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Neuron—The fundamental nerve cell that conducts impulses across the cell membrane.

Scoliosis—An abnormal, side-to-side curvature of the spine.

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

seizures, constipation, irregular breathing, scoliosis, swallowing problems, teeth grinding, sleep disturbances, and poor circulation. As patients with Rett syndrome get older, their ability to move decreases and spasticity (rigidity of muscles) increases.

Diagnosis

The diagnosis of Rett syndrome is made when the majority of the symptoms associated with the disease are present. If a physician suspects an individual has Rett syndrome, DNA testing is recommended. Approximately 75% of patients with Rett syndrome have a mutation in the *MECP2* gene. DNA testing can be performed on a blood sample, or other types of tissue from the body. If a mutation is found in the *MECP2* gene, the diagnosis of Rett syndrome is confirmed.

Treatment and management

Currently there is no cure for Rett syndrome. Treatment of patients with Rett syndrome focuses on the symptoms present. Treatment may include medications that inhibit seizures, reduce spasticity, and prevent sleep disturbances. Nutrition is monitored in females with Rett

QUESTIONS TO ASK YOUR DOCTOR

- What are the typical signs and symptoms of Rett syndrome?
- Why does this disorder occur almost exclusively among females?
- Given that we already have one daughter with Rett syndrome, what is the probability of having a second child with the same genetic disorder?
- What is the prognosis for our daughter with Rett syndrome, and on what information do you base that prognosis?

syndrome due to their small stature and the constipation associated with the disorder.

Prognosis

In the absence of severe medical problems, most patients with Rett syndrome live into adulthood.

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ORGANIZATIONS

Alliance of Genetic Support Groups, 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008, (202) 966-5557, (202) 966-8553, <http://www.geneticalliance.org>

International Rett Syndrome Association, 9121 Piscataway Rd., Clinton, MD 20735, (800) 818-RETT, <http://www.rettssyndrome.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>
Rett Syndrome Research Foundation, 4600 Devitt Dr., Cincinnati, OH 45246, <http://www.rsfr.org>

Holly A. Ishmael, MS, CGC

RFH1 see **Renal failure due to hypertension**

Rheumatoid arthritis

Definition

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting the joints, most often in the hands and feet. It results in swelling; stiffness; pain; and sometimes joint, bone, and cartilage destruction.

Description

Rheumatoid arthritis (RA) belongs to a group of diseases called autoimmune disorders that affects joints. In RA, the immune system, the function of which is to protect the body, produces antibodies that attack the soft tissues lining the joints. Eventually the cartilage, bone, and ligaments of the joint deteriorate, causing deformity, instability, and scarring within the joint. The rate at which the joints deteriorate varies with the individual. A number of risk factors including genetic predisposition, gender, and unspecified environmental factors may put a person at risk for developing the disease, as well as influence the pattern of the disease.

As with other forms of arthritis, RA involves inflammation of the joints. A membrane called the synovium lines each of the body's movable joints. In RA, white blood cells that normally protect against invaders such as bacteria and viruses move from the bloodstream into the synovium, causing inflammation to the synovial membrane. This inflammation is called synovitis and results in the release of proteins that over time cause thickening of the synovium. These proteins can also damage cartilage, bone, tendons, and ligaments. Gradually the joint loses its shape and alignment, and eventually may be destroyed.

Genetic profile

RA is a genetically complex disease. Studies in monozygotic (identical) and dizygotic (fraternal) twins indicate that genetic factors are involved in acquiring the susceptibility or tendency to RA rather than the disease itself. People with certain human leukocyte antigen (HLA) genes—specifically, the genetic marker called

HLA-DR4 (the *DR4* refers to the specific antigen)—are more likely to develop the disease than those without the genes. However, people without this antigen can develop the disease as well.

The *HLA-DR4* marker is found in white blood cells and plays a role in helping the body distinguish between its own cells and foreign invaders. In addition, these genes help predict the severity of the disease and how effectively the disease responds to treatment. The mechanism by which HLA alleles (HLA genetic variations) affect disease risk is still under investigation.

In one study, French scientists found 63 genes that appear to be linked to the development of RA. The group studied and compared the expression of 5,200 genes in the synovial fluid of a group of patients with RA and another group with osteoarthritis. The researchers found 48 known and 15 unknown genes that were either overexpressed or underexpressed in RA patients compared with osteoarthritis patients. Two of the novel genes were located on chromosome 6, at the p21 region, which is an area already linked to inflammatory disease. Four other genes were located on the X chromosome.

RA is three times more common in smokers than in nonsmokers, particularly in men. Vitamin D deficiency has also been linked to RA prevalence. While the link is

not well understood and some of the data are conflicting, it is thought that because the active metabolite 1,25-dihydroxyvitamin D3 (1,25D) indirectly affects bone metabolism, a deficiency in vitamin D may also contribute to RA.

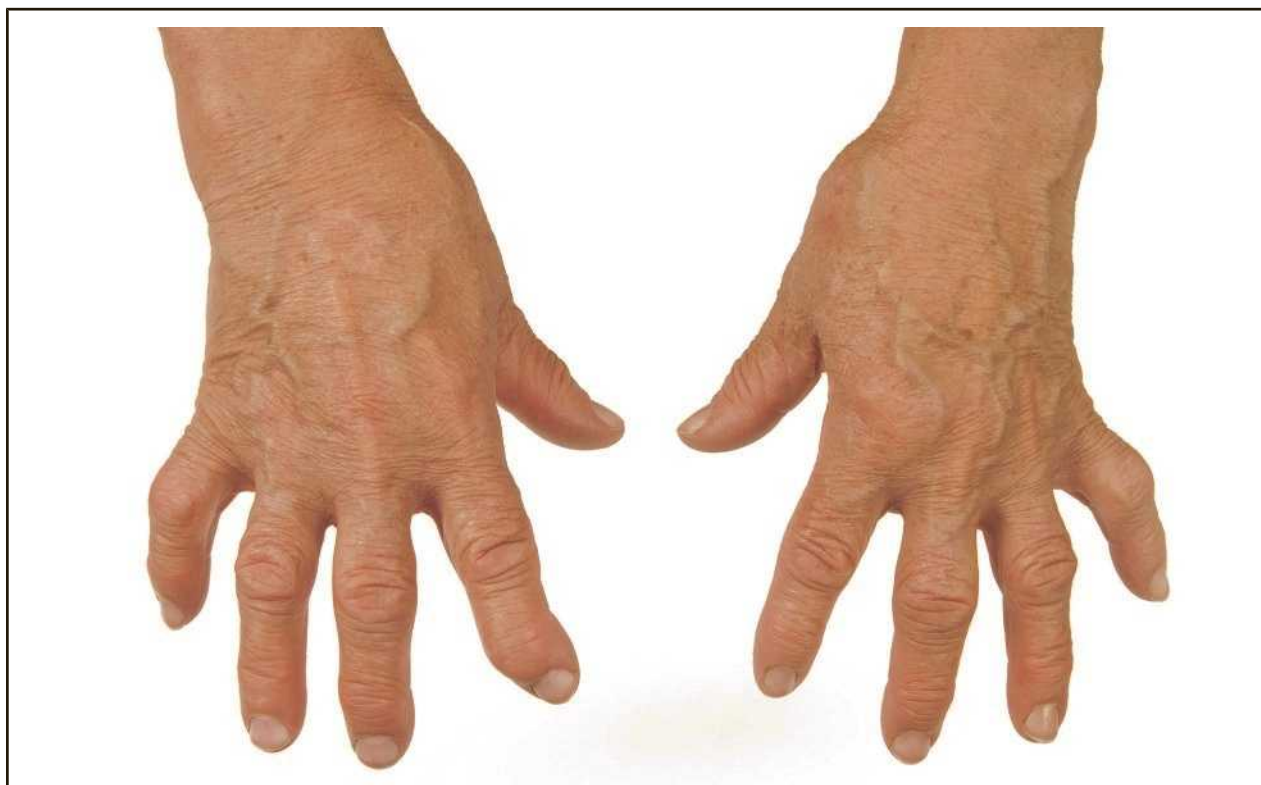
Demographics

Rheumatoid arthritis affects approximately 1% of the worldwide population. Although some people have a mild form of RA, 70% eventually develop chronic problems and 15% have a severe, crippling form of the disease.

The disease occurs in all races and countries, and although RA affects women two to three times more often than men, men tend to be affected more severely by it. The onset of RA most commonly occurs between the ages of 25 and 50, but children and adolescents as well as the elderly may also be affected. When the disease occurs in children it is referred to as juvenile RA.

Signs and symptoms

The course of RA can vary with each case; some people may have mild symptoms, occasional flare-ups, and long periods without disease (remission), or they



A woman's hands affected by rheumatoid arthritis. (Hriana/Shutterstock)

may have RA that progresses steadily at different rates. The disease may begin suddenly with many joints becoming inflamed simultaneously. Most often, however, RA begins subtly and gradually affects different joints. Usually the inflammation is symmetric with joints on both sides of the body affected. Typically the small joints in the hands, feet, wrists, elbows, and ankles become inflamed first. The inflamed joints are usually painful and often stiff, especially just after awakening or after prolonged inactivity. This stiffness generally lasts for at least 30 minutes but can also last much longer. Some people feel tired and weak, especially in the early afternoon. In addition, RA may produce a low-grade fever.

Affected joints enlarge because of swelling of the soft tissue and can quickly become deformed. Joints may freeze in one position and cannot bend or open fully. The fingers may tend to dislocate from their normal position toward the little finger on each hand, causing tendons in the fingers to slip out of place.

Swollen wrists can pinch a nerve and result in numbness or tingling due to carpal tunnel syndrome. Cysts can develop behind affected knees and rupture, causing pain and swelling in the lower legs. Up to 30% of people with RA have hard bumps (rheumatoid nodules) just under the skin, usually near sites of pressure. Common areas for rheumatoid nodules to develop are on the back of the forearm near the elbow.

In rare cases, RA causes an inflammation of blood vessels called vasculitis; this condition reduces the blood supply to tissues and may cause nerve damage or leg sores (ulcers) that may become infected. Inflammation of the membranes covering the lungs (pleura) or of the sac surrounding the heart (pericardium), or inflammation and scarring of the lungs, can lead to chest pain and shortness of breath. Some people develop swollen lymph nodes, dry eyes or mouth, or red, painful eyes as a result of inflammation associated with RA.

Diagnosis

In addition to the important characteristic pattern of symptoms, many tests may be used to support the diagnosis.

Laboratory tests may include rheumatoid factor, white blood cell count, anemia, erythrocyte sedimentation rate (ESR or sed rate), and C-reactive protein, which is a marker for inflammation.

Many people with RA have certain characteristic antibodies in their blood that are present in 70% of people with RA. The rheumatoid factor antibody occurs in RA and several other diseases, such as hepatitis and other infections. Some people even have rheumatoid factor in their blood without any evidence of disease. A higher level of rheumatoid factor in the blood usually results in



X-ray of a patient's hand with severe rheumatoid arthritis in all of the fingers. (Zephyr/Science Photo Library/Alamy)

a more severe RA and a poorer prognosis, and the level may decrease when joints are less inflamed.

Most people who suffer from RA have mild anemia (an insufficient number of red blood cells). Rarely the white blood cell count becomes abnormally low but when a person with RA has a low white blood cell count and an enlarged spleen, the disorder is called Felty's syndrome.

Nine out of ten people with RA have an elevated sed rate, which depends on certain proteins present in the blood. An elevated sed rate suggests that active inflammation is present; however, this test alone cannot identify the cause of the inflammation. Doctors may monitor the sed rate when symptoms are mild to help determine whether RA is still active.

A needle biopsy may be recommended to examine joint fluid or a tissue sample from rheumatoid nodules.

Characteristic changes in the joints may be monitored through the use of x-rays.

Treatment and management

Treatments for RA have improved in recent years, although most treatments involve medications and in some cases surgical procedures may be necessary.

Medications for RA can relieve its symptoms and slow or halt its progression. Nonsteroidal anti-inflammatory drugs (NSAIDs) help to alleviate both pain and inflammation if taken on a regular basis. These drugs are available without a prescription and include aspirin, ibuprofen, and naproxen. These medications are available at higher dosages by prescription.

Taking NSAIDs on a regular basis can lead to adverse side effects, such as indigestion and stomach bleeding. Other potential harmful side effects may include damage to the liver and kidneys, ringing in the ears (tinnitus), fluid retention, and hypertension (high blood pressure).

Initially, it was thought that COX-2 inhibitors, another class of NSAIDs, were less damaging to the stomach than the traditional NSAIDs. It was believed that NSAIDs work against two versions of the COX enzyme present in the body: COX-1 and COX-2. However, there is increasing evidence to suggest that by suppressing COX-1, which is the enzyme responsible for protecting the stomach lining, NSAIDs may cause stomach and other problems. Unlike other NSAIDs, COX-2 inhibitors suppress only COX-2, the enzyme involved in inflammation. Celecoxib (Celebrex), which is one of the few COX-2 inhibitors still on the market in the United States, suppresses an enzyme called cyclooxygenase (COX) that is active in joint inflammation.

Side effects of COX-2 inhibitors may include fluid retention and causing or exacerbating high blood pressure. Furthermore, this class of drugs has been linked to an increased risk of heart attack and stroke. These are reasons why Merck Pharmaceuticals chose to remove its COX-2 inhibitor rofecoxib (Vioxx) from the worldwide market in September 2004. About 1.3 million people in the United States and about 700,000 abroad were using the drug. In April 2005, the COX-2 inhibitor valdecoxib (Bextra) manufactured by Pfizer was voluntarily removed from the market at the request of the FDA due to the reported potential risks of heart attack, stroke, and potentially life-threatening skin reactions that were greater than its benefits. The FDA also announced new label requirements for both prescription and nonprescription NSAIDs. Prescription labels for COX-2 inhibitors like celecoxib were required to carry a “black box warning” that stressed the life-threatening effects associated with the drug.

In December 2004, the FDA issued a Public Health Advisory recommending limited use of COX-2 inhibitors. The guidelines warned patients against the use of COX-2 inhibitors if they were at high risk of gastrointestinal bleeding and had a history of intolerance to certain NSAIDs. The risks commonly associated with NSAIDs should be taken into account for each patient as

KEY TERMS

Antibodies—Protein molecules the body produces to fight infection.

Autoimmune disorder—Disorder occurring when the body's tissues are attacked by its own immune system.

Cyclooxygenase-2 (COX-2) inhibitors—Anti-inflammatory drugs that work by blocking the COX-2 enzyme, which plays a role in the inflammatory process. COX-2 inhibitors do not block the COX-1 enzyme, which helps protect the digestive tract.

Inflammation—A localized protective response elicited by injury or destruction of tissues and characterized by pain, heat, redness, swelling, or loss of function.

Tumor necrosis factor (TNF)—A protein that plays an early and major role in the rheumatic disease process.

individuals can respond differently to the medication. Consumers are advised that all nonprescription pain relievers, including NSAIDs, should be used exactly as specified on the label. If NSAIDs are needed for more than 10 days, the FDA suggests that a doctor be consulted.

The FDA's actions differ from the recommendations of an FDA expert advisory panel, which, in February 2005, voted in favor of allowing COX-2 inhibitors celecoxib and valdecoxib to remain available. The panel also voted to allow rofecoxib back on the market but under strict conditions.

Corticosteroids like prednisone (Deltasone) and methylprednisolone (Medrol) reduce inflammation and pain, and slow the progression of joint damage and destruction associated with RA. In the short term, corticosteroids alleviate pain significantly but when used for many months or years these drugs tend to lose their efficacy and cause serious side effects that may include bruising, thinning of bones, cataracts, weight gain, and diabetes. Doctors often prescribe corticosteroids to alleviate acute symptoms with the goal of gradually tapering off the medication when the patient's pain decreases.

Physicians prescribe disease-modifying antirheumatic drugs (DMARDs) to limit the amount of joint damage that occurs in RA. Taking these drugs during the early stages in the development of RA is especially important in an attempt to slow disease progression and save the joints and other tissues from permanent damage.

Because many of these drugs act slowly it may take weeks to months to detect any benefit. Typically DMARDs are used in combination with an NSAID or a corticosteroid. Although the NSAIDs or corticosteroids alleviate any immediate symptoms and limits inflammation, the DMARDs act directly on the disease. Commonly used DMARDs include hydroxychloroquine (Plaquenil), the gold compound auranofin (Ridaura), sulfasalazine (Azulfidine), and minocycline (Dynacin and Minocin). Additional forms of DMARDs include immunosuppressants and tumor necrosis factor (TNF) blockers.

Immunosuppressants are used to suppress the immune system, which is overactive in RA. In addition, some of these drugs attack and destroy cells associated with the disease. Some of the commonly used immunosuppressants include methotrexate (Rheumatrex), leflunomide (Arava), azathioprine (Imuran), cyclosporine (Neoral, Sandimmune), and cyclophosphamide (Cytoxan). These medications may have potentially serious adverse side effects; for example, increased susceptibility to infection.

The TNFs are a class of DMARDs known as biologic response modifiers. TNF is a type of protein called a cytokine. Cytokines act as inflammatory agents in RA. TNF blockers target or block cytokine activity and can help reduce pain, morning stiffness, and tender or swollen joints, typically within one or two weeks after initiating treatment. There is evidence that TNF blockers may halt the progression of the disease. Often these medications are taken in combination with the immunosuppressant methotrexate. The TNF blockers approved for treatment of RA include etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira). These medications should not be taken if active infection is present because they inhibit the immune response.

Interleukin-1 receptor antagonist (IL-1RA) is a molecule that competes with the naturally occurring molecule interleukin-1 (IL-1) for the binding of the interleukin-1 receptor (IL-1R). IL-1RA is an inhibitor of inflammatory responses, where IL-1 promotes inflammation and occurs at high levels in people with RA or other types of inflammatory arthritis. As IL-1RA outcompetes IL-1 for binding of IL-1R, the inflammatory response is decreased. IL-1RA is a naturally occurring molecule but can also be produced synthetically as a treatment for inflammatory disease.

The first IL-1RA approved by the FDA for use in individuals with moderate to severe RA who have not responded adequately to conventional DMARD therapy is anakinra (Kineret). This drug may be used alone or in combination with methotrexate. Anakinra is administered as a daily self-injection. Some potential side effects

include injection-site reactions, decreased white blood cell counts, headache, and increased upper respiratory tract infections, especially in people with asthma or chronic obstructive pulmonary disease. If active infection is present, anakinra should not be used.

Some people with RA also experience symptoms of depression. The most common antidepressants used for RA pain and for sleep that is not restful are amitriptyline (Elavil), nortriptyline (Aventyl, Pamelor), and trazodone (Desyrel).

Although a combination of medication and self-care is the first course of action for RA, other methods are available in severe cases of the disease. The Prosorba column is a blood-filtering technique used to remove certain antibodies that contribute to pain and inflammation in the joints and muscles and is usually performed once a week for 12 weeks on an outpatient basis. Some of the side effects of this procedure include fatigue and a temporary increase in joint pain and swelling for the first few days after the treatment. The Prosorba column treatment is not recommended in combination with angiotensin-converting enzyme (ACE) inhibitors or if heart problems, high blood pressure, or blood-clotting problems are present.

Joint replacement surgery is an option chosen by many people with RA when less invasive methods or medications are not able to alleviate pain and deter joint destruction. Joint replacement surgery can often help restore joint function, reduce pain, or correct a deformity when joints are severely damaged. In some cases the entire joint may need to be replaced with a metal, ceramic, or plastic prosthesis. Surgery may also involve tightening or loosening tendons, fusing bones to reduce pain, or removing a portion of a diseased bone to improve mobility. The inflamed joint lining may also require removal (synovectomy).

Prognosis

In rare cases, RA resolves spontaneously; however, at least 1 out of 10 people with RA eventually becomes severely disabled.

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American Academy of Orthopaedic Surgeons, PO Box 2058, Des Plaines, IL 60017, (800) 824-2263, <http://www.aaos.org>

American College of Rheumatology, 1800 Century Place, Suite 250, Atlanta, GA 30345, (404) 633-3777, <http://www.rheumatology.org>

Arthritis Foundation, 1330 W. Peachtree St., Atlanta, GA 30309, (800) 283-7800, <http://www.arthritis.org>

National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health. 1 AMS Circle, Bethesda, MD 20892-3675, (877) 226-4267, <http://www.niams.nih.gov>

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Rhizomelic chondrodysplasia punctata

Definition

Rhizomelic chondrodysplasia punctata is a rare and severe inherited disease that affects brain development. The main features are limb shortening, bone and cartilage abnormalities that are visible on x-ray, abnormal facial appearance, severe intellectual disability, profound psychomotor retardation, and cataracts. Skeletal abnormalities can be seen prenatally, and most affected individuals die in infancy. No treatments are available.

Description

Rhizomelic chondrodysplasia punctata (RCDP) causes an abnormal protein that is localized to the peroxisome cells. The inside of the cell contains compartments called organelles that perform specific functions. Cells contain several peroxisome compartments that function in many metabolic processes, especially those involving lipids (fats) and hydrogen peroxide. RCDP is considered to be a peroxisomal disorder, as well as a metabolic disorder.

KEY TERMS

Anticoagulant—Drugs used to prevent blood clots.

Cell—The smallest living unit of the body, which group together to form tissues and help the body perform specific functions.

Differentiate—Specialized development to perform a particular function.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Metabolism—The total combination of all of the chemical processes that occur within cells and tissues of a living body.

Plasmalogens—The fat molecules that are important components of cells and of the myelin sheath that protects nerve cells.

Protein—Important building blocks of the body composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

Psychomotor—Movement produced by action of the mind or will.

Chondrodysplasia punctata describes similar conditions to RCDP because they describe a feature that is present in all four conditions but that differ in cause, associated features, and inheritance patterns; however, the causes, features, and patterns of inheritance of the other chondrodysplasia punctata conditions are different from those of RCDP.

There are three types of RCDP that have similar features and can be distinguished by the mutations in the different genes that cause them. RCDP1 is the most common and is caused by mutations in the *PEX7* gene; RCDP2 is due to a mutation in *GNPAT*; and RCDP3 is caused by mutations in *AGPS*. All these genes function in the synthesis of lipids called plasmalogens, whose function is not well understood but are found in the membranes in cells throughout the body. It is not yet clear how the loss of plasmalogens leads to the symptoms seen in RCDP.

Genetic profile

Rhizomelic chondrodysplasia punctata is an autosomal recessive condition. This means that it occurs in both males and females and can affect people who have no family history of the condition. Humans have two copies

of every gene, one maternally and one paternally inherited. Autosomal recessive conditions occur when a person has two abnormal copies of the same gene. People who have one abnormal copy and one normal copy of a particular gene are unaffected and are considered to be carriers for that disorder. A person affected with RCDP has inherited two abnormal genes, one from each parent. The risk for carrier parents to have another affected child is 25% with each pregnancy.

In 1997, *PEX7* was identified as the gene that causes RCDP. Fifteen genes involved in the synthesis of peroxisomes have been identified in humans and are classified as *PEX* genes. The proteins they code for are called peroxins. Disorders caused by abnormalities of peroxin proteins are often called peroxisomal biogenesis disorders.

The *PEX7* gene codes for a peroxisomal component that helps transport other important proteins into the peroxisome. The proteins to be transported contain a signal, called peroxisome targeting sequence 2 (PTS2) that is recognized by the receptor on the peroxisome. When *PEX7* is abnormal, the receptor that normally recognizes and helps transport the PTS2 proteins is not functional, thus having a cascade effect on many other cellular processes.

Demographics

RCDP is quite rare, occurring in fewer than 1 in 100,000 births. The incidence of peroxisomal biogenesis disorders is approximately 1 in 50,000 births, with RCDP accounting for less than one-fifth of these.

Signs and symptoms

Rhizomelic refers to shortening of the bones near the center of the body (the bones of the thighs and upper arms more so than the bones of the forearms and lower legs). Chondro refers to cartilage and dysplasia to abnormal development. Punctata refers to specific abnormal spotting on the ends of bones near the hip, knee, elbow, and shoulder joints that can be seen on radiological studies. The spots represent unusually dense cartilage and are also called punctate calcifications. Other abnormalities include frozen joints (called contractures), abnormal facial features, cataracts, hearing loss, severe intellectual disability, and profound psychomotor retardation. People with RCDP may also have other bone abnormalities, small heads, coarse and sparse hair, and dry, red skin.

The proximal shortening of the bones causes short stature, which is apparent before birth. Growth after birth is stunted as well. The rhizomelic shortening is severe and occurs to the same degree on both sides of the body. Severe intellectual disability is defined as a level of cognitive deficits worse than those of typical Down

QUESTIONS TO ASK YOUR DOCTOR

- What is the meaning of the term “rhizomelic chondrodysplasia punctata”?
- What causes this disorder?
- Is there any cure for this disease or any treatment to slow its progress?
- How long does a child with rhizomelic chondrodysplasia punctata typically survive?

syndrome. Some researchers have described degeneration of brain tissue after birth but the reason for this is unclear; it may be due to toxic effects of excess phytanic acid. Due to the abnormal facial features, those with RCDP have been called “koala bear faces.” Facial features include a broad forehead and a saddle nose.

Not all people with RCDP present all of the typical symptoms, and because the spectrum of features in RCDP is variable, some are more mildly affected than is typical. These differences in severity appear to be associated with different mutations in the *PEX7* gene.

Diagnosis

Although the physical and radiographic features can raise suspicion of RCDP, laboratory testing is required for making an accurate diagnosis. People with RCDP have very specific biochemical abnormalities, due to the underlying defect in the peroxisome. The specific abnormalities are (1) deficient plasmalogen synthesis leading to very low plasmalogen levels in red blood cells, (2) inability to process (oxidize) phytanic acid leading to elevated levels of phytanic acid in the blood, and (3) an unprocessed form of peroxisomal thiolase. Phytanic acid levels are normal at birth and increase to at least 10 times the normal level by one year of age. Some experts recommend that additional studies be performed on cells obtained by skin biopsy to confirm the diagnosis.

The biochemical studies to diagnose RCDP can be performed prenatally on cells obtained by chorionic villus sampling (CVS) or amniocentesis. CVS is usually performed from 10–12 weeks of pregnancy and amniocentesis after 15 weeks of pregnancy. RCDP may also be suspected in a fetus based on ultrasound findings.

The features of RCDP are seen in many other conditions; for example, rhizomelic limb shortening is seen in dwarfism, and chondrodysplasia punctata is a symptom of many inherited conditions but can also be caused by

prenatal exposure to the anticoagulant drug Warfarin. Doctors who specialize in diagnosing rare genetic conditions use subtle differences between the symptoms of these conditions to narrow their search for the suspected diagnosis. Many peroxisomal disorders have abnormal very long-chain fatty acids (VLCFAs) but VLCFA levels are normal in RCDP.

RCDP is the only condition that is caused by abnormal *PEX7* gene. Genetic testing is one method to confirm the diagnosis. A doctor who specializes in medical genetics can determine whether this testing is available clinically.

Treatment and management

The only treatments for RCDP are supportive therapies that address symptoms. People with RCDP, especially those who are less severely affected benefit from symptomatic support of various specialties such as ophthalmology and physical therapy. Dietary restrictions or supplements have shown promise in the treatment of some peroxisomal disorders. A serious issue in the severe cases is that many of the abnormalities develop before birth and are irreversible. The multiple biochemical abnormalities of RCDP also complicate treatment efforts. Some treatments try to improve the function of the deficient metabolic process and, if they work, will probably benefit patients mildly affected with RCDP more so than those that are severely affected by the disease.

The underlying cause of the severe intellectual disability is not well understood, although some abnormalities of nerve tissue have been described and are implicated in contributing to this symptom. In many peroxisomal disorders similar to RCDP, the nerve tissue migrates abnormally before birth. This abnormal migration is not present in RCDP, suggesting that in RCDP the nerve tissue may not differentiate properly once it has migrated to the correct location in the body.

Prognosis

The prognosis for the typical individual with RCDP who is severely affected is death in infancy. Most affected infants die in the first two years of life; however, exceptions have been reported in the medical literature. Individuals who lived past the age of ten years have been reported. For atypical or mildly affected patients the prognosis is variable.

Scientists' understanding of peroxisomal disorder, and of the peroxisome itself, increased enormously, but developing effective treatments of RCDP is a great challenge. Increased awareness of RCDP is leading to more

accurate diagnoses and higher clinical suspicion. A correct diagnosis is critical in providing accurate recurrence, prognosis, and prenatal diagnosis information.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

RhizoKids International, 50 Cross Creek Lane, Alpine, AL 35014, <http://www.rhizokids.com>

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Rhodopsin

Definition

Rhodopsin is the visual pigment that "senses" light in the rod cells of the retina.

Description

Rhodopsin is found at the back of the eye, in the retina. The retina is the area of the eye that senses light, interprets that information, and transmits it to the brain for further interpretation. Two types of light-sensing cells are found in the retina: rods and cones. In a simplified explanation, rod cells are responsible for black and white vision, whereas cone cells are responsible for color vision. This is true as far as it goes, but there are many more differences between rods and cones.

In rod cells, rhodopsin is responsible for phototransduction, the process of turning light into chemical and electrical energy. Rhodopsin is responsible for

phototransduction in rod cells, but not in cone cells. Three different proteins, similar to rhodopsin, govern phototransduction in the cone cells. Each of these three phototransducers responds to a different color of light, which allows persons with normal color vision to see the entire color spectrum.

In order to understand more of the structure, function, and location of rhodopsin, a discussion of cells and cell membranes is necessary. Every human cell has a cell membrane that separates the environment inside the cell (intracellular environment) from the extracellular (outside the cell) environment. Cell membranes are made up of lipids, which are hydrophobic substances. Hydrophobic literally means fear of water. Oil is an example of a hydrophobic substance. If oil is added to water, the oil will separate itself from the water. Basically, the lipids in the cell membrane form a similar water-excluding ball, but the inside of the ball will contain water and other intracellular fluids. Each rhodopsin molecule crosses the cell membrane seven times, and each area of the protein in the cell membrane is called a transmembrane domain. These transmembrane domains (which are hydrophobic) dictate an interesting structure for rhodopsin. Imagine folding a hose seven times to hold it in your hand. The structure for rhodopsin is at least that complex. Rhodopsin has seven transmembrane domains because that structure is common to G proteins, and rhodopsin is a G protein. G proteins are generally involved in a biological cascade. A biological cascade is a system where a small initial input (like a brief flash of light) can result in a rather large output.

Rhodopsin is a combination of two different molecules: retinal and opsin. Retinal is a derivative of vitamin A, and opsin is a protein. When rhodopsin is not activated, retinal is in the 11-cis configuration. When light hits 11-cis retinal, it changes its shape to become all-trans retinal. This is the only light-sensitive step in vision (in the rod cells). What the configurations are called and what those names mean is not as important as the fact that this light-dependent change in conformation results in light being converted into chemical energy.

Once retinal reaches the all-trans conformation, opsin also changes its shape. The new opsin-retinal complex is called metarhodopsin II. Metarhodopsin II is a semistable complex that is the active form of rhodopsin. Metarhodopsin II, unlike the inactive rhodopsin, is able to bind a protein called transducin. Each metarhodopsin II can bind to many transducins (literally hundreds). These transducins then cause a decrease in cGMP concentration, and one transducin molecule can cause the breakdown of more than 1,000 cGMP per second. One can clearly see why the G protein cascades are excellent systems for amplifying a signal.

QUESTIONS TO ASK YOUR DOCTOR

- What is rhodopsin, and what is its function in the process of vision?
- What abnormalities in rhodopsin can lead to genetic disorders?
- How serious are these disorders?
- Are there treatments for genetic rhodopsin abnormalities?

Genetic profile

Mutations in rhodopsin can result in two different disorders—retinitis pigmentosa and congenital stationary night blindness. Retinitis pigmentosa (RP) affects about 1 in 3,000 persons living in the United States, and about 1.5 million persons worldwide. Many mutations, not just mutations of the rhodopsin gene, lead to RP. The disorder may be inherited in an X-linked recessive fashion in 8% of all cases, an autosomal dominant fashion in 19% of cases, or as an autosomal recessive disorder in 19% of all cases. In the rest of the cases (54%), the mutations do not follow classical genetic patterns of inheritance. Mutations in rhodopsin have been found to cause approximately 20% of the autosomal dominant form of RP. The rhodopsin gene is located at the 3q locus of the chromosome.

Patients with retinitis pigmentosa exhibit symptoms that include night blindness, abnormal pigment accumulation in the retina, and a progressive decrease in the visual fields. The patient's vision decreases from the outermost edges in. The age of onset of the disorder may be as young as six months, but most patients experience the first symptoms between ages 10 and 30. In RP, the patient's rod cells usually degenerate first, followed by a loss of cone cells.

Signs and symptoms

Symptoms may often present after a motor vehicle accident. Not only is the age of onset variable, but the severity of the disease is as well. Patients with the same mutation, even within the same family, exhibit differing severities of the disorder. Mutations in rhodopsin may also cause autosomal recessive cases of RP.

Congenital stationary night blindness (CSNB) is another disorder that can be caused by mutations in the rhodopsin gene. Patients with CSNB, as may be deduced from the name, experience night blindness. However, unlike RP, patients with CSNB do not

experience degeneration (death) of cells of the retina (rod and cone cells). Patients with CSNB are thought to have an overactive transducin molecule, which prevents their rods from functioning normally. A mutation in transducin that also causes CSNB supports this theory, since this transducin is also thought to be overly active.

Treatment and management

No effective treatment for RP exists. However, new treatments are being explored for RP. Experiments in rats have shown that rod cells can be affected by gene therapy. Although gene therapy has not been successfully demonstrated as of this printing, at least the hope now exists that eventually gene therapy may be applied to the problem of RP. Previously, addition of a new gene into a nondividing cell line had been thought to be technically insurmountable. Another experiment in rodents offers hope for those who have autosomal recessive RP. Rats with autosomal recessive RP have been successfully treated with retinal pigment transplantation, according to Columbia University's *Retinal Transplant* newsletter. This technique might prove promising in humans.

Prognosis

The prognosis for persons with RP is extremely variable. Persons with CSNB will experience night blindness throughout their lives.

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Rhodopsin-related retinitis pigmentosa see **Rhodopsin**

Rhymes syndrome see **Retinitis pigmentosa**

Ribonucleic acid see **RNA (ribonucleic acid)**

RIEG see **Rieger syndrome**

Rieger syndrome

Definition

Rieger syndrome is a rare disorder characterized by absence and/or malformation of certain teeth, mild craniofacial (relating to the head and the face) abnormalities, and various eye abnormalities. The eye abnormalities, referred to as Rieger eye malformations, may be present separately or as a part of Rieger syndrome.

Description

First characterized by Herwigh Rieger, an Austrian ophthalmologist, in 1935, Rieger syndrome is a dominantly inherited disease. Disease expression is highly variable, including craniofacial, ocular, and dental malformations. Symptoms may also include myotonic dystrophy (a condition characterized by delay in the ability to relax muscles), umbilical abnormalities (abnormalities relating to where the umbilical cord attaches to a baby), and other defects. Psychomotor retardation, a slowing of the motor action directly proceeding from mental activity, occurs in some cases.

Rieger syndrome is also sometimes referred to as goniodysgenesis hypodontia, iridogoniodysgenesis with somatic anomalies, or RGS. It is a multiple congenital anomaly syndrome, a syndrome marked by multiple abnormalities at birth. Currently, there are two genetic types of Rieger syndrome identified. Type I results from a mutation on chromosome 4, and Type II from a mutation on chromosome 13.

Genetic profile

Rieger syndrome is inherited as an autosomal dominant disease. In autosomal dominant inheritance, a single abnormal gene on one of the autosomal chromosomes (one of the first 22 nonsex chromosomes) from either parent can cause the disease. One of the parents will have the disease (since it is dominant) and is the carrier. Only one parent needs to be a carrier in order for the child to inherit the disease. A child who has one parent with the disease has a 50% chance of also having the disease.

There is evidence that there is more than one genetic form of Rieger syndrome. The disease gene responsible for Rieger syndrome Type I is caused by mutations in the *RIEG1* gene, which is located on the long arm (q) of chromosome 4 (4q25-Q26).

Linkage studies have indicated that a second type of Rieger syndrome, type II, maps to the long arm of chromosome 13, at 13q14 (gene *RIEG2*).

Demographics

Rieger syndrome is very rare. Little is known in regard to the number of affected individuals or whether certain areas or ethnic groups are at a greater risk. Since the disease appears to be inherited in an autosomal dominant manner, meaning that it is transmitted on one of the nonsex chromosomes, males and females have an equal chance of acquiring the abnormal gene from their parents.

Signs and symptoms

The symptoms of Rieger syndrome are expressed variably. The main symptoms of Rieger syndrome are:

- Ocular malformations, called Rieger eye malformations, include underdeveloped iris, a small cornea (microcornea), an opaque ring around the outer edge of the cornea, adhesions (abnormal union of surfaces normally separate) in the front of the eye, and/or displacement of the pupil of the eye so that it is not centered.
- Dental abnormalities include a congenital condition causing a fewer number of teeth than normal (hypodontia); a condition in which a single tooth, pairs of teeth, or all the teeth are smaller than normal (microdontia) and/or cone-shaped.
- Craniofacial abnormalities include a protruding lower lip, a broad, flat bridge of the nose, and/or underdeveloped bones of the upper jaw (hypoplasia) causing the face to have a flat appearance.

Other conditions that have been found in some patients with Rieger syndrome are:

- Anal stenosis (a small anal opening).
- Failure of the skin around the navel to decrease in size after birth.
- Protrusion of intestine through a weakness in the abdominal wall around the navel (umbilical hernia).
- Glaucoma (increased pressure within the eyeball) may result from the ocular malformations associated with Rieger syndrome, including defects in the angle of the eye that is created by the iris and cornea (trabecula), the vein at the corner of the eye that drains the water in the eye into the bloodstream (Schlemm's canal), and the associated adhesions. Glaucoma can result in damage

KEY TERMS

Cornea—The transparent structure of the eye over the lens that is continuous with the sclera in forming the outermost, protective layer of the eye.

Craniofacial—Relating to or involving both the head and the face.

Hypoplasia—Incomplete or underdevelopment of a tissue or organ.

Iris—The colored part of the eye, containing pigment and muscle cells that contract and dilate the pupil.

Microcornea—Abnormal smallness of the cornea.

Microdontia—Small teeth.

Myotonia—The inability to normally relax a muscle after contracting or tightening it.

Myotonic dystrophy—A form of muscular dystrophy, also known as Steinert's condition, characterized by delay in the ability to relax muscles after forceful contraction and wasting of muscles, as well as other abnormalities.

Ocular—A broad term that refers to structure and function of the eye.

Oligodontia—The absence of one or more teeth.

Psychomotor—Movement produced by action of the mind or will.

Stenosis—The constricting or narrowing of an opening or passageway.

to the optic disk and gradual loss of vision, causing blindness in approximately 50% of affected individuals.

Additional conditions have sometimes occurred in conjunction with Rieger syndrome. Whether they are separate entities in which the Rieger eye malformations are present or part of Rieger syndrome is not determined. These conditions are:

- Myotonia (a condition in which the muscles do not relax after contracting).
- Myotonic dystrophy (a chronic progressive disease causing muscles to atrophy, slurred speech, failing vision, droopy eyelids, and general muscle weakness).
- Conductive deafness (hearing loss in which sound does not travel well to the inner ear).
- Less than average intellectual function associated with problems in learning and social behavior.

Diagnosis

This disorder can be detected soon after birth if the eye defects are visible. When the eye defects are not visible during the first month of life, Rieger syndrome is usually detected in early childhood when the eye and dental defects become apparent.

Molecular genetic testing for the *RIEG1* and *RIEG2* genes is not generally available. But since the molecular structure of the genes has been identified, the possibility now exists for DNA-based testing for diagnosis and genetic counseling.

Genetic counseling

Genetic counseling may be beneficial for patients and their families. Only one parent needs to be a carrier in order for the child to inherit the disease. A child has a 50% chance of having the disease if one parent is diagnosed with the disease and a 75% chance of having the disease if both parents have Rieger syndrome.

Prenatal testing

For couples known to be at risk for having a baby with Rieger syndrome, testing may be available to assist in prenatal diagnosis. Prior testing of family members is usually necessary for prenatal testing.

Either chorionic villus sampling (CVS) or amniocentesis may be performed for prenatal testing. CVS is a procedure to obtain a small sample of placental tissue, called chorionic villi tissue, for testing. Examination of fetal tissue can reveal information about the defects that leads to Rieger syndrome. Chorionic villus sampling can be performed at 10–12 weeks gestation.

Amniocentesis is a procedure that involves inserting a thin needle into the uterus and the amniotic sac and withdrawing a small amount of amniotic fluid. DNA can be extracted from the fetal cells contained in the amniotic fluid and tested. Amniocentesis is performed at 16–18 weeks gestation.

Tissue showing the gene mutation for Rieger syndrome type I or II obtained from CVS or in amniotic fluid is diagnostic.

Related disorders

A number of disorders are similar to Rieger syndrome. Comparisons may be useful for a differential diagnosis. These related disorders include:

- Cat-eye syndrome, a rare disorder marked by a cleft along the eyeball affecting the iris, the membrane that covers the white of the eyeball (choroid), and/or the retina and causing a vertical pupil; abnormalities such as small polyps or pits

QUESTIONS TO ASK YOUR DOCTOR

- How do the two types of Rieger syndrome differ from each other?
- Are prenatal tests for Rieger syndrome recommended? Why or why not?
- What are the most serious medical complications associated with Rieger syndrome?
- How should the medical progress of a child with Rieger syndrome be monitored throughout his or her life?

near the front of the outer ear; and absence of the opening, duct, or canal of the anus. Other symptoms may include mild intellectual disability and heart defects.

- Ectodermal dysplasias, a group of hereditary syndromes affecting the skin, its derivatives, and some other organs. Symptoms include predisposition to respiratory infection, eczema, poorly functioning sweat glands, abnormal hair and nails, and difficulties with the nasal passages and ear canals.
- Eye, anterior segment dysgenesis, a rare congenital disorder resulting in abnormal tissue development of the outer eye segment. In less severe cases, the back of the outer surface of the cornea is nontransparent (embryotoxin). Symptoms include ocular abnormalities and malformations of the teeth, abdominal wall, skeleton, and heart.

It is generally thought that Axenfeld anomaly, marked by defects limited to the outer part of the field of vision of the eye, should not be considered a separate entity of Rieger syndrome.

Treatment and management

A physician familiar with the range of problems seen in individuals with Rieger syndrome is important for appropriate health supervision. Treatment should include assistance finding support resources for the family and the individual with Rieger syndrome.

Treatment of Rieger syndrome is focused on treating the symptoms expressed. Depending on what they are, these treatments may include:

- Drug therapy for glaucoma; usually a topical beta blocker in the form of eye drops. Laser surgery may be performed on those patients in whom the pressure in the eye is not relieved by medications.
- Prostheses (false teeth) or other orthodontic interventions for dental malformations.

The single nucleotides (monomers) of RNA form a linear chain by linking their phosphate groups and sugars in phosphodiester bonds. RNA does not form a double stranded alpha-helix as does DNA. In some parts of the RNA molecule, there is folding into alpha-helical-like regions. Corresponding to their unique functions, mRNA, rRNA, and tRNA all have different three-dimensional structures. In higher eukaryotic organisms, different RNAs are found distributed throughout the cell—in the nucleus, cytoplasm, and also in cytoplasmic organelles such as mitochondria and, in plants, chloroplasts.

The nucleus is the chief site of RNA synthesis and the source of all cytoplasmic RNA, while mitochondria and chloroplasts synthesize their RNA from their own DNA. rRNA is synthesized by the nucleoli within the nucleus, while the high molecular weight precursor to cytoplasmic mRNA, sometimes termed heterogeneous nuclear or hnRNA, is transcribed on the DNA chromatin. Low molecular weight RNA also occurs in the nucleus and consists partly of tRNA and partly of RNA, which has a regulatory function in gene activation. The cytoplasm contains tRNA and rRNA in the ribosomes and mRNA in polysomes, or polyribosomes. The latter are the structural units of protein biosynthesis, consisting of several ribosomes attached to a strand of mRNA.

The function of mRNA is to transcribe the information held in DNA. In the cells of eukaryotic organisms, the first transcriptional product is the long, heterogeneous nuclear RNA, or hnRNA. This contains both the nucleotide sequences eventually transcribed into polypeptides and large tracts of sequences not translated. Nontranslated sequences are termed introns (or intervening sequences). Removal of introns, and other untranslated portions of the molecule, edits hnRNA into mRNA molecules. After editing removes as much as 90% of hnRNA, the resulting mRNA molecules are transported into the cytoplasm.

rRNA is located within ribosomes, the sites of protein biosynthesis. Ribosomes are large ellipsoid cytoplasmic organelles consisting of RNA and protein.

tRNA, the smallest known functional RNA, is essential for protein biosynthesis. Its purpose is to transfer a specific amino acid from the cytoplasm and incorporate it into the growing polypeptide chain on the polysome. Different tRNAs contain between 70 and 85 nucleotides. The most characteristic feature of tRNA is that it contains the anticodon, a sequence of three nucleotides specific for the mRNA codon sequence. There is at least one tRNA per cell bearing the anticodon for each of the 20 amino acids. The aminoacyl-tRNA (the tRNA carrying the amino acid) binds to the large subunit of a ribosome, where antiparallel base pairing occurs between the anticodon of the tRNA and the complementary codon of the associated mRNA. The specificity of this base pairing

ensures that the amino acid inserts into the correct position in the growing protein polypeptide chain. During translation, the deacylated tRNA (i.e., with its amino acid removed) is released from the ribosome and becomes available once again for recharging with its amino acid.

DNA-dependent RNA synthesis is the process of RNA synthesis on a template of DNA. According to the rules of base pairing, the base sequence of DNA determines the synthesis of a complementary base sequence in RNA. Assisted (catalyzed) by the enzyme RNA polymerase, the growing RNA chain releases from the template so that the process can start again, even before the previous molecule is complete. Termination codons and a termination factor known as rho-factor end the synthesis process. In certain viruses, RNA-dependent RNA synthesis occurs, with the viral RNA acting as a template for the synthesis of new RNA.

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Roberts SC phocomelia

Definition

Roberts SC phocomelia is a rare genetic condition that causes severe abnormalities in arm and leg bones. Other abnormalities, such as intellectual disability, may also be present.

Description

Roberts SC phocomelia was first described in the year 1919. In the past, Roberts SC phocomelia syndrome

was described as two separate syndromes: Roberts syndrome and SC or pseudo-thalidomide syndrome. More recent examination, however, indicated that they are the same disorder. The term “pseudo-thalidomide” was originally used to describe individuals with limb shortening, as the medication thalidomide is known to cause limb abnormalities in the babies of women taking it during pregnancy.

Phocomelia is a condition in which the hands and feet are present, but the arms and legs are absent. The hands and feet are attached directly to the body. Usually there is greater shortening in the arms than in the legs. People with Roberts SC phocomelia syndrome have varying degrees of hypomelia, which means that the limbs are not fully developed. Some are born without the upper bones of the arms or the legs. This is referred to as tetraphocomelia. Some people, though, have a less severe form of limb shortening.

In addition to the limb abnormalities, 80% of individuals with the syndrome have a small head (microcephaly). In addition, most people with the syndrome have some degree of intellectual disability. Most also have facial problems affecting the development of the upper lip (cleft lip), and incomplete development of the palate (the roof of the mouth).

Genetic profile

Roberts SC phocomelia is inherited in an autosomal recessive fashion. This is a pattern in which the child receives one nonfunctioning (abnormal) gene from each parent. When a woman and a man who both carry one abnormal gene for Roberts SC phocomelia have children, there is a 75% chance that they will each pass along the gene for the syndrome and a 25% chance that they will have a child with the fully expressed syndrome. People who are termed “carriers” are not affected by the disorder, as they have only one copy of the gene that causes Roberts SC phocomelia. The chances are 50% that they will have a child who is also a carrier of the disorder. The chances are 25% that they will have a baby who is neither a carrier nor affected with Roberts SC phocomelia.

The specific gene that causes the syndrome is not yet known, and there is no direct genetic test to identify a potential carrier of the disease.

In many of the individuals who have been diagnosed with Roberts SC phocomelia, a unique feature may be observed on some of their chromosomes. The exact association of this unusual observation with the syndrome is not yet understood.

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman’s abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Amniotic fluid—The fluid that surrounds a developing baby during pregnancy.

Cell—The smallest living units of the body, which group together to form tissues and help the body perform specific functions.

Genetic test—Testing of chromosomes and genes from an individual or unborn baby for a genetic condition. Genetic testing can only be done if the gene is known.

Ultrasound evaluation—A procedure that examines the tissue and bone structures of an individual or a developing baby.

Demographics

While the exact number of people with the syndrome is not known, as some infants who die before or shortly after birth are never diagnosed or are diagnosed incorrectly, there have been around 150 confirmed reports of the condition. The syndrome affects males and females equally. There is no specific country or region of the world where the disorder is more common.

Signs and symptoms

In the bones of the lower arm (radius and ulna), limb shortening or absence of limbs is evident in approximately 97% of people with the syndrome. The upper arm (humerus) is affected 77% of the time. A missing or shortened thigh bone (femur) occurs in about 65% of affected individuals. The bones in the lower leg (tibia and fibula) are shortened or absent in 77% of those with the disorder.

It is often very hard to flex or bend the knees, ankles, wrists, and/or elbows. While the feet and hands are almost always present, there may be fewer than normal fingers and toes, or shortened fingers. Sometimes the fingers are fused together (syndactyly).

People with the syndrome are smaller than other babies the same age, both before and after birth. Babies

with Roberts SC phocomelia syndrome may have thin hair that is often described as silvery in color. In addition, most people with Roberts SC phocomelia syndrome are born with a cleft lip (a failure of the upper lip to close completely) and cleft palate (an opening in the roof of the mouth). Other abnormalities that may occur include a small and underdeveloped chin, a short neck, heart and kidney problems, prominent and widely spaced eyes, and unusually shaped ears.

Diagnosis

This disorder has been diagnosed during pregnancy at 12 weeks, through a test called an ultrasound evaluation. In these incidences, developmental problems with the growth and formation of both the arms and legs were noted. Sometimes the syndrome cannot be diagnosed by ultrasound until later in the pregnancy, when the limb shortening or absence becomes more obvious, and sometimes it cannot be diagnosed by ultrasound at all. Other abnormalities that might be seen by ultrasound include cleft lip, increased distance between the eye sockets, and extra fluid in some of the structures of the brain (hydrocephalus). Excess amniotic fluid levels, kidney problems, and an opening in the spine (spina bifida) have also been found. However, an exact diagnosis of the syndrome cannot be made by ultrasound evaluation alone.

Checking for the unusual chromosome feature is done through amniocentesis, a procedure that collects the developing fetus's cells for evaluation. But this test is not typically recommended, because not all affected individuals have this chromosome finding. In addition, the chromosome is not always evident in the cells from the amniotic fluid.

There is no accurate prenatal test to diagnose the syndrome during pregnancy.

After a baby is born with characteristics of Roberts SC phocomelia syndrome, a diagnosis can be made through a complete physical examination. In addition, analysis of the baby's chromosomes may also be useful. The chromosomes can be analyzed through a blood or tissue sample.

Treatment and management

At this time there is no treatment available for individuals with Roberts SC phocomelia syndrome. The shortness or absence of limbs makes it difficult for any type of limb-lengthening therapies to be useful in most instances.

Prognosis

The majority of severely affected individuals will die in the womb, or during or shortly after birth. Those who

QUESTIONS TO ASK YOUR DOCTOR

- What are the usual signs and symptoms associated with Roberts SC phocomelia syndrome?
- Please explain the meaning of the term "phocomelia."
- Are there prenatal tests of Roberts SC phocomelia syndrome, and under what circumstances would they be recommended?
- What is the progress for a child diagnosed with Roberts SC phocomelia syndrome?

survive will have very obvious growth deficiency as well as intellectual disability. Babies who are not as severely affected, with less dramatic limb shortening and no facial cleft, have a better overall prognosis.

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ORGANIZATIONS

- American Pediatric Surgical Association, 1061 E. Main St., Suite 300, East Dundee, IL 60118, (309) 733-7874, info@apsapedsurg.org, <http://www.apsapedsurg.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

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Roberts syndrome see **Roberts SC phocomelia**

Robinow dwarfism see **Robinow syndrome**
 Robinow-Silverman-Smith syndrome see **Robinow syndrome**
 Robinow-Sorauf syndrome see **Saethre-Chotzen syndrome**
 Robin sequence see **Pierre-Robin sequence**

Robinow syndrome

Definition

Robinow syndrome encompasses two different hereditary disorders, both rare, with a similar pattern of physical abnormalities. Typical features of these conditions include mild-to-moderate short stature, distinctive facial features, skeletal abnormalities, and abnormal development of the genitalia.

Description

A family that included several individuals with a characteristic pattern of facial features, accompanied by short stature (dwarfism), skeletal abnormalities, and underdevelopment (hypoplasia) of the external genitalia (sex organs) was first described in 1969 by Dr. Meinhard

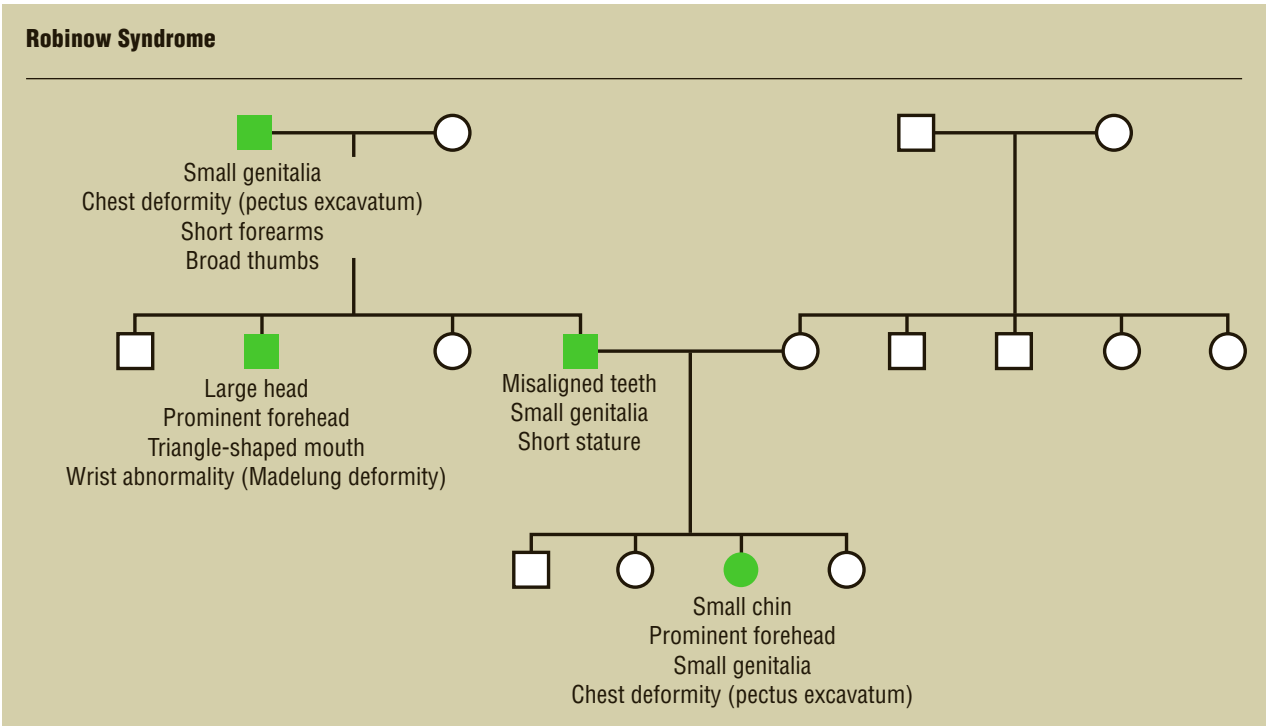
Robinow. He named the condition “fetal face syndrome,” because the facial features are similar to those of a normal fetus. Only later was Dr. Robinow’s name used to identify the syndrome. Other names for the condition include Robinow dwarfism, as well as “acral dysostosis with facial and genital abnormalities.”

Skeletal abnormalities of varying types and severity occur in every case of Robinow syndrome. Most people with the condition have abnormal development of specific bones of the arms and legs resulting in some degree of short stature. Spinal abnormalities are also common. Most females are fertile, but only a few males with the condition have had children.

Genetic profile

Chromosomes are the microscopic structures inside cells that carry the genes. Each cell of the body contains 46 chromosomes in 23 pairs. The exceptions are sperm and eggs, which normally carry 23 chromosomes—one of each pair. The first 22 pairs of chromosomes in humans are known as the autosomes. An inherited condition is autosomal if the abnormal gene that causes it resides on one of the first 22 pairs of chromosomes.

Several years after Dr. Robinow’s first report, it became clear that some families affected by Robinow syndrome have an autosomal dominant pattern of inheritance, while in other families the syndrome is inherited



Robinow syndrome: pedigree analysis chart (Gale)

as an autosomal recessive trait. The reason for this genetic discrepancy is unknown.

Dominant inheritance means that an error in only one gene of a pair is enough to produce symptoms of the disorder. In other words, the abnormally functioning gene of the pair is dominant over the normal gene. A person who carries the gene for autosomal dominant Robinow syndrome has a 50% chance of passing it on to each of his or her offspring.

In autosomal recessive inheritance, a person must have errors in both copies of a gene pair in order to be affected. Someone who carries just one copy of the disease gene has another normally functioning gene of that pair to compensate for it. Therefore, a carrier of a single recessive gene typically shows no symptoms of the disorder. If two people who both carry the gene for recessive Robinow syndrome conceive a pregnancy, there is a 25% chance that they will each contribute the Robinow syndrome gene and have an affected child.

Mutations in the *ROR2* gene are responsible for recessive Robinow syndrome. The exact function of the protein encoded by the *ROR2* gene has not been determined, and the gene responsible for dominant Robinow syndrome has not been located.

Demographics

Both the dominant and recessive forms of Robinow syndrome are rare. There are fewer than 200 people affected worldwide. Dominant Robinow syndrome does not appear to occur more frequently in any particular ethnic group. A significant proportion of recessive Robinow syndrome cases, however, have occurred in Czechoslovakia, Turkey, and the Middle East. In addition, some children with recessive Robinow syndrome have parents who are genetically related (consanguineous), such as first cousins. Parental consanguinity is sometimes seen in rare, autosomal recessive conditions, since people who are genetically related are more likely to carry the same recessive gene(s).

Signs and symptoms

The signs and symptoms of Robinow syndrome can be grouped into those that involve the face, those that affect the skeleton, and those affecting the genitalia. There is a good deal of overlap of symptoms between the dominant and recessive forms. In general, however, people with recessive Robinow syndrome tend to be more severely affected.

The facial features of Robinow syndrome include a flat nasal bridge, slightly upturned nose, triangular-shaped mouth, protruding forehead (frontal bossing),

KEY TERMS

Acromelic—The anatomical term used to denote the end of a limb (arm or leg). In the context of Robinow syndrome, it refers to bones of the hands and feet.

Brachymelia—A general medical term used to describe short limbs.

Hypertelorism—A wider-than-normal space between the eyes.

Hypoplasia—Incomplete or underdevelopment of a tissue or organ.

Mesomelic—The anatomical term used to describe the middle of a limb. The bones that constitute the middle of the arm are the radius and ulna, and mesomelic bones of the leg are the tibia and fibula.

Vertebra—One of the 23 bones that compose the spine. "Vertebrae" is the plural form.

wide space between the eyes (hypertelorism), wide eye openings, low-set ears, long philtrum (groove from nose to upper lip), small lower jaw (micrognathia), excessive growth of the gums, and crowding of teeth.

People with Robinow syndrome have what is known as acromesomelic brachymelia. Acromesomelic refers to bones at the end (acro) and in the middle (meso) of the limbs. Brachymelia is the medical term for short limbs. Thus, short limbs in Robinow syndrome are due to shortened bones in the hands, feet, lower arms, and lower legs. Dominant Robinow syndrome is associated with normal height to borderline short stature, while recessive Robinow syndrome always results in short stature. Abnormalities of the spine often involve misshapen or fused vertebrae (so-called segmentation defects), as well as scoliosis. Vertebral abnormalities are more frequent and more pronounced in the recessive form of Robinow syndrome. Ribs may be fused together or abnormally shaped, and this may lead to pectus excavatum (sunken breastbone).

Males with Robinow syndrome typically have a hypoplastic penis, and may have undescended testicles (cryptorchidism). Females can have a small clitoris and hypoplastic labia. A dysfunctional sex-steroid response-and-feedback mechanism may be partly to blame for some of the signs of Robinow syndrome, particularly the genital anomalies.

Physical anomalies found less frequently in Robinow syndrome include heart defects, kidney abnormalities, cleft lip/palate, and hearing loss. Most individuals with

QUESTIONS TO ASK YOUR DOCTOR

- What is the genetic mechanism responsible for Robinow syndrome?
- What are the most distinctive physical characteristics of a child with Robinow syndrome?
- Are there prenatal tests I can have to discover if my child is likely to have Robinow syndrome?
- Where can I obtain additional information about Robinow syndrome on the Internet?

Robinow syndrome have normal intelligence, but a few have mild intellectual disability.

Diagnosis

The diagnosis of Robinow syndrome is made by physical examination. Several other genetic syndromes have some of the same physical signs as Robinow syndrome, which can make arriving at the correct diagnosis more difficult. However, the pattern of skeletal abnormalities in Robinow syndrome has a distinct appearance when seen on x-rays, which may help in confirming the diagnosis. Testing of the *ROR2* gene is theoretically possible for recessive Robinow syndrome, but would only be offered on a research basis, if at all.

Treatment and management

There is no cure for either type of Robinow syndrome. Future research may help to determine if some type of hormone therapy can be used to treat the short stature and/or hypoplastic genitalia. Otherwise, no specific protocol is recommended for managing children and adults with either form of the condition. An orthopedic surgeon might be needed to address any problems that arise related to skeletal abnormalities, especially in the spine. Special educational intervention would be indicated for anyone with learning disabilities or intellectual disability.

People with pronounced physical signs of the condition (short stature and facial features) may have difficulties with their self-image. Males with a hypoplastic penis can present a special problem. In those cases, added psychological and social support is particularly important. Genetic counseling should be offered to individuals/families affected by Robinow syndrome to help them understand the condition, its inheritance, and any testing (including prenatal) that might be available.

Prognosis

Any one person with Robinow syndrome may have a good prognosis, depending on how well they cope with their particular symptoms. A child with recessive Robinow syndrome is more likely to have long-term difficulties than a child with the dominant form of the condition, but no blanket statements can be made. Overall, lifespan should not be significantly decreased in most cases of Robinow syndrome, since the majority of affected individuals do not have life-threatening complications.

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"Robinow Syndrome." NORD. <https://rarediseases.org/rare-diseases/robinow-syndrome/> (accessed June 19, 2021).

ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>
Robinow Syndrome Foundation, PO Box 934, Anoka, MN 55303, <http://www.robinow.org>

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Romano-Ward syndrome see **Long QT syndrome**

Rothmund-Thomson syndrome

Definition

Rothmund-Thomson syndrome (RTS) is an extremely rare inherited disorder that appears in infancy and features skin degeneration (atrophic dermatosis), clouding of the lenses of the eyes (juvenile cataracts), skeletal abnormalities, short stature, and an increased risk of skin and bone cancers.

Description

Rothmund-Thomson syndrome is usually first apparent between three and six months of age. This disorder is characterized by early sun sensitivity and progressive degeneration or wasting (atrophy) of the skin, as well as scarring and abnormal pigmentation of the skin. Other characteristic signs include sparse hair; clouding of the lenses of the eyes (juvenile cataracts); short stature; malformations of the face and head, teeth, nails, and bone; and other physical abnormalities. In rare cases, intellectual disability may be present.

The syndrome was first described in 1868 by August von Rothmund, a German ophthalmologist, and in both 1923 and 1936 by Matthew S. Thomson, a British dermatologist. Both independently noted a familial disorder with cataracts, saddle nose, and skin degeneration. It is believed that Thomson's finding was the same disease that was seen long before by Rothmund. Other names for Rothmund-Thomson syndrome include poikiloderma congenita and poikiloderma atrophicans with cataract.

Genetic profile

Rothmund-Thomson is attributed to a mutation in a gene located on chromosome 8. Mutations in the gene *RecQL4* (chromosomal locus 8q24), also called the Rothmund-Thomson gene, have been identified in four patients with Rothmund-Thomson syndrome.

Rothmund-Thomson syndrome is inherited as an autosomal recessive trait. This means that both parents have one copy of the Rothmund-Thomson gene but do not have the disease. Each of their children has a 25% chance of not having the gene, a 50% chance of having one Rothmund-Thomson gene (and, like the parents, being unaffected), and a 25% risk of having both Rothmund-Thomson genes and the disease.

Demographics

There is no specific population group that is at greater risk for this disorder, although it is more common in women (2:1). Evidence of Rothmund-Thomson syndrome has been found to occur in all races and many nationalities. The majority of affected people are from full-term pregnancies. As of 2015, 300 cases had been reported worldwide. The number of carriers for Rothmund-Thomson syndrome is unknown.

Signs and symptoms

The major characteristics of Rothmund-Thomson syndrome are skin abnormalities, short stature, juvenile cataracts, small hands, and delayed activities of the

KEY TERMS

Alopecia—Loss of hair or baldness.

Atrophic dermatosis—Wasting away of the skin.

Depigmentation—Loss of pigment or skin color.

Dysplastic—The abnormal growth or development of a tissue or organ.

Edema—Extreme amount of watery fluid that causes swelling of the affected tissue.

Frontal bossing—A term used to describe a rounded forehead with a receded hairline.

Hyperpigmentation—An abnormal condition characterized by an excess of melanin in localized areas of the skin, which produces areas that are much darker than the surrounding unaffected skin.

Hypogonadism—Small testes in men and scarce or irregular menstruation for females.

Keratosis—A raised thickening of the outer horny layer of the skin.

Microdontia—Small teeth.

Poikiloderma—A condition characterized by skin atrophy, widening of the small blood vessels (telangiectasia), and pigment changes giving a mottled appearance.

Prognathism—A protruding lower jaw.

Saddlenose—A sunken nasal bridge.

Telangiectasia—An abnormal widening of groups of small blood vessels in the skin.

ovaries in females or testes in males. Symptoms vary from individual to individual.

Skin abnormalities usually appear in infancy, between three and six months of age. Skin changes begin as red inflamed patches, occasionally with blistering, on the cheeks along with swelling and then spread to other areas of the face, the arms and legs, and buttocks. Skin inflammation eventually subsides and a condition develops known as poikiloderma, characterized by abnormal widening (dilation) of groups of small blood vessels (telangiectasia), skin tissue degradation (atrophy), and patchy areas of abnormally decreased and/or unusually increased brown pigmentation (depigmentation and hyperpigmentation), giving the skin a mottled look. Skin that is exposed to the sun usually shows greater abnormalities. Sun sensitivity typically continues throughout the affected person's life. Those with extreme sun sensitivity can develop thickening of the skin (keratosis) of the face, hands, and feet, or cancerous skin changes later

in life. Affected individuals are at increased risk of developing skin cancers (basal cell carcinoma and squamous cell carcinoma) and bone cancer (osteosarcoma).

There are many other physical abnormalities that affect people with Rothmund-Thomson syndrome. Juvenile cataracts, the clouding of the lenses of the eyes, develop in almost half of the people with RTS between the ages of four and seven. Severe growth delays result in short stature throughout life. Skeletal abnormalities such as unusually small hands and feet are common. Less typical are stubby fingers and toes, underdeveloped (hypoplastic) or absent thumbs, and/or underdeveloped (hypoplastic) or missing forearm bones (ulna and radii). Hypogonadism, the deficient activity of the ovaries in females or testes in males, causes irregular menstruation in females, and delayed sexual development and reduced fertility in both males and females. Facial skeletal abnormalities include a triangular-shaped face with a prominent forehead (frontal bossing), a sunken nasal bridge (saddle nose), and a protruding lower jaw (prognathism). Scalp hair is usually thin and fine, although alopecia (balding) occasionally occurs in early childhood. Often the eyebrows and eyelashes are sparse or absent. Dental abnormalities include excessive cavities, unusually small teeth (microdontia), or delayed or failure of teeth to erupt. Dysplastic, or abnormally developed, nails are also seen in many people with Rothmund-Thomson syndrome.

Diagnosis

A diagnosis of Rothmund-Thomson syndrome is made based on clinical examination. Mutations of the *RecQL4* gene have been found two-thirds of individuals with Rothmund-Thomson syndrome.

There are no published diagnostic criteria. Diagnosis is usually based on the presence of the characteristic poikilodermatous rash in childhood, along with one or more of the following features: small stature, sparse or absent hair, cataracts, and cancer.

Treatment and management

Essential management of Rothmund-Thomson syndrome includes avoiding sun exposure and diligently using sunscreen that has both UVA and UVB protection.

An ophthalmologic evaluation for the detection and management of cataracts is recommended for affected people on an annual basis up to age 15. Surgical removal of significant cataracts may be necessary.

Because skin cancer is a risk, it is important to monitor the affected individual closely for lesions with unusual color or texture. They should also be watched

QUESTIONS TO ASK YOUR DOCTOR

- At what age can Rothmund-Thomson syndrome be diagnosed, and how is that diagnosis made?
- How common is Rothmund-Thomson syndrome, and are there certain populations at greater risk for the disease than the general public?
- What types of treatment are recommended for Rothmund-Thomson syndrome, and what risks are associated with each kind of treatment?
- What is the prognosis for an infant diagnosed with Rothmund-Thomson syndrome?

carefully for any signs and symptoms of osteosarcoma, a cancerous bone tumor, including bone pain, swelling, or a growing lesion on the arms or legs.

Pulsed-dye laser therapy has been used to treat the widening of small blood vessels (telangiectasia). Medications called retinoids can reduce the potential for skin cancer. Keratolytic drugs are used to cause thick skin to swell, soften, and then fall away.

Prognosis

Individuals with Rothmund-Thomson syndrome usually have a normal lifespan, although an increased risk for bone and skin cancer has been found. Most affected individuals will have normal intelligence; however, learning disabilities and intellectual disability have been reported in a small number of patients.

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National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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RSH/SLO syndrome see **Smith-Lemli-Opitz syndrome**

RSH syndrome see **Smith-Lemli-Opitz syndrome**

Rubinstein syndrome see **Rubinstein-Taybi syndrome**

Rubinstein-Taybi syndrome

Definition

Rubinstein-Taybi syndrome (RSTS) is a rare genetic disorder involving moderate to severe intellectual impairment, short stature, broad thumbs and great toes, and characteristic facial features. First described in 1963 by the American physicians Dr. Jack Rubinstein and Dr. Hooshang Taybi, over 550 cases have since been reported.

Description

The clinical picture of RSTS is highly variable. The most prominent features include intellectual impairment, thumb and great toe abnormalities, and distinct facial characteristics.

RSTS may also be referred to as broad-thumb-hallux syndrome or Rubinstein syndrome. The abbreviation for Rubinstein-Taybi syndrome is denoted “RSTS” or “RTS,” although “RSTS” is preferred so as not to be confused with other syndromes such as Rett syndrome and Rothmund-Thomson syndrome.

Genetic profile

RSTS may be inherited if both parents carry a mutation of one of the genes known to cause RSTS; however, the majority of people with RSTS have random, or *de novo*, genetic mutations that caused their RSTS.

KEY TERMS

Great toe—The first and largest toe on the foot.

Hallux—The great toe.

Recurrence risk—The possibility that the same event will occur again.

Respiratory—Having to do with breathing.

Of the cases of inherited RSTS, more than 55%, are caused by mutations in the *CREBBP* gene. Located on chromosome 16, the *CREBBP* gene carries instructions for making the CREB binding protein, a protein that is important to the activity of many other genes and is important in cell growth and division. The functions of the CREB protein are essential for normal fetal development. Researchers have not identified the exact mechanisms; however, mutation in only one of the pair of *CREBBP* genes cause only half the normal amount of CREB protein to be produced. This reduction interrupts normal development both before and after birth, causing the symptoms of RSTS.

Another inherited genetic cause of RSTS is mutation of the *EP300* gene. This gene is important in the formation of a protein called p300. Like the CREB protein, p300 is significant in cell growth and division and in fetal development. Similarly, mutations in the *EP300* gene cause too little of the p300 protein to be made and this leads to the symptoms of RSTS. Researchers estimate that approximately 33% of inherited RSTS cases are caused by mutations in the *EP300* gene.

RSTS caused by mutations of the *CREBBP* and *EP300* genes are inherited in an autosomal dominant pattern, which means that only one copy of the mutated gene must be present for a person to have RSTS.

Most cases of RSTS, however, are sporadic. That is, the majority of affected individuals do not have a parent with RSTS; rather, RSTS arose due to a new mutation in the *CEBBP* gene. Sporadic mutations in genes occur by chance. They are rare and there is nothing a person can do during a pregnancy to cause or prevent them.

Demographics

The incidence of RSTS has been estimated at between 1 in 100,000 and 1 in 125,000 live births. Males and females are affected equally. Cases of RSTS have been observed throughout the world. Although RSTS is thought to be a rare disease, more cases are being diagnosed each year. In part, this is thought to be due to

physicians' increasing awareness of the signs and symptoms involved in RSTS.

Signs and symptoms

RSTS is a genetic disorder involving primarily physical malformations and intellectual impairment.

Babies with RSTS may be born small compared to other newborns. They often have trouble feeding and may need to be assisted in this area. In conjunction with feeding problems, there may be respiratory (breathing) difficulties.

As the child matures, growth remains delayed, with short stature persistent throughout life. An average height of 60 in (153 cm) in males and 58 in (147 cm) in females and an average weight of 106 lb (48 kg) in males and 120 lb (55 kg) in females has been reported.

Developmental milestones are usually delayed. Although most children with RSTS learn to walk and talk, they tend to develop these skills much later than their peers. For example, the average age at which children with RSTS learn to walk is 30 months, compared to 12 months in unaffected children.

There are several unique physical characteristics associated with RSTS. Typical facial features include down-slanting eyes, beaked nose, and the fleshy septum of the nose extending beyond the nostrils. By two to three years of age, most affected children grow into what is considered the classic physical picture of RSTS. Because of their similar facial appearances, they may resemble other children with RSTS as much as or more than they resemble family members.

The most well-known features of patients with RSTS are the broad thumbs and great toes (halluces). This finding may be observed at birth, although some patients with RSTS have only broad thumbs, only broad toes, or neither.

Other findings that occur on a less frequent basis include malignant (cancerous) and benign (noncancerous) tumors, chronic ear infections, early onset of breast development in females, kidney abnormalities, high arched palate (roof of the mouth), malformed teeth (named talon cusps after their shape), heart defects, small head, and short upper lip with a pouting bottom lip.

Intellectual impairment of varying degrees is a constant in RSTS. Affected individuals may present mild to severe intellectual impairment. They have particular difficulty in expression through speech. Although affected individuals are usually able to understand what is spoken to them, they have a difficult time responding with spoken words. In general, it has been observed that many

QUESTIONS TO ASK YOUR DOCTOR

- How is Rubinstein-Taybi syndrome distinguished from other genetic disorders with similar signs and symptoms?
- Are there organizations from which I can get additional information about this genetic disorder?
- If I have one child with Rubinstein-Taybi syndrome, what is the probability of having a second child with the same condition?
- What kinds of medical care will I have to provide for my Rubinstein-Taybi child as he or she grows older?

patients with RSTS do not progress beyond a first-grade level.

It has been noted that affected individuals tend to have happy, outgoing, and energetic personalities. They have been described as people who “know no strangers.” People with RSTS tend to smile often, although, due to their physical differences, this smile is sometimes described as a grimace.

Not every person with RSTS will have all of the aforementioned medical, physical, and social characteristics. Although people with RSTS have much in common, it is important to remember that each person is unique with his or her own qualities and challenges.

Diagnosis

Diagnosis is usually based on clinical findings; therefore, the doctor will perform a complete physical examination and record a detailed medical history. Laboratory techniques for definitive diagnosis by genetic screening may be used if mutations in the *CEBBP* gene or *EP300* gene are suspected; however, these tests are only able to identify approximately 25% of affected individuals. This is due to the considerable number of different changes within the same gene that all may lead to RSTS.

Prenatal diagnosis is available for RSTS; however, again, only approximately 25% of cases are picked up by current available techniques. Because the physical features associated with RSTS are difficult to distinguish prenatally, and the available DNA test does not identify most cases, the vast majority of individuals with RSTS are diagnosed after birth.

The age at which a person is diagnosed varies from patient to patient due to the range in severity of clinical findings. Those with a more mild presentation tend to be diagnosed later in life. Diagnosis may be more difficult in non-Caucasian persons due to the great majority of research and published data having been done on Caucasian patients.

Misdiagnosis is sometimes made between RSTS and Saethre-Chotzen syndrome because of their similar clinical findings.

A correct diagnosis is important when providing a family with genetic counseling. A family with a child with RSTS can have many questions. Genetic counseling may be helpful in providing the family with some answers, including information about the risk of having another child with RSTS.

In general, a recurrence risk of 0.1% is given to couples that have had one child with RSTS. For individuals with RSTS there is a 50% chance of passing the condition on in each pregnancy.

Treatment and management

Treatment and management is aimed at encouraging and supporting cognitive development and alleviating medical symptoms. There is no cure for Rubinstein-Taybi syndrome.

Medical problems, such as ear and respiratory infections, are treated as they occur. Chronic ear infections may lead to hearing loss and it is therefore important to have this infection treated as quickly as possible.

Early intervention and occupational and physical therapy are encouraged along with behavioral management. It has been shown that children with intellectual impairment and developmental delay, due to any cause, benefit from these therapies. In particular, for children with RSTS, speech therapy and alternate forms of communication, such as sign language, have been found to be helpful. Alternative avenues of communication may help children with RSTS express their thoughts and feelings and reduce the frustration they may feel at not being understood verbally.

Prognosis

Prognosis is variable due to the wide range of presentations among affected individuals. Intellectual impairment and developmental delay may range from mild to severe, with a reported average IQ of 51 (the general population average IQ is 100). Medical problems also vary in number and severity.

Most individuals with RSTS will have a normal lifespan. As adults, affected individuals may live in group

homes or supervised apartments. Many work in sheltered workshops or in supervised employment situations.

Individuals with RSTS are capable of having children of their own. In a study of 502 individuals with RSTS, two had reproduced. In total they had three children, one affected with RSTS and two unaffected. It has also been the case that a very mildly affected woman was not diagnosed with RSTS until her child was born with the same disorder.

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ORGANIZATIONS

- The Arc, 1825 K St. NW, Suite 1200, Washington, DC 20006, (202) 534-3700 or (800) 433-5255, (202) 534-3731, <https://www.thearc.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

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Russell-Silver syndrome

Definition

Russell-Silver syndrome (RSS) is one of the recognized forms of intrauterine growth retardation (IUGR) disease. It was first independently described by H. K. Silver in 1953 and by A. Russell in 1954.

Description

Russell-Silver syndrome is one of more than 300 recognized forms of genetic disorders that lead to short stature. It is characterized by:

- the presence of a triangular-shaped face
- an incurving fifth finger (clinodactyly)
- low birth weight and length (intrauterine growth retardation, or IUGR)
- a poor appetite in the first few years of life

This disorder is alternately known as Russell syndrome, Silver syndrome, or Silver-Russell syndrome. Some clinicians use the term “Russell syndrome” to indicate this disorder when the size of the sides of the body and the limbs are equal, and the term “Silver syndrome” to indicate this disorder when the size of the sides of the body or the length of the limbs is different (body asymmetry).

Genetic profile

The exact genetic cause, or causes, of RSS have not been fully identified. It is currently believed that almost all cases of RSS are the result of mutations on a gene, or possibly more than one gene, on chromosome 7.

Demographics

RSS has an estimated incidence rate of 1 in 75,000 to 100,000 people. Almost all cases of RSS are sporadic; that is, they appear for the first time in individuals with no family history of RSS. However, case studies indicating all three modes of inheritance—autosomal recessive, autosomal dominant, and X-linked—have been reported.

RSS does not appear to affect any particular race or ethnic group in a greater frequency than others. It is also observed equally in males and females.

Signs and symptoms

There are six characteristics that define Russell-Silver syndrome: a triangular-shaped face; down-turned corners of the mouth; inwardly curved little fingers (clinodactyly); a combination of low birth weight (intrauterine growth retardation) and short birth length after a full-term gestation; a long, narrow head (scaphocephaly); and a poor appetite that causes slow growth after birth. These characteristics are commonly observed in people affected with RSS.

Several other characteristics are found in most, but not all, RSS-affected individuals. These include:

- low blood sugar (hypoglycemia) in infancy and early childhood

KEY TERMS

Body asymmetry—Abnormal development of the body in which the trunk and/or the limbs are not of equal size from one side of the body to the other.

Clinodactyly—An abnormal inward curving of the fingers or toes.

Delayed bone age—An abnormal condition in which the apparent age of the bones, as seen in x-rays, is less than the chronological age of the patient.

Hypoglycemia—An abnormally low glucose (blood sugar) concentration in the blood.

Intrauterine growth retardation—A form of growth retardation occurring in the womb that is not caused by premature birth or a shortened gestation time. Individuals affected with this condition are of lower than normal birth weight and lower than normal length after a complete gestation period.

Precocious puberty—An abnormal condition in which a person undergoes puberty at a very young age. This condition causes the growth spurt associated with puberty to occur before the systems of the body are ready, which causes these individuals to not attain normal adult heights.

Russell syndrome—An alternative term for Russell-Silver syndrome. Many doctors use this term to mean a Russell-Silver syndrome affected individual who does not have body asymmetry.

Scaphocephaly—An abnormally long and narrow skull.

Silver syndrome—An alternative term for Russell-Silver syndrome. Many doctors use this term to mean an individual with Russell-Silver syndrome who also has body asymmetry.

- unequal body and limb size from one side of the body to the other (body asymmetry)
- late closure of the soft spot in the front of the skull
- a broad forehead
- a small chin and jaw
- crowding of the teeth or abnormally small teeth caused by a smaller than normal jaw
- an abnormally thin upper lip
- low-set, small, and prominent ears
- fusion or webbing of the toes (syndactyly)
- poor muscle tone (hypotonia)

- a condition in which the bones are not as mature as the bones of a typical person of the same age (delayed bone age)
- developmental delays

In males affected with RSS, undescended testicles and a misplacement of the urethral opening (hypospadias) on the bottom of the penis rather than on the tip of the glans is often seen.

People affected with RSS may show other symptoms on a less uniform basis. These include:

- water on the brain
- a bluish coloration of the whites of the eyes
- a highly arched palate
- an absence of certain teeth
- frequent ear infections caused by fluid in the ear, which can lead to temporary hearing loss
- migraine headaches
- a curvature of the spine (scoliosis) or other problems with the spine, often caused by body asymmetry
- abnormalities of the kidneys
- an abnormally early onset of puberty (precocious puberty)
- irregularly colored spots on the skin (café-au-lait spots)
- high energy levels
- attention-deficit disorder (ADD)
- fainting spells

Diagnosis

Diagnosis of RSS is generally accomplished by performing a genetic test on cells grown from a skin sample. This test must be performed prior to the fifth year of life and it is not always accurate.

A diagnosis of RSS is supported by examination of the affected individual's growth curve and daily food intakes. In a child affected with RSS, these will fall well short of the mean for children of the same age.

Body measurements for asymmetry and x-rays to determine the bone age versus the actual age of the patient are also useful. Additionally, a blood test indicating hypoglycemia may indicate RSS. When RSS is suspected in males, an examination of the genitals may reveal undescended testicles or a misplacement of the urethral opening.

Treatment and management

Treatment of RSS varies on a case-by-case basis depending on the symptoms of the affected individual.

QUESTIONS TO ASK YOUR DOCTOR

- Please explain the meaning of the expression "intrauterine growth retardation."
- How I am responsible for my child's having Russell-Silver syndrome?
- What kinds of treatment will my child need because of his genetic disorder?
- What is your prognosis for the child's long-term development?

Dietary changes to increase food intake are required by all people with RSS. Many patients with RSS also require a diet high in sugars to treat hypoglycemia. When the necessary food intake cannot be accomplished by dietary changes, it may be necessary to treat patients with the antihistamine periactin, which also serves as an appetite stimulant. Some patients may also benefit from a feeding pump or gastrostomy. Gastrostomy is a surgical procedure in which a permanent opening is made directly in the stomach for the introduction of food.

In cases of severe growth retardation, certain people will require the administration of an artificial form of growth hormone (recombinant growth hormone) to stimulate growth, increase the rate of growth, and to increase their final adult height.

Ear tubes may be required to improve fluid drainage from the ears of some patients affected with RSS.

In cases of body asymmetry, limb-lengthening surgeries may be recommended. Alternatively, shoe lifts may be all that is necessary for the attainment of a normal gait.

Depending on the severity of physical, emotional, and psychological symptoms, some affected individuals may benefit from physical and/or occupational therapy. If ADD or other developmental problems exist, individuals with RSS may require educational assistance, such as remedial reading. In cases where the jaw is extremely small, talking may be difficult. These patients may require speech therapy.

Precocious puberty is the entrance of a child into puberty prior to the age of eight or nine. This early onset of puberty is generally accompanied by a growth spurt prior to puberty. While entering puberty before one is emotionally ready is certainly a serious problem, it is the growth spurt prior to puberty that is of major medical significance and concern.

If this growth spurt occurs prior to puberty, it is generally not as robust as if it had occurred during puberty, which causes the individual undergoing this growth spurt to grow less than a person who undergoes this process during puberty. The result is that a person who undergoes precocious puberty will generally end up much shorter in adulthood than his or her peers.

There are three hormonal therapies available in the United States to treat precocious puberty. Histrelin (trade name: Supprelin) is administered by daily injection. Leuprolide acetate (trade name: Lupron) is available as a depot formulation every four weeks. A depot formulation places medication in a tiny pump that is attached to the patient's body and releases the medication over time. Nafarelin acetate (trade name: Synarel) is administered as a nasal spray three times daily. Because of the age of people being treated, Lupron is most often the medication of choice because it is only administered once a month.

Some doctors have noticed that persons affected with RSS may have a slightly elevated chance of developing Wilms' tumor, the most common form of kidney cancer. Most cases of this type of cancer occur before the age of eight, and this condition is extremely rare in adults. It is important that children with RSS be screened with ultrasound every three months until the age of eight to make sure they have not developed Wilms' tumor. Wilms' tumor is quite treatable via surgery, chemotherapy, and/or radiation.

Prognosis

With proper medical treatment to address their individual symptoms, people affected with RSS do not, in general, have a reduced quality of life relative to the remainder of the population. As these people age, the symptoms of RSS tend to become less noticeable: the triangular shape of the face tends to lessen, muscle tone

and coordination improve, appetite improves, speech improves, and learning occurs. An affected adult is generally not less happy and/or healthy than any other person.

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ORGANIZATIONS

MAGIC Foundation, 6645 W. North Ave., Oak Park, IL 60302, (708) 383-0808, ContactUs@magicfoundation.org, <http://www.magicfoundation.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

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Saethre-Chotzen syndrome

Definition

Saethre-Chotzen syndrome is an inherited disorder that affects 1 in every 50,000 individuals. The syndrome is characterized by early and uneven fusion of the bones that make the skull (cranium). This affects the shape of the head and face, which may cause the two sides to appear unequal. The eyelids are droopy; the eyes widely spaced. The disorder is also associated with minor birth defects of the hands and feet. In addition, some individuals have mild intellectual disability. Some individuals with Saethre-Chotzen syndrome may require some medical or surgical intervention.

Description

Saethre-Chotzen (say-thre chote-zen) syndrome belongs to a group of rare genetic disorders with craniosynostosis. Craniosynostosis means there is premature closure of the sutures (seams) between certain bones of the cranium. This causes the shape of the head to be tall, asymmetric, or otherwise altered in shape (acrocephaly). There is also webbing (syndactyly) of certain fingers and toes. Another name for Saethre-Chotzen syndrome is acrocephalosyndactyly type III. It is one of the more mild craniosynostosis syndromes.

The story of Saethre-Chotzen syndrome goes back to the early 1930s. It was then that a Norwegian psychiatrist, Haakon Saethre, wrote about a mother and two daughters in the medical literature. Each had a low frontal hairline; long and uneven facial features; short fingers; and webbing of the second and third fingers and second, third, and fourth toes. A year later in 1931, F. Chotzen, a German psychiatrist, reported a family with similar features. However, these individuals were also quite short and had additional features of mild intellectual disability and hearing loss.

Genetic profile

Mutations in the *TWIST1* gene, located on the short (p) arm of chromosome 7 at position 21.2, cause Saethre-Chotzen syndrome. It is an autosomal dominant disorder and can be inherited, and passed on, by men as well as women. Almost all genes come in pairs. One copy of each pair of genes is inherited from the father and the other copy of each pair of genes is inherited from the mother. Therefore, if a parent carries a gene mutation for Saethre-Chotzen, each of his or her children has a 50% chance of inheriting the gene mutation. Each child also has a 50% chance of inheriting the working copy of the gene, in which case they would not have Saethre-Chotzen syndrome.

The search for the gene for Saethre-Chotzen syndrome is an interesting story. The first clue as to the cause of the disorder came in 1986, with the identification of patients who had a chromosome deletion of the short arm of chromosome 7. Linkage studies in the early 1990s narrowed the region for this gene to a specific site, at 7p21. Then, in 1996, scientists at Johns Hopkins Children's Center began to study *TWIST1* as the candidate gene for Saethre-Chotzen syndrome because of earlier studies that showed how this gene works in the mouse.

The mouse *TWIST* gene normally works in forming the skeleton and muscle of the head, face, hands, and feet. Mice lacking both copies of the gene die before birth. Many have severe birth defects, including failure of the neural tube to close. They have an abnormal head and limb defects. However, mice with just one nonworking copy of the *TWIST* gene did not die. Closer examination of these mice showed that they had only minor hand, foot, and skull defects. The features were similar to those seen in Saethre-Chotzen syndrome.

It was also known that the mouse *TWIST* gene was located on chromosome 12 in mice, a location that corresponds to the short arm of chromosome 7 in humans. With this evidence, the researchers went on to map and isolate the human *TWIST1* gene on human chromosome

KEY TERMS

Acrocephaly—An abnormal cone shape of the head.

Chromosome deletion—A missing sequence of DNA or part of a chromosome.

Craniosynostosis—Premature, delayed, or otherwise abnormal closure of the sutures of the skull.

Cranium—The skeleton of the head, which includes all of the bones of the head except the mandible.

Exon—The expressed portion of a gene. The exons of genes are those portions that actually chemically code for the protein or polypeptide that the gene is responsible for producing.

Linkage—The association between separate DNA sequences (genes) located on the same chromosome.

Syndactyly—Webbing or fusion between the fingers or toes.

Transcription—The process by which genetic information on a strand of DNA is used to synthesize a strand of complementary RNA.

Transcription factor—A protein that works to activate the transcription of other genes.

7. They showed that this gene was in the same location that was missing in some individuals with Saethre-Chotzen. The *TWIST1* gene is a small gene, containing only two exons (coding regions). Upon searching for alterations (mutations) in this gene, they found five different types of mutations in affected individuals. Since none of these mutations were found in unaffected individuals, this was proof positive that the *TWIST1* gene was the cause of Saethre-Chotzen syndrome.

Scientists have also used animal models and the fruit fly *Drosophila* to study the function of the *TWIST1* gene. They have found that it takes two *TWIST1* protein molecules to combine together, in order to function as a transcription factor for DNA. The normal function of the *TWIST1* protein is to bind to the DNA helix at specific places. By doing so, it works to regulate which genes are activated or “turned on.” Most of the mutations identified in the *TWIST1* gene so far seem to interfere with how the protein product binds to DNA. In effect, other genes that would normally be activated during development of the embryo may in fact not be turned on.

More recent studies suggest that the *TWIST1* protein may induce the activation of genes in the fibroblast

growth factor receptor (FGFR) pathway. Mutations in the FGFR family of genes cause other conditions with craniosynostosis such as Crouzon syndrome. Crouzon syndrome, like Saethre-Chotzen syndrome, is a mild craniosynostosis disorder. There is much overlap in the features of the face and hands in each condition. In fact, some patients initially thought to have Saethre-Chotzen were given a new diagnosis of Crouzon syndrome after studying both the *TWIST1* and the *FGFR* genes for mutations.

In all, it is thought that the *TWIST1* protein most likely acts to turn on the *FGFR* genes. These genes, in turn, instruct various cells of the head, face, and limb structures to grow and differentiate. If the *TWIST1* gene or other genes of the FGFR pathway are altered, an individual will have one of the craniosynostosis syndromes.

Demographics

Saethre-Chotzen syndrome affects both males and females equally. It most likely occurs in every racial and ethnic group and is believed to be underdiagnosed. The estimated incidence of the syndrome is 1 in every 25,000 to 50,000 individuals, making it the most common of the craniosynostosis syndromes.

Signs and symptoms

The cranium is made up of three main sections. The three sections are the face, the base of the cranium, and the top and sides of the head. Most of the cranium assumes its permanent shape before birth. However, the bones that make up the top and side of the head are not fixed in place, and the seams between the bones (cranial sutures) remain open. This allows the top of the head to adjust in shape, as the unborn baby passes through the narrow birth canal during labor. After birth, the cranial sutures will close, most often within the first few years of life. The shape of the cranium is then complete.

In Saethre-Chotzen, the shape of the cranium is abnormally formed. The reason is that the coronal suture closes too early, sometimes even before birth. The coronal suture separates the two frontal bones (forehead) from the parietal bones (top of the head). If the early closure is unilateral or asymmetric, then the forehead and face will form unevenly, from one side to the other. This also forces the top of the head to become more pointed, almost tower-like. The forehead looks high and wide. The face will appear uneven on each side, especially in the area of the eyes and cheeks.

There is also less space for the normal features of the face to develop. For instance, the eye sockets are shallower, and the cheekbones are flat. This makes the eyes more prominent and spaced further apart than normal.

QUESTIONS TO ASK YOUR DOCTOR

- My friend's baby was just diagnosed with Saethre-Chotzen syndrome. How serious is this disease?
- Will the child survive to adulthood, or is death at an early age likely?
- What are the characteristic symptoms of this disorder?
- Will the child have to remain under medical care throughout life?

Adding to the unevenness of the face is drooping of the upper eyelids, and a slight down-slant to the eyes. The nose may look beaked or bent slightly downward at the tip. In some individuals, the ears look small and low-set on the face.

The other main feature of the syndrome is minor abnormalities of the hands and feet. Webbing (syndactyly) commonly occurs between the second and third fingers and toes. The thumbs are short and flat. The fifth finger may be permanently curved or bent at the tip.

Each individual with Saethre-Chotzen is affected somewhat differently. The features are usually quite variable even within the same family. Most individuals are mildly affected. Their facial features may be somewhat flat and uneven, but not strikingly so. However, if more than one cranial suture closes too early (and this can happen in some individuals), there is more severe disfigurement to their face.

In addition to the physical characteristics, individuals with Saethre-Chotzen may have growth delays, leading to less than average adult height. Most individuals are of normal intelligence, although some may have mild to moderate intellectual disability (IQ from 50–70). For the growth and mental delays, it becomes necessary to provide special assistance and anticipatory guidance.

Diagnosis

For many years, there was widespread discussion among physicians (geneticists) over whether a given patient would have either Saethre-Chotzen or Crouzon syndrome. There may even be confusion with other craniosynostosis syndromes or with isolated craniosynostosis. However, the availability of direct gene testing now allows for a more definitive diagnosis for these patients. Simply using a blood sample, a direct gene test for

mutations in the *TWIST1* gene can be done. If an individual also has intellectual disability or other significant birth defects, it is suggested that they be screened more fully for deletions of the *TWIST1* gene.

Treatment and management

Very often, the physical characteristics of Saethre-Chotzen are so mild that no surgical treatment is necessary. The facial appearance tends to improve as the child grows. However, sometimes surgery is needed to correct the early fusion of the cranial bones. A specialized craniofacial medical team, experienced with these types of patients, should do this surgery. Surgery may also be done to release the webbing of the fingers and toes.

Some of the more severely affected individuals with Saethre-Chotzen may experience problems with their vision. There may be less space in the eye socket due to the bone abnormalities of the face. This can lead to damage of the nerves of the eye and may require corrective surgery. The tear ducts of the eye can also be missing or abnormal. Reconstructive surgery is sometimes performed to correct the drooping of the eyelids or narrowing of the nasal passage.

Prognosis

Most individuals with Saethre-Chotzen syndrome appear to have a normal lifespan.

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Children's Craniofacial Association (CCA), 13140 Coit Rd., Suite 517, Dallas, TX 75240, (800) 535-3643, contactCCA@ccakids.com, <http://www.ccakids.com>

March of Dimes Foundation, 1275 Mamaroneck Ave., White Plains, NY 10605, (914) 997-4488, <http://www.marchofdimes.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Sanfilippo syndrome (MPS III) see **Mucopolysaccharidoses**

Sarcoma-breast-leukemia-adrenal gland (SBLA) syndrome see **Li-Fraumeni syndrome**

SC syndrome see **Roberts SC phocomelia**

Scheie syndrome (MPS I) see **Mucopolysaccharidoses**

Schilder disease see **Adrenoleukodystrophy**

Schinzel acrocallosal syndrome see **Acrocallosal syndrome**

Schinzel-Giedion syndrome

Definition

Schinzel-Giedion syndrome, or Schinzel-Giedion midface-retraction syndrome, is a rare malformation syndrome characterized by skeletal anomalies, a coarse face, urogenital defects, and severe intellectual disability.

Description

In affected individuals, the ureter, or tube that carries urine from the kidney into the bladder, is obstructed, causing the pelvis and kidney duct to become swollen with excess urine. This is called hydronephrosis. Other features of the syndrome include hypertrichosis or the excessive growth of hair, a flat midface, abnormal brain activity, skeletal abnormalities, and severe mental impairment.

Patients show abnormal bone maturation including broad and dense ribs and short arms and legs. Severely delayed mental and motor development is accompanied by seizures and spasticity.

Genetic profile

Some scientists have suggested that the syndrome is inherited as an autosomal recessive trait because they

KEY TERMS

Hydronephrosis—Obstruction of the tube that carries urine from the kidney into the bladder causing the pelvis and kidney duct to become swollen with excess urine.

observed that the syndrome appeared in two sibs of different sex, which suggested autosomal recessive inheritance. However, other researchers have hypothesized that Schinzel-Giedion syndrome may be a dominant disorder with gonadal mosaicism in one parent. Gonadal mosaicism can occur when either the testes or ovaries contain some cells with an extra chromosome. Scientists have also postulated that the syndrome may be caused by an unbalanced structural chromosome abnormality.

Demographics

Schinzel-Giedion syndrome is extremely rare, and the exact prevalence remains unknown. About 25 to 30 well-documented cases have been reported, beginning in 1978. The syndrome was originally observed in a brother who lived less than 24 hours and a sister who survived for 16 months. Both displayed multiple skull abnormalities and profound midface retraction. They each had congenital heart defects, hydronephrosis, clubfoot, and hypertrichosis. Eight other cases, all sporadic, including two offspring of consanguineous parents, were subsequently identified that year. Fewer than 30 cases are described in the medical literature detailing major and minor features of the syndrome. Only one case has been described in Japan. The other described cases have occurred in Western countries.

Signs and symptoms

Clinical signs include a flat midface, low-set ears, a prominent forehead, skull abnormalities including large fontanels or openings, a short broad neck, genital malformations, congenital heart defects including atrial septal defect, clubfoot, and growth retardation.

Diagnosis

The detection of renal defects using prenatal ultrasound is one of the primary means of diagnosis. Clinical observation of coarse facial features, skeletal anomalies, and MRI studies aid diagnosis after birth. Serial cranial MRI studies that show a progressive neurodegenerative process affecting both gray and white matter typify

QUESTIONS TO ASK YOUR DOCTOR

- What does the term “gonadal mosaicism” mean, and how is it related to Schinzel-Giedion syndrome?
- Are there tests by which this genetic disorder can be detected prenatally?
- What information can a genetic counselor provide my spouse and me about Schinzel-Giedion syndrome?
- What is the prognosis for a child born with Schinzel-Giedion?

Schinzel-Giedion syndrome. Clinical signs of abnormal cortical gray matter include seizures, dementia, and blindness in some cases. Abnormalities in the white matter can produce spasticity and hyperreflexia.

Treatment and management

MRI studies indicate the syndrome is a progressive neurodegenerative process and patients have a limited lifespan. Nursing care and supportive measures are required to keep the patient comfortable.

Prognosis

Death prior to the second year of life represents the most common outcome.

Resources

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Julianne Remington

Schizophrenia

Definition

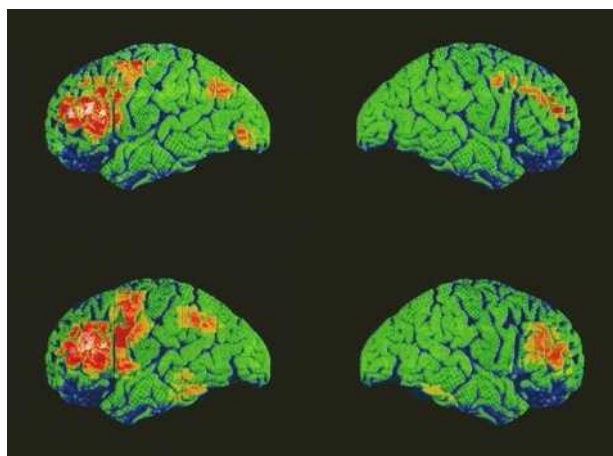
Schizophrenia is a psychotic disorder (or a group of disorders) marked by severely impaired thinking, emotions, and behaviors. Schizophrenic patients are typically unable to filter sensory stimuli and may have enhanced perceptions of sounds, colors, and other features of their environment. Most schizophrenics, if untreated, gradually withdraw from interactions with other people and lose their ability to take care of personal needs and grooming.

Description

The course of schizophrenia in adults can be divided into three phases or stages. In the acute phase, the patient has an overt loss of contact with reality (psychotic episode) that requires intervention and treatment. In the second, or stabilization, phase, the initial psychotic symptoms have been brought under control but the patient is at risk for relapse if treatment is interrupted. In the third, or maintenance, phase, the patient is relatively stable and can be kept indefinitely on antipsychotic medications. Even in the maintenance phase, however, relapses are not unusual and patients do not always return to full functioning.

The term “schizophrenia” comes from two Greek words that mean “split mind.” Around 1908, a Swiss doctor named Eugen Bleuler described a splitting-apart of mental functions that he regarded as the central characteristic of schizophrenia.

Recently, some psychotherapists have begun to use a classification of schizophrenia based on two main types. People with type I, or positive, schizophrenia, have a rapid (acute) onset of symptoms and tend to respond well to drugs. They also tend to suffer more from the “positive” symptoms, such as delusions and hallucinations. People with type II, or negative, schizophrenia, are usually described as poorly adjusted before their schizophrenia slowly overtakes them. They have predominantly



Colored PET brain scans of a normal patient (top) and one with schizophrenia (bottom). (Wellcome/Science Source)

“negative” symptoms, such as withdrawal from others and a slowing of mental and physical reactions (psychomotor retardation).

The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* specified five subtypes of schizophrenia—paranoid, disorganized, catatonic, undifferentiated, and residual—but those have been removed from *DSM-5* due to their low reliability as diagnostic tools.

Schizoaffective disorder

A condition commonly diagnosed as schizophrenia is schizoaffective disorder. This relatively rare disorder is characterized by psychotic symptoms in a patient with a mood disorder, usually manic depression. The psychotic symptoms may or may not be present at the same time as the mood disorder. Another complicating factor, especially in younger patients, is that distinguishing between manic depression and schizophrenia can be difficult in adolescents, since psychotic features are common during manic episodes in this age group.

Genetic profile

The risk of schizophrenia among first-degree biological relatives is 10 times greater than that observed in the general population. Furthermore, the presence of the same disorder is higher in monozygotic twins (identical twins) than in dizygotic twins (fraternal, or nonidentical, twins). The research on adoption and identical twins also supports the notion that environmental factors are important, because not all relatives who have the disorder express it. There are several chromosomes and loci (specific locations on chromosomes that contain mutated genes) that have been identified. Recent research has

implicated chromosomal 11 translocations in both schizophrenia and manic depression. In addition, there are now mutations of several genes that are postulated to be involved in schizophrenia, including *DTNBPI*, *NRG1*, *DAO*, *DAOA*, and *RSG4*. The mode of inheritance is not yet clear either. Some researchers believe there is an autosomal recessive pattern, some an irregular dominant inheritance, and others a polygenic inheritance, especially considering the spectrum of clinical symptoms that occur within the population of schizophrenic patients. Research is actively ongoing to elucidate the causes, types, and variations of these mutations. Genome sequencing, genome-wide association studies, and the understanding of DNA methylation and the relationship between genes and promoters and expression of such may be able to provide important information about dysregulation of genes and schizophrenia in the future. Animal models are already being done to study the genetic link to schizophrenia.

Demographics

A number of studies indicate that about 1% of the world’s population is affected by schizophrenia, without regard to race, social class, level of education, or cultural influences (outcomes may vary from culture to culture, depending on the familial support of the patient). Most patients are diagnosed in their late teens or early 20s, but the symptoms of schizophrenia can emerge at any age in the life cycle. The male/female ratio in adults is about 1.2:1. Male patients typically have their first acute episode in their early 20s, while female patients are usually closer to age 30 when they are recognized with active symptoms.

Schizophrenia is rarely diagnosed in preadolescent children, although patients as young as five or six have been reported. Childhood schizophrenia is at the upper end of the spectrum of severity and shows a greater gender disparity. It affects 1 or 2 children in every 10,000; the male/female ratio is 2:1.

Signs and symptoms

One of the reasons for the ongoing difficulty in classifying schizophrenic disorders is an incomplete understanding of their causes. Since 1998, it has been thought that these disorders were the end result of a combination of genetic, neurobiological, and environmental causes. A leading neurobiological hypothesis looks at the connection between the disease and excessive levels of dopamine, a chemical (neurotransmitter) that transmits signals in the brain. The genetic factor in schizophrenia has been underscored by recent findings that first-degree biological relatives of schizophrenics

are 10 times as likely to develop the disorder as are members of the general population.

Prior to recent findings of abnormalities in the brain structure of schizophrenic patients, several generations of psychotherapists advanced a number of psychoanalytic and sociological theories about the origins of schizophrenia. These theories ranged from hypotheses about the patient's problems with anxiety or aggression to theories about stress reactions or interactions with disturbed parents. Psychosocial factors are now thought to influence the expression or severity of schizophrenia, rather than cause it directly.

Another hypothesis suggests that schizophrenia may be caused by a virus that attacks the hippocampus, a part of the brain that processes sense perceptions. Damage to the hippocampus would account for schizophrenic patients' vulnerability to sensory overload. Researchers are preparing to test antiviral medications on schizophrenics.

Patients with a possible diagnosis of schizophrenia are evaluated on the basis of a set or constellation of symptoms; there is no single symptom that is unique to schizophrenia. In 1959, the German psychiatrist Kurt Schneider proposed a list of so-called first-rank symptoms, which he regarded as diagnostic of the disorder. These symptoms include:

- delusions
- somatic hallucinations
- hearing voices commenting on the patient's behavior
- thought insertion or thought withdrawal

Somatic hallucinations refer to sensations or perceptions concerning body organs that have no known medical cause or reason, such as the notion that one's brain is radioactive. Thought insertion and/or withdrawal refers to delusions that an outside force (for example, the FBI, the CIA, Martians, etc.) has the power to put thoughts into one's mind or remove them.

The so-called positive symptoms of schizophrenia are those that represent an excessive or distorted version of normal functions. Positive symptoms include Schneider's first-rank symptoms as well as disorganized thought processes (reflected mainly in speech) and disorganized or catatonic behavior. Disorganized thought processes are marked by characteristics: looseness of association, in which the patient rambles from topic to topic in a disconnected way; tangentially, which means that the patient gives unrelated answers to questions; and "word salad," in which the patient's speech is so incoherent that it makes no grammatical or linguistic sense. Disorganized behavior means that the patient has difficulty with any type of purposeful or goal-oriented behavior, including

personal self-care or preparation of meals. Other forms of disorganized behavior may include dressing in odd or inappropriate ways, sexual self-stimulation in public, or agitated shouting or cursing.

The *DSM-5* definition of schizophrenia includes three so-called negative symptoms. They are called negative because they represent the lack or absence of behaviors. The negative symptoms that are considered diagnostic of schizophrenia are a lack of emotional response (affective flattening), poverty of speech, and absence of volition or will. In general, the negative symptoms are more difficult for doctors to evaluate than the positive symptoms.

Diagnosis

A doctor must make a diagnosis of schizophrenia on the basis of a standardized list of outwardly observable symptoms, not on the basis of internal psychological processes. There are no specific laboratory tests that can be used to diagnose schizophrenia. Researchers have, however, discovered that patients with schizophrenia have certain abnormalities in the structure and functioning of the brain compared to normal test subjects. These discoveries have been made with the help of imaging techniques, such as computed tomography (CT) scans.

When a psychiatrist assesses a patient for schizophrenia, physical conditions will be excluded that can cause abnormal thinking and some other behaviors associated with schizophrenia. These conditions include organic brain disorders (including traumatic injuries of the brain), temporal-lobe epilepsy, Wilson disease, Huntington's chorea, and encephalitis. Substance abuse disorders, especially amphetamine use, will need to be ruled out.

After ruling out organic disorders, the clinician will consider other psychiatric conditions that may include psychotic symptoms or symptoms resembling psychosis. These disorders include mood disorders with psychotic features; delusional disorder; dissociative disorder not otherwise specified (DDNOS), or multiple personality disorder; schizotypal, schizoid, or paranoid personality disorders; and atypical reactive disorders. In the past, many individuals were incorrectly diagnosed as schizophrenic. Patients who were diagnosed prior to the changes in categorization introduced by *DSM-IV* should have their diagnoses, and treatment, reevaluated. In children, the psychiatrist must distinguish between psychotic symptoms and a vivid fantasy life, and also identify learning problems or disorders. After other conditions have been ruled out, the patient must meet a set of criteria, including:

- Characteristic symptoms: The patient must have symptoms over the course of six months with two (or more) active symptoms during a one-month period: delusions;

KEY TERMS

Affective flattening—A loss or lack of emotional expressiveness; sometimes called blunted or restricted affect.

Akathisia—Agitated or restless movement, usually affecting the legs and accompanied by a sense of discomfort; a common side effect of neuroleptic medications.

Catatonic behavior—Behavior characterized by muscular tightness or rigidity and lack of response to the environment.

Delusion—A fixed, false belief that is resistant to reason or factual disproof.

Depot dosage—A form of medication that can be stored in the patient's body tissues for several days or weeks, thus minimizing the risk of the patient forgetting daily doses.

Dopamine receptor antagonists (DAs)—The older class of antipsychotic medications, also called neuroleptics, which primarily block the site on nerve cells that normally receive the brain chemical dopamine.

Dystonia—Painful involuntary muscle cramps or spasms.

Extrapyramidal symptoms (EPS)—A group of side effects associated with antipsychotic medications, including parkinsonism, akathisia, dystonia, and tardive dyskinesia.

First-rank symptoms—A set of symptoms designated by Kurt Schneider in 1959 as the most important diagnostic indicators of schizophrenia: delusions, hallucinations, thought insertion or removal, and thought broadcasting.

Hallucination—A sensory experience of something that does not exist outside the mind.

Huntington's chorea—A hereditary disease that typically appears in midlife, marked by gradual loss

of brain function and voluntary movement; some symptoms resemble those of schizophrenia.

Negative symptoms—Symptoms of schizophrenia characterized by the absence or elimination of certain behaviors: affective flattening, poverty of speech, and loss of will or initiative.

Neuroleptic—Another name for the older type of antipsychotic medications given to schizophrenic patients.

Parkinsonism—A set of symptoms originally associated with Parkinson's disease that can occur as side effects of neuroleptic medications: trembling of the fingers or hands, a shuffling gait, and tight or rigid muscles.

Positive symptoms—Symptoms of schizophrenia that are characterized by the production or presence of behaviors that are grossly abnormal or excessive, including hallucinations and thought-process disorder.

Poverty of speech—A negative symptom of schizophrenia, characterized by brief and empty replies to questions.

Psychotic disorder—A mental disorder characterized by delusions, hallucinations, or other symptoms of lack of contact with reality.

Serotonin dopamine antagonists (SDAs)—The newer second-generation antipsychotic drugs, also called atypical antipsychotics, including clozapine (Clozaril), risperidone (Risperdal), and olanzapine (Zyprexa).

Wilson disease—A rare hereditary disease marked by high levels of copper deposits in the brain and liver.

Word salad—Speech that is so disorganized that it makes no linguistic or grammatical sense.

hallucinations; disorganized speech; disorganized or catatonic behavior; negative symptoms.

- The patient must show a decline in social, interpersonal, or occupational functioning, including self-care.
- Duration: The disturbed behavior must last for at least six months.
- Diagnostic exclusions: Mood disorders, substance abuse disorders, medical conditions, and developmental disorders have been ruled out.

Treatment and management

The treatment of schizophrenia depends in part on the patient's stage or phase. Patients in the acute phase are hospitalized in most cases, to prevent harm to the patient or others and to begin treatment with antipsychotic medications. A patient having a first psychotic episode should be given a CT or magnetic resonance imaging (MRI) scan to rule out structural brain disease.

The primary form of treatment of schizophrenia is antipsychotic medication. Antipsychotic drugs help to

control almost all the positive symptoms of the disorder. They have minimal effects on disorganized behavior and negative symptoms. Between 60% and 70% of schizophrenics will respond to antipsychotics. In the acute phase of the illness, patients are usually given medications by mouth or by intramuscular injection. After the patient has been stabilized, the antipsychotic drug may be given in a long-acting form called a depot dose. Depot medications last two to four weeks; they have the advantage of protecting the patient against the consequences of forgetting or skipping daily doses. In addition, some patients who do not respond to oral neuroleptics have better results with depot form. Patients whose long-term treatment includes depot medications are introduced to the depot form gradually during their stabilization period. Most people with schizophrenia are kept on antipsychotic medications indefinitely during the maintenance phase of their disorder to minimize the possibility of relapse.

The most frequently used antipsychotics have fallen into two classes: the older dopamine receptor antagonists, or DAs, and the newer serotonin dopamine antagonists, or SDAs. (Antagonists block the action of some other substance; for example, dopamine antagonists counteract the action of dopamine.) The exact mechanisms of action of these medications are not known, but it is thought that they lower the patient's sensitivity to sensory stimuli and so indirectly improve the patient's ability to interact with others.

The DAs include the older antipsychotic (also called neuroleptic) drugs, such as haloperidol (Haldol), chlorpromazine (Thorazine), and fluphenazine (Prolixin). These drugs have two major drawbacks: it is often difficult to find the best dosage level for the individual patient, and a dosage level high enough to control psychotic symptoms frequently produces extrapyramidal side effects, or EPS. EPS include parkinsonism, in which the patient cannot walk normally and usually develops a tremor; dystonia, or painful muscle spasms of the head, tongue, or neck; and akathisia, or restlessness. A type of long-term EPS is tardive dyskinesia, which features slow, rhythmic, automatic movements. Schizophrenics with AIDS are especially vulnerable to developing EPS.

The SDAs, also called atypical antipsychotics, are newer medications that include clozapine (Clozaril), risperidone (Risperdal), and olanzapine (Zyprexa). The SDAs have a better effect on the negative symptoms of schizophrenia than do the older drugs and are less likely to produce EPS than the older compounds. The newer drugs are significantly more expensive in the short term, although the SDAs may reduce long-term costs by reducing the need for hospitalization. They are also presently unavailable in injectable forms. The SDAs are commonly used to treat patients who respond poorly to the DAs. However, many psychotherapists now regard the use of

these atypical antipsychotics as the treatment of first choice.

Most schizophrenics can benefit from psychotherapy once their acute symptoms have been brought under control by antipsychotic medication. Psychoanalytic approaches are not recommended. Cognitive-behavioral therapy (CBT), however, is often helpful in assisting patients to acquire skills for daily living and social interaction. It can be combined with occupational therapy to prepare the patient for eventual employment.

Nutritional advancements have also been made for the management of schizophrenia. Vitamins and minerals important for brain health have been successful in the management of schizophrenia and its symptoms, including but not limited to omegas, vitamin D, B vitamins, serine, alanine, melatonin, choline, and antioxidants, among others. An anti-inflammatory-type diet may also be helpful in the management of schizophrenia.

Family therapy is often recommended for the families of schizophrenic patients, to relieve the feelings of guilt that they often have as well as to help them understand the patient's disorder. The family's attitude and behaviors toward the patient are key factors in minimizing relapses (i.e., reducing stress in the patient's life), and family therapy can often strengthen the family's ability to cope with the stresses caused by the schizophrenic's illness. Family therapy focused on communication skills and problem-solving strategies is particularly helpful. In addition to formal treatment, many families benefit from support groups and similar mutual help organizations for relatives of schizophrenics.

Prognosis

One important prognostic sign is the patient's age at onset of psychotic symptoms. Patients with early onset of schizophrenia are more often male, have a lower level of functioning prior to onset, a higher rate of brain abnormalities, more noticeable negative symptoms, and worse outcomes. Patients with later onset are more likely to be female, with fewer brain abnormalities and thought impairment, and more hopeful prognoses. Recent research has indicated that schizophrenia should be approached as a neurodevelopmental disorder and has even gone as far as saying that focuses on the abnormal development of the brain leading to schizophrenia could prove instrumental in the prevention of the early stages of schizophrenia. Prevention and early detection are key to the treatment and therefore the prognosis of schizophrenia.

The average course and outcome for schizophrenics are less favorable than those for most other mental disorders, although as many as 30% of patients diagnosed with schizophrenia recover completely and the majority do

QUESTIONS TO ASK YOUR DOCTOR

- Is schizophrenia always a genetic-based disorder, or are there other causes for the condition?
- What are the probabilities that my child will inherit schizophrenia from my spouse, who has the disorder?
- What kinds of treatment are available for dealing with schizophrenia, and how effective are those treatments?
- What factors determine the prognosis for a person with schizophrenia and, based on my spouse's current status, what is his prognosis for the disease?

experience some improvement. Two factors that influence outcomes are stressful life events and a hostile or emotionally intense family environment. Schizophrenics with a high number of stressful changes in their lives, or who have frequent contacts with critical or emotionally overinvolved family members, are more likely to relapse. Overall, the most important component of long-term care of schizophrenic patients is complying with their regimen of antipsychotic medications.

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ORGANIZATIONS

- National Alliance on Mental Illness, 3803 N. Fairfax Dr. Suite 100, Arlington, VA 22203, (703) 524-7600 or (800) 950-NAMI, (703) 524-9094, info@nami.org, <https://www.nami.org>
- Schizophrenics Anonymous, 15920 W. Twelve Mile, Southfield, MI 48076, (248) 477-1983

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Schwartz-Jampel syndrome

Definition

Schwartz-Jampel syndrome (SJS) is a rare, inherited condition of the skeletal and muscle systems that causes short stature, joint limitations, and particular facial features.

Description

First described in 1962, SJS is now a clearly defined syndrome that is divided into two types. Type 1A is the classical form that develops in early childhood, usually between the first and third year of life. Type 1B is less common but more severe and its symptoms are present at birth. Both types of SJS involve generalized disease of the muscles called myopathy. The muscles tend to be quite stiff and are unable to relax normally. This is a condition known as myotonia. The myotonia causes many joints in the body to stay in a bent or flexed position (joint contractures).

In addition to muscle problems, the bones in the skeleton do not develop normally and this is why SJS may also be called a type of skeletal dysplasia. Abnormal bone shape and poor bone growth result in decreased total height, incorrect arm and leg postures, as well as curving of the spine (scoliosis).



Owen Howkins, a boy with Schwartz-Jampel syndrome, has become inseparable with his dog, Haatchi, who has proven to be a natural helper. (AP Images/Rex Features)

Unique facial features of SJS include narrow eye openings with drooping eye lids, a small mouth, and puckered lips. These features are also due to the stiffness of the muscles that support the face and individuals with SJS appear to have a fixed facial expression.

Persons affected with SJS often have normal intelligence, although varying degrees of intellectual disability may affect as many as 25% of patients. However, the myotonia may lead to poor speech articulation and drooling so that affected individuals are sometimes misdiagnosed as having intellectual disability.

Respiratory and feeding difficulties are frequent with SJS Type 1B due to the more severe nature of the muscle and bone disease. These problems may be fatal in early infancy. Persons with SJS Type 1A have a much longer life expectancy, although this depends on how their disease progresses.

SJS has also been referred to as:

- myotonic myopathy, dwarfism, chondrodystrophy, and ocular and facial abnormalities
- Schwartz-Jampel–Aberfeld syndrome

- Schwartz syndrome
- Aberfeld syndrome
- chondrodystrophic myotonia
- osteochondromuscular dystrophy
- spondylo-epimetaphyseal dysplasia with myotonia

Genetic profile

Both types of SJS are known to be inherited in an autosomal recessive manner. This was concluded after the following observations were made. SJS affects males and females alike. Parents of affected individuals rarely show any signs or symptoms of SJS. Parents have been reported to have more than one affected child. Consanguineous relationships were seen in some families.

Genetic studies of many families revealed that all cases of SJS were linked to an area on chromosome 1, described as 1p36.1. A gene in this region, heparan sulfate proteoglycan 2 (*HSPG2*), makes a protein called perlecan that plays an important role in maintaining cell membranes of the body's connective tissue (bone, cartilage, muscles, ligaments, tendons, and blood vessels).

Studies have shown that perlecan helps keep cartilage and bone strong and is essential for certain chemical processes in muscle tissues. It is also thought that perlecan helps to regulate the normal growth of some cells.

Mutations in the *HSPG2* gene have been found in some persons with SJS. These gene mutations change how the perlecan protein is made and usually prevent it from doing its normal job in the muscles and bones of the body.

The location 1p36.1 means that the gene is near the top or end of the short arm of chromosome number one. Human beings have 23 pairs of chromosomes in nearly every cell of their bodies. One of each kind (23 total) is inherited from the mother and another of each kind (23 total) is inherited from the father, for a total of 46. One chromosome may hold hundreds to thousands of individual genes and as the chromosomes exist in pairs, so do the genes. Therefore, every person has two copies of the *HSPG2* gene that makes perlecan. Individuals that have a diagnosis of SJS are thought to have a mutation in both copies of their *HSPG2* gene, each of which was inherited from one of their parents. Unaffected parents of children with SJS are therefore carriers for SJS. Their one normal *HSPG2* gene appears to make enough perlecan so those carriers do not show any symptoms of SJS. Most parents do not know that they are carriers for SJS until they have an affected child. When both parents are carriers for the same autosomal recessive disease such as SJS, there is a 25% chance with each and every pregnancy that they have together that their child will inherit both mutated *HSPG2* genes and develop SJS.

Demographics

SJS is a very rare genetic syndrome reported to affect males and females. It was initially described in the United States, but has also been reported in other countries. However, the exact incidence is unknown as no significant information is available on racial or sexual distribution.

Signs and symptoms

A child born with SJS Type 1A may show no outward signs of the condition at birth. Over the following one to three years, progressive myotonia of the muscles and resulting joint contractures develop. The typical bone problems become obvious and growth in height slows down. These symptoms are evident at birth in children with SJS Type 1B. The following descriptions apply to both SJS Type 1A and SJS Type 1B. However, each person with SJS may be affected to a different degree and their kinds of symptoms may vary.

Head and neck

Myotonia of the muscles in the face causes a tight and fixed facial expression. The eye openings are almost always narrowed and small and the upper and lower eyelids are not joined properly at the corners of the eye (blepharophimosis). The upper eyelid may also appear droopy (ptosis). Nearsightedness (myopia) is present in 50% of patients and occasionally cataracts and lens dislocation may develop in the eye. The mouth is small and the lips are puckered due to tight facial muscles. This may lead to speech difficulty. The chin may also be small or set back.

Body

Hernias of the groin and navel area are often noticed at birth. A hernia is the bulging of a tissue outside of its normal space and a simple operation can usually place it back inside. *Pectus carinatum* is a common bony deformity of the chest that causes the breast bone to protrude forward. Abnormalities in the growth and development of the bones of the spinal column (vertebrae) lead to scoliosis that usually worsens with age. Development of puberty is most often normal for persons with SJS.

Limbs

Some babies with SJS are born with a dislocation of their hip joint. This is common in infants without SJS as well. As the muscle disease of SJS progresses, the joints become very stiff. The hips, knees, and elbows in particular have very limited range of motion. These joint contractures worsen until puberty and then tend to stay the same from that point on. Eventually, a wheelchair is needed due to significant limitation of movement. The long bones in the body (e.g., the thigh bone) are bowed and shortened. This can cause a person with SJS to waddle as they walk and to stand in a crouching position. Therefore, an individual with SJS tends to be shorter than 90% of unaffected persons their age. A few have been reported to reach average height. Typically, their arms and legs have an increased amount of body hair as well.

Muscles

The muscles of the body show progressive myotonia, as they remain tight and are unable to relax normally. The muscle bulk may be increased in some areas, such as the thighs, and may waste away in others. As the muscles are unable to function normally, physical activity is restricted and a person may tire very easily.

Central nervous system and behavior

Most individuals with SJS have normal intelligence, although some degree of intellectual disability has been

KEY TERMS

Blepharophimosis—A small eye opening without fusion of the upper eyelid with the lower eyelid at the inner and outer corner of the eye.

Consanguineous—Sharing a common bloodline or ancestor.

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Myopathy—Any abnormal condition or disease of the muscle.

Myotonia—The inability to normally relax a muscle after contracting or tightening it.

reported. Developmental language problems and attention difficulties have also been seen in some cases. Reflexes tend to be slower than normal. A high-pitched voice and drooling may be noticed due to muscle stiffness in the mouth and throat area. This may cause feeding difficulties and choking may be of concern.

Diagnosis

The diagnosis of SJS Type 1A or Type 1B is made mainly by the presence of the symptoms described above. There is no specific biochemical or muscle testing that confirms a suspected diagnosis. Although research studies have identified mutations in the *HSPG2* gene in some families, widespread genetic testing is not clinically available. Such genetic mutations may be unique to each family and therefore may not be found in other persons affected with SJS.

Several different studies may be performed to determine the type and severity of muscle disease when considering a diagnosis of SJS. This may include a muscle biopsy that samples a piece of muscle and examines the appearance of the muscle cells. A muscle biopsy may appear normal or it may show signs of myopathy. A particular chemical, called creatine kinase, can be measured in a person's blood. Very high levels of creatine kinase usually indicate the presence of muscle disease or wasting. An electromyogram (EMG) is a test that measures the electrical currents made within an active muscle. The EMG pattern is usually abnormal in persons with SJS. These tests will confirm the presence of muscle disease but there are no specific changes in any of them that are unique to SJS.

The following are some abnormalities of the bones that are frequently noticed on x-rays:

- flat and irregularly formed vertebrae
- deformity of the upper part of the thigh bone
- a flattened joint socket where the hip and thigh bone meet
- specific changes in the development of the bones in the hand
- bowing of the long bones, especially the leg bones
- curvature of the spine that causes a hunchback appearance

Many of the symptoms of SJS are also present in other conditions, and it is important to distinguish SJS from the following disorders:

- Stuve-Wiedemann syndrome (which was previously called SJS type 2)
- Freeman-Sheldon syndrome (also known as whistling face syndrome)
- Marden-Walker syndrome
- Kniest dysplasia
- Seckel syndrome
- myotonic dystrophy
- the mucopolysaccharidoses

Treatment and management

There is not a cure for SJS. The treatment involves managing the symptoms of the condition as they develop and supporting the needs of the individual as the disability progresses. Several medical specialists may monitor a person with SJS for particular symptoms or complications. An orthopedic doctor manages the abnormal bone development and may offer surgical options for treatment of hip dislocation, scoliosis, or bone curvature. An ophthalmologist monitors eye problems such as nearsightedness and cataracts, for which glasses and surgery may be available. Cosmetic repair of blepharophimosis by plastic surgery may also be considered.

For those with a mental deficiency, special-education programs with options for activities in regular classrooms may offer the best opportunities for learning. Physical therapy may help maintain the greatest possible range of motion of the joints and speech therapy may improve speech problems due to a small and tight mouth. Physical activities of children are usually limited due to their stiff joints. As the condition progresses, persons with SJS are often wheelchair-bound by their teenage years and occupational therapy may help improve their everyday living skills. Adults who live independently may require some assistance with everyday tasks that their disability prevents them from doing, such as household chores or even bathing.

QUESTIONS TO ASK YOUR DOCTOR

- How do the two major types of Schwartz-Jampel syndrome differ from each other?
- What is the life expectancy of a person with each type of this disorder?
- What kinds of medical treatments are needed for each type of Schwartz-Jampel syndrome?

Prognosis

Individuals with SJS can live well into adulthood despite progressive disability but the average life expectancy is unclear. They are usually wheelchair-bound by their teenage or young adult years. Although puberty development may be normal, no reports have been made of an individual with SJS fathering children or carrying a pregnancy.

SJS Type 1B may be fatal in the newborn period due to serious respiratory and feeding problems. As the muscles in the face and neck may be very tight, it can be difficult to place a tube down the throat (intubation) to allow a baby to breathe. Feeding may be a continuous struggle due to problems with or an inability to swallow.

Both types of SJS cause persons to be more prone to develop chest infections and pneumonia. There is also an increased risk for complications from anesthesia, specifically malignant hyperthermia (MH). MH is an abnormal chemical reaction in the body to the use of some anesthesia medications. It causes high fevers, breathing difficulty, rigid muscles, and general serious illness. This condition may be life threatening.

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ORGANIZATIONS

- National Eye Institute (NEI), 31 Center Dr., MSC 2510, Bethesda, MD 20892, (301) 496-5248, 2020@nei.nih.gov, <http://www.nei.nih.gov>
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Information Clearinghouse, 1 AMS Circle, Bethesda, MD 20892, (877) 226-4267, NIAMSinfo@mail.nih.gov, http://www.niams.nih.gov/Health_Info
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave, Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Jennifer Elizabeth Neil, MS, CGC

SCIDX see **Severe combined immunodeficiency**

Sclerocornea see **Microphthalmia with linear skin defects**

Scleroderma

Definition

Scleroderma is a progressive disease that affects the skin and connective tissue, including cartilage, bone, fat, and the tissue that supports the nerves and blood vessels throughout the body. There are two major forms of the disorder: localized scleroderma, which mainly affects the skin, and systemic scleroderma, or systemic sclerosis, which affects the smaller blood vessels and internal organs of the body.

Description

Scleroderma is an autoimmune disorder characterized by the hardening of the skin. In scleroderma, there is an overproduction of abnormal collagen as it accumulates throughout the body, causing hardening (sclerosis), scarring (fibrosis), and other damage. The damage may affect the appearance of the skin, or in more severe cases it may also affect internal organs. The symptoms and severity of scleroderma vary from person to person.

Genetic profile

The role of genetics in the transmission of scleroderma is unclear, although mutations in the human leukocyte antigen (HLA) play a role in some cases of the disease. Some cases clearly run in families, but most



Line of hardened skin on the forehead in a teenaged female patient with linear scleroderma. Scleroderma is a chronic autoimmune disease characterized by a hardening of the skin, in this case in an isolated region. (Dr. Harout Tanielian/ Science Source)

occur in people without any family history of the disease. In 2021, research has linked new candidate genes to several aspects of scleroderma pathology that might help explain the disease's complexity at the molecular level. Gene expression, which is regulated by biological factors such as expression quantitative trait loci (eQTLs), affect cell activity. By identifying eQTLs that turn cells on or off in tissues most affected by scleroderma, investigators can begin to identify targeted therapies.

Demographics

Scleroderma occurs in all races of people, all over the world, but it affects about four females for every male. Among children, localized scleroderma is more common, and systemic sclerosis is comparatively rare. Most patients with systemic sclerosis are diagnosed between ages 30 and 50. Scleroderma occurs in about 20 people per million in the United States. Young African American women and Native Americans of the Choctaw tribe have especially high rates of the disease. Exact incidence is difficult to determine.

Signs and symptoms

The cause of scleroderma is still uncertain, although the accumulation of collagen appears to be a hallmark of the disease. Some theories suggest that damage to blood vessels may cause the tissues of the body to receive an inadequate amount of oxygen—a condition called ischemia. Some research suggests that the resulting damage causes the immune system to over-react and leads to an autoimmune response. Cells in the immune system called antibodies react to the body's own tissues as if they were foreign pathogens. The antibodies turn against the

already-damaged blood vessels and supporting tissues. These immune cells are designed to deliver potent chemicals in order to kill foreign invaders, and when some of these chemicals are delivered to the body's own tissues instead, the results include inflammation, swelling, damage, and scarring.

Most cases of scleroderma have no recognizable triggering event. Some cases, however, have been traced to exposure to toxic or poisonous substances. For example, coal miners and gold miners who are exposed to high levels of silica dust have above-average rates of scleroderma. Other chemicals associated with the disease include polyvinyl chloride, benzene, toluene, and epoxy resins. In 1981, 20,000 people in Spain were stricken with a syndrome similar to scleroderma when their cooking oil was accidentally contaminated. Certain medications, especially a drug used in cancer treatment called bleomycin (Blenoxane), may lead to scleroderma. Women with silicone breast implants have made some claims of a scleroderma-like illness, but a link has not been proven in scientific studies.

Symptoms of systemic scleroderma

A condition called Raynaud's phenomenon is the first symptom in about 95% of all patients with systemic scleroderma. Raynaud's phenomenon is characterized by the blood vessels of the fingers and/or toes reacting to cold in an abnormal way. The vessels clamp down, preventing blood flow to the tips of the digits. Eventually, the flow is cut off to entire fingers or toes, and over time oxygen deprivation may result in open ulcers on the skin surface. These ulcers can lead to tissue death (gangrene) and loss of digits. When Raynaud's phenomenon is the first sign of scleroderma the next symptoms usually appear within two years.

SKIN AND EXTREMITIES. Sclerosis of the skin can lead to swelling underneath the skin of the hands, feet, legs, arms, and face. This swelling can, in turn, contribute to the thickening and tightening of the skin, which becomes taut and shiny. Severe tightening may promote physical abnormalities, such as the fingers becoming permanently curled or flexed, structures within the skin getting damaged (e.g., the production of hair, oil, and sweat), and the skin becoming dry and scaly. Ulcers may form and lead to infection, and calcium deposits often appear under the skin.

As the skin on the face tightens, the mouth and nose may become smaller, which may interfere with eating and dental hygiene. Blood vessels under the skin may become enlarged and show through the skin, appearing as purplish marks or red spots. This chronic dilation of the small blood vessels is called telangiectasis.

Muscle weakness, joint pain and stiffness, and carpal tunnel syndrome are common in scleroderma. Carpal tunnel syndrome involves scarring in the wrist, which puts pressure on the median nerve running through that area. Pressure on the nerve causes numbness, tingling, and weakness in some of the fingers.

DIGESTIVE TRACT. The esophagus connects the mouth to the stomach and can become stiff and scarred in more serious cases of scleroderma. Patients may have trouble swallowing food, and the acid contents of the stomach may start to flow backward into the esophagus, causing it to become inflamed, a condition known colloquially as heartburn.

The intestines can become sluggish in processing food, causing bloating and pain, which can lead to foods not being digested properly, in turn resulting in diarrhea, weight loss, and anemia. Telangiectasis in the stomach or intestine may cause rupture and bleeding.

RESPIRATORY AND CIRCULATORY SYSTEMS. The lungs are affected in about 66% of all people with systemic scleroderma. Complications include shortness of breath, coughing, difficulty breathing due to tightening

of the tissue around the chest, inflammation of the air sacs in the lungs (alveolitis), increased risk of pneumonia, and an increased risk of cancer. For these reasons, lung disease is the most likely cause of death associated with scleroderma.

The lining around the heart (pericardium) may become inflamed in some cases of systemic scleroderma. The heart may have greater difficulty pumping blood effectively, thus causing irregular heart rhythms and enlargement of the heart.

Kidney disease is another common complication. The kidneys may stop filtering blood and go into failure. Damage to blood vessels in the kidneys often causes a major rise in the person's blood pressure. The blood pressure may be so high that there is swelling of the brain, causing severe headaches, damage to the retinas of the eyes, seizures, and failure of the heart to pump blood into the body's circulatory system. Treatments for high blood pressure have greatly improved these kidney complications. Before these treatments were available, kidney problems were the most common causes of death for people with scleroderma.



Scleroderma results in thickening and toughening of the skin, which may also become inflamed. (Dr. P. Marazzi/Science Source)

Other problems associated with scleroderma include painful dryness of the eyes and mouth, enlargement and destruction of the liver, and a low-functioning thyroid gland.

Diagnosis

Diagnosis of scleroderma is complicated by the fact that some of its symptoms can accompany other connective-tissue diseases. The most important symptom is thickened or hardened skin on the fingers, hands, forearms, or face, which is found in 98% of people with scleroderma and can be detected in the course of a physical examination. The person's medical history may also reveal important clues, such as exposure to toxic substances.

There are a number of nonspecific laboratory blood tests that may indicate the presence of an inflammatory disorder but not specifically scleroderma. The antinuclear antibody (ANA) test is positive in more than 95% of people with scleroderma and can be used to help confirm a diagnosis.

Other tests can be performed to evaluate the extent of the disease. They include a test of the electrical system of the heart (an electrocardiogram), lung-function tests, and x-ray studies of the gastrointestinal tract. Various blood tests can be given to study kidney function. Biomarkers can help assess risk for severe complications. One example is vasohibin-1, which is likely linked to the disease process; measuring levels of the protein could help determine a patient's risk for pulmonary fibrosis. A computer algorithm called DETECT has correctly identified patients with pulmonary arterial hypertension, a sometimes-fatal complication of scleroderma. If the test proves accurate for early detection, doctors can treat pulmonary arterial hypertension before it becomes critical.

Treatment and management

At this time, there is no cure for scleroderma. A drug called D-penicillamine has been used to interfere with the abnormal collagen production that is characteristic to scleroderma. It is thought to help decrease the degree of skin thickening and tightening and to slow the progress of the disease in other organs. Taking vitamin D and using ultraviolet light may be helpful in treating localized scleroderma. Corticosteroids have been used to treat joint pain, muscle cramps, and other symptoms of inflammation. Other drugs have been studied that reduce the activity of the immune system (immunosuppressants), but because these medications can have serious side effects, they are used in only the most severe cases of scleroderma.

KEY TERMS

Autoimmune disorder—A disorder in which the body's immune cells mistake its own tissues as foreign invaders; the immune cells then work to destroy tissues in the body.

Collagen—The main supportive matrix protein of cartilage, connective tissue, tendon, skin, and bone.

Connective tissue—A group of tissues responsible for support throughout the body, including cartilage, bone, fat, organs, blood vessels, and nerves.

Fibrosis—The abnormal development of fibrous tissue; scarring.

Limited scleroderma—A subtype of systemic scleroderma with limited skin involvement. It is sometimes called the CREST form of scleroderma, after the initials of its five major symptoms.

Localized scleroderma—Thickening of the skin from overproduction of collagen.

Morphea—The most common form of localized scleroderma.

Raynaud's phenomenon/Raynaud's disease—A condition in which blood flow to tissues is reduced by a malfunction of the nerves that regulate the constriction of blood vessels. When attacks of Raynaud's occur in the absence of other medical conditions, it is called Raynaud's disease. When attacks occur as part of a disease, as in scleroderma, it is called Raynaud's phenomenon.

Sclerosis—Hardening.

Systemic sclerosis—A rare disorder that causes thickening and scarring of multiple organ systems.

Telangiectasis—Very small arteriovenous malformations or connections between the arteries and veins. The result is red spots on the skin known colloquially as "spider veins."

The various symptoms of scleroderma are often treated individually. Raynaud's phenomenon requires that people try to keep their hands and feet warm constantly, and nifedipine is a medication that is also sometimes given to help control this symptom. Thick ointments and creams are used to treat dry skin. Exercise and massage may help joint involvement, and they may also help people retain more movement despite skin tightening. Skin ulcers need prompt attention and may require antibiotics.

People with esophageal reflux will be advised to eat small amounts more often rather than three large meals

QUESTIONS TO ASK YOUR DOCTOR

- What type of scleroderma do I have?
- How do we know that scleroderma is a genetic disorder?
- Am I likely to transmit scleroderma to any children that I may have in the future?
- Are there resources on the Internet from which I can get additional information about my scleroderma?

per day. They also should avoid spicy foods and items containing caffeine. Some patients with esophageal reflux have been treated successfully with surgery. Acid-reducing medications may be given for heartburn.

People with scleroderma must be monitored for the development of high blood pressure, and if that is found, they should be promptly treated with appropriate medications, usually ACE inhibitors or other vasodilators. When fluid accumulates due to heart failure, diuretics are prescribed to treat the accumulation of excess fluid. Lung disease also is possible, and a 2021 report showed possible treatment of lung problems in patients with scleroderma with tocilizumab, an anti-inflammatory drug used to treat rheumatoid arthritis. Detecting possible lung involvement early can improve the chance that the drug will help.

Another 2021 study demonstrated the possible use of fat grafts using the patient's own fat enhanced with adipose-derived skin cells to improve treatment of localized facial scleroderma by ensuring that the autologous fat graft survives longer.

Prognosis

The prognosis for people with scleroderma varies, depending on the severity of their condition. Some have a very mild form of the disease, called morphea, which affects only the skin, and these individuals have a very good prognosis. Others have a subtype of mild systemic scleroderma, called limited scleroderma. Limited involvement of the patient's skin and a cluster of five symptoms, called the CREST syndrome, characterize limited scleroderma. CREST stands for:

- C = Calcinosis
- R = Raynaud's disease (phenomenon)
- E = Esophageal dysmotility (stiffness and malfunctioning of the esophagus)

- S = Sclerodactyly (thick, hard, rigid skin over the fingers)
- T = Telangiectasis

In general, people with very widespread skin involvement have the worst prognosis. This level of disease is usually accompanied by involvement of other organs and the most severe complications. Although women are more commonly stricken with scleroderma, men more often die of the disease. The most common causes of death include heart, kidney, and lung diseases. About 65% of all patients survive 10 years or more following a diagnosis of scleroderma.

There are no known ways to prevent scleroderma. People can try to decrease occupational exposure to high-risk substances, however.

Resources

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ORGANIZATIONS

American College of Rheumatology, 2200 Lake Boulevard NE,
Atlanta, GA 30319, (404) 633-3777, <http://www.rheumatology.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 798-6481, <http://www.rarediseases.org>

Scleroderma Foundation, 300 Rosewood Drive Suite 105,
Danvers, MA 01923, (978) 463-5843 or (800) 722or4673,
(978) 463-5809, sfinfo@scleroderma.org, <http://www.scleroderma.org>

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Sclerosing bone dysplasias

Definition

Sclerosing bone dysplasias are rare genetic disorders characterized by the creation of abnormally dense and overgrown bones. The abnormal bone formation in sclerosing bone dysplasias is caused by a defect in the replacement of old bone with new bone.

Description

Bone consists of living cells, called osteocytes, embedded in a calcium carbonate matrix that makes up the main bone material. The calcium carbonate matrix includes inorganic mineral components like calcium and organic components, such as collagen. The replacement of old bone with new bone is mediated by two types of bone cells: osteoblasts and osteoclasts. The osteoblasts make bone, while osteoclasts resorb, or take away, bone. Problems with the ability of the osteoclasts and osteoblasts to remodel bone can result in the increased skeletal density (sclerosis) and bony overgrowth (hyperostosis) seen in the sclerosing bone dysplasias. The first description of sclerosing bone dysplasia occurred in 1904 when Professor Albers-Schönberg of Hamburg described a patient suffering from a benign form of thickened and very strong hard bone.

Currently, sclerosing bone dysplasias are subdivided into types based upon the problems in bone remodeling. The three main categories of sclerosing bone dysplasias are increased bone density without modification of bone shape; increased bone density with involvement of the main body of the bone and primary region of bone formation (diaphysis); and increased bone density with involvement of the area of the developing long bone that is the growing portion of the bone (metaphysis). Although all of the sclerosing bone dysplasias share some overlapping

features, it is usually possible to distinguish between these types of sclerosing bone dysplasias based on the age at which symptoms appear, the pattern of inheritance in the family, radiographic skeletal surveys, and genetic studies.

Genetic profile

Although all of the genes involved in sclerosing bone dysplasias encode proteins that direct the remodeling of bone, each type of sclerosing bone dysplasia has specific symptoms and inheritance patterns caused by different gene defects.

Many types of sclerosing bone dysplasia are autosomal dominant genetic disorders. In autosomal dominant genetic disorders, the genes that cause a particular disorder are carried on one of the 22 pairs of numbered autosomal chromosomes, rather than on the X or Y sex chromosomes. In the case of sclerosing bone dysplasia, only one copy of the mutated, or nonworking, gene is necessary for the development of the disorder. An individual who inherits a normal gene copy from one parent and an abnormal gene copy from the other parent is likely to have symptoms of a sclerosing bone dysplasia. The children of an individual with one normal gene copy and one mutated copy have a 50% chance of inheriting the disorder. Types of sclerosing bone dysplasias inherited in an autosomal dominant pattern include osteopetrosis, autosomal dominant 1 and 2 (caused by mutations in over 12 different genes); progressive diaphyseal dysplasia/Camurati-Engelmann disease (caused by a mutation in the beta-1 transforming growth factor gene, *TGFBI*); some forms of craniodiaphyseal dysplasia; and some forms of craniometaphyseal dysplasia (caused by a mutation in a progressive ankylosis protein homolog, *ANKH*).

Many other types of sclerosing bone dysplasias are inherited in an autosomal recessive pattern. In an autosomal recessive condition, two copies of the mutated gene are needed to develop the symptoms of the disorder. In these cases, both parents each carry one copy of a mutated gene. Individuals with only one copy of a mutated gene for a recessive condition are known as carriers and have no symptoms related to the condition. In fact, every person carries between five and 10 mutated genes for harmful, recessive conditions. However, when two people with the same mutated recessive gene for sclerosing bone dysplasia have children together, there is a 25% chance with each pregnancy for the child to inherit two mutated copies, one from each parent. That child then has no working copies of the gene and will display the signs and symptoms associated with sclerosing bone dysplasia. Sclerosing bone dysplasias that are inherited in an autosomal recessive manner include osteopetrosis,

autosomal recessive (types 1, 2, 3, 4, 5, 6, 7, and 8) caused by mutations in at least 28 different genes; pycnodysostosis (caused by mutations in the cathepsin K gene, *CTSK*); some forms of craniodiaphyseal dysplasia, van Buchem disease, and sclerosteosis (all caused by a mutation in the sclerostin gene, *SOST*); and some forms of craniometaphyseal dysplasia caused by a mutation in the *GJAI* gene.

One type of sclerosing bone dysplasia, frontometaphyseal dysplasia, is caused by a mutation in the filamin A gene (*FLNA*) and is inherited in an X-linked recessive pattern. As opposed to genes that are carried on one of the 22 pairs of numbered autosomal chromosomes, X-linked genes are found on the sex chromosomes called X. Females have two X chromosomes, while males have a single X chromosome and a single Y chromosome. When a female inherits a mutated gene on the X chromosome, she is known as a carrier. Carriers most often have no symptoms related to the condition because the gene on her other chromosome continues to function properly. However, males only inherit one copy of the information stored on the X chromosome. When a male inherits a mutated copy of the gene that causes an X-linked recessive condition, he will experience the symptoms associated with the disease. The chance for a carrier female to have an affected son is 50%, while the chance to have a daughter who is also a carrier for the condition is 50%. An affected male has a 100% chance of having carrier daughters and a 0% chance of having affected sons.

One type of sclerosing bone dysplasia, osteopathia striata with cranial sclerosis, is caused by mutations in the *WTX* gene located on the X chromosome. This condition is inherited in an X-linked dominant pattern. X-linked dominant inheritance occurs when the gene mutation is located on the X chromosome, but the gene acts in a dominant manner. This means that both males and females can display the trait or disorder, while having only one copy of the gene. Furthermore, in X-linked dominant conditions, only one copy of the mutated gene is necessary for the development of the disorder. Therefore, an individual who inherits a normal gene copy from one parent and an abnormal gene copy for sclerosing bone dysplasia from the other parent is likely to have symptoms of sclerosing bone dysplasia. The children of an individual with one normal gene copy and one mutated copy have a 50% chance of inheriting a mutated sclerosing bone dysplasia gene.

Demographics

Sclerosing bone dysplasias are rare conditions. Estimates of general population frequency range by ethnic group and type of sclerosing bone dysplasia described. Affected individuals can occur within a variety of ethnic

backgrounds and cases have been found in Denmark, Egypt, the United States, Germany, Japan, Italy, Brazil, Spain, Senegal, South Africa, the Netherlands, and Cyprus. A large number of individuals affected by sclerosing bone dysplasias exist in the Afrikaner population of South Africa and the Dutch population of the Netherlands. The carrier rate for the single founder-derived mutation that causes sclerosteosis in the Afrikaner population is approximately 1 in 100. Van Buchem disease has been recognized predominantly in the Dutch population (± 20 cases). Several of the affected families have ancestral origins on the former island of Urk in the Zuider Zee. The prevalence of later-onset osteopetrosis or Albers-Schonberg is about 1 in 18,000 in Denmark.

Signs and symptoms

Sclerosing bone dysplasias are rare genetic disorders characterized by increased skeletal density and excessive bone formation, or overgrowth, due to a defect in the method of replacing old bone with new bone (bone remodeling). Each of the three main categories of sclerosing bone dysplasias exhibit different symptoms, including age of onset, skeletal involvement, and prognosis.

The specific disorders in the group of sclerosing bone dysplasias that exhibits increased bone density without modification of bone shape include osteopetrosis disorders (autosomal dominant osteopetrosis types I and II and autosomal recessive osteopetrosis); pycnodysostosis; and osteopathia striata with cranial sclerosis.

The osteopetrosis disorders are conditions that involve increased bone density without modification of bone shape. They include two dominant conditions known as osteopetrosis, autosomal dominant 1 and osteopetrosis, autosomal dominant 2, and one form of the recessive form of osteopetrosis, type 1.

Autosomal dominant osteoporosis, types 1 and 2 typically present in childhood, adolescence, or young adult life with multiple fractures, mild anomalies in head and face proportions, mild anemia, hearing loss, bone inflammation/infection, or increased bone density found on routine x-ray studies.

Autosomal dominant osteopetrosis type I (OPTA1) is characterized by a generalized increase in the hardness, thickness, and density of bone tissue (osteosclerosis), most pronounced in the cranial vault. Patients are often asymptomatic, but some suffer from pain and hearing loss. OPTA1 appears to be the only type of osteopetrosis not associated with an increased fracture rate.

Autosomal dominant osteopetrosis type II (OPTA2) is characterized by an increase in the hardness, thickness, and density of bone tissue (sclerosis), predominantly involving the spine, the pelvis, and the skull base.

Fragility of bones and dental abscesses are the leading complications. Other symptoms include arthritis of the hip (hip osteoarthritis), bone infections (osteomyelitis), thoracic or lumbar scoliosis, and cranial nerve involvement responsible for hearing loss, bilateral optic atrophy, and/or facial palsy.

Osteopetrosis, autosomal recessive 1 (OPTB1) is characterized by a generalized increase in bone density found at or soon after birth. The sclerosis of the bones causes a decrease in size of the bone marrow cavities, a progressively enlarging spleen, low blood iron (anemia), and blood cell production that occurs in other parts of the body (extramedullary haemopoiesis). Additionally, enlarging skull bones compress the optic nerves, auditory nerves, facial nerves, and the foramen magnum (the large hole at the base of the skull that allows passage of the spinal cord). The most frequent presentations in infancy are seizures, low calcium level, convulsions, failure of visual fixation (nystagmus), large spleen and liver (hepatosplenomegaly), and frequent broken bones.

Pycnodysostosis is characterized by an increase in bone density of the skeleton (osteosclerosis), skull deformities, short stature, short limbs, characteristic facial features, and bone fragility. Onset of the symptoms occurs around two or three years of age. Other features of the condition include separated cranial sutures; large fontanel with delayed closure; obtuse mandibular angle; delayed teeth eruption; enamel hypoplasia; dysplastic acromial ends of the clavicles; frontal bossing; ocular proptosis; and dysplastic nails.

Osteopathia striata with cranial sclerosis (OSCS) presents with longitudinal striations of dense bone in the long bones and formation of dense bone in the cranial and facial bones in infancy and childhood. The formation of dense bone in the head and face leads to facial disfigurement and to neurological complications, such as deafness due to pressure on cranial nerves. Other features include a large head (macrocephaly); congenital heart defects, such as aortic stenosis and ventricular septal defects; scoliosis of the back; narrowed visual fields; cleft palate; long fingers; curving of the third to fifth fingers (clinodactyly); clubfoot; facial nerve palsy; and mild mental retardation. Unfortunately most males with this condition die before delivery or shortly after birth. Males that do survive have short stature, intestinal abnormalities, and kidney defects.

The disorders involving increased bone density with diaphyseal involvement include progressive diaphyseal dysplasia, or Camurati-Engelmann disease; craniodiaphyseal dysplasia; and SOST-related sclerosing bone dysplasias (van Buchem disease and sclerosteosis).

Progressive diaphyseal dysplasia (PDD), or Camurati-Engelmann disease, is characterized by childhood onset of bone overgrowth (hyperostosis) and increased density (sclerosis) of the diaphyses of the long bones and the skull. Other features may include a slender build with long limbs; angular profile; prominent bones (asthenic habitus); hearing loss; protruding eyeballs (exophthalmos); optic nerve compression; double vision (diplopia); cavities (dental caries); sclerosis of skull base; lower jaw (mandible) involvement; sclerosis of posterior part of vertebrae (body and arches); scoliosis; progressive diaphyseal widening; thickened cortices; narrowing of medullary canal; Erlenmeyer flask defect of the bone; clubfoot (genu varus and valgus deformities); relative muscle weakness, especially in pelvic girdle; atrophic muscle fiber; headaches; delayed puberty; bone marrow hypoplasia; anemia; waddling gait; and leg pain. The most severely affected individuals will have progression of mild skull hyperostosis to severe skull thickening and cranial nerve compression over many years. Presentation of the disease can be very different from one individual to another.

Craniodiaphyseal dysplasia includes a wide variety of symptoms and age of onset from infancy to childhood. Facial and cranial thickening and distortion are particularly striking in this form. The characteristic facial features of craniodiaphyseal dysplasia occur from the overgrowth of bone in the face and skull that results in progressive facial anomalies, a broad nasal bridge, and wide-spaced eyes. Other symptoms of craniodiaphyseal dysplasia, like hearing loss and facial paralysis, are caused by the overgrowth of the skull as it gradually eliminates the perinasal sinuses and the large hole at the base of the skull that allows passage of the spinal cord (foramina of the skull base). Individuals with craniodiaphyseal dysplasia often are affected by mental retardation. Unlike the situation in the craniometaphyseal dysplasias, the long bones do not show metaphyseal flaring, but are shaped like a policeman's nightstick.

SOST-related sclerosing bone dysplasias include van Buchem disease and sclerosteosis as well as the autosomal dominant form of craniodiaphyseal dysplasia. Sclerosteosis and van Buchem disease include many similar features. The two disorders can be distinguished from each other via their different appearance of the bone changes on x-ray. Additionally, sclerosteosis includes the presence of asymmetric fusion (cutaneous syndactyly) of the index and middle fingers in many cases, and van Buchem disease does not.

Van Buchem disease (or hyperostosis corticalis familiaris) is characterized by progressive enlargement of the lower jaw in childhood and symptoms, including

KEY TERMS

Bone dysplasia—Abnormal bone development.

Bone remodeling—The process of breaking down old bone and building up new bone.

Bone sclerosis—Increased bone density and hardness.

Diaphysis—Primary region of ossification found in the shaft of the long bones.

Hyperostosis—Overgrowth of the bone.

Metaphysis—The growing portion of the developing long bone.

Osteoblasts—A bone cell that makes bone.

Osteoclasts—A bone cell that breaks down and reabsorbs bone.

hearing loss and facial paralysis, in adulthood caused by the overgrowth of the skull.

The symptoms of van Buchem disease begin in childhood or puberty and include features resulting from bone overgrowth. Symptoms include cranial bone overgrowth (hyperostosis) leading to optic nerve compression; hearing loss; headaches; cranial nerve palsy; osteosclerosis; thickened cortex of long bones; and abnormally high blood levels of phosphorous (hyperphosphatasemia).

Sclerosteosis is characterized by tall stature; overgrowth of the nasal and facial bones; broad, flat nasal bridge; wide-spaced eyes (hypertelorism); and minor hand malformation, such as finger fusion (syndactyly). Other symptoms may include small nails (nail dysplasia); square jaw due to overgrowth of the mandible; difficulties in chewing; inability to smell (anosmia); massive bone density (sclerosis) of the long tubular bones, ribs, pelvis, and skull; and multiple cranial nerve involvement resulting in optic atrophy, facial palsy, and trigeminal nerve pain episodes (neuralgia). Facial nerve paralysis may be present as early as birth or develop soon afterward. Facial palsy and deafness as a result of cranial nerve entrapment often develop in childhood. Increased intracranial pressure may result in sudden death from impaction of the brain stem in the foramen magnum.

The disorders involving increased bone density with metaphyseal involvement include craniometaphyseal dysplasia and frontometaphyseal dysplasia.

Craniometaphyseal dysplasia involves overgrowth bone anomalies that commonly present in infancy. Some of the first indications of craniometaphyseal dysplasia

include breathing difficulties and narrowing nasal passages due to bone overgrowth. The characteristic facial features of craniometaphyseal dysplasia occur from the overgrowth of bone in the face and skull that result in progressive facial anomalies, a broad nasal bridge, and wide-spaced eyes. Other symptoms of craniometaphyseal dysplasia, like hearing loss and facial paralysis, are caused by the overgrowth of the skull as it gradually eliminates the perinasal sinuses and the large hole at the base of the skull that allows passage of the spinal cord (foramina of the skull base). The features of craniometaphyseal dysplasia are more severe than the sclerotic or hyperostotic features, except in the lower jaw where they are less severe than craniodiaphyseal dysplasia. If not treated, individuals with craniometaphyseal dysplasia may develop blindness due to the compression of cranial nerves.

Frontometaphyseal dysplasia's most striking feature is a characteristic facial appearance that includes a very prominent supraorbital ridge above the eyes resulting from bone overgrowth. In many cases, the prominent ridge may be present at birth, along with a small, pointed chin, wide-spaced eyes (hypertelorism), wide nasal bridge, poor sinus development, clubfoot (coxa valga and genu valgum), and flared metaphyses. Later findings may include progressive mixed conductive and sensorineural hearing loss; high palate/cleft palate; teeth issues; mitral valve prolapse; narrow trachea; winged shoulder blade (scapulae); irregular rib contours; "coat hanger" deformity of lower ribs; distended kidneys and ureters (hydronephrosis and hydroureter); scoliosis; cervical vertebral fusion; flared pelvis; elbow contractures; knee and ankle contractures; Erlenmeyer-flask appearance of femur and tibia; increased density of long bone diaphyses; finger and wrist contractures; long and wide fingers; partial fusion of the bones of the feet; large feet; overgrowth of hair on the buttocks and thighs; and muscle wasting (especially legs and arms). The skeletal dysplasia and the associated clinical findings show significant variability from affected individual to individual. Females with frontometaphyseal dysplasia may also develop the same characteristic craniofacial appearances seen in the males, but they do not have many of the other characteristic features of this condition.

Diagnosis

Diagnosis of sclerosing bone dysplasias is most often based upon age of onset, clinical features, radiological evaluation, and family history. Radiologic examination will detect the dense bones (sclerosis) and their locations. Genetic studies may help confirm a diagnosis of a specific sclerosing bone dysplasia, but some affected individuals will not have a genetic mutation that can be

identified. While many types of sclerosing bone dysplasias have a known or suspected genetic cause, genetic testing is not always available because the gene has recently been discovered or the genetic cause is not yet fully understood.

Treatment and management

The sclerosing bone dysplasias are genetic disorders and do not have specific therapies that remove, cure, or fix all signs of the disorder. Treatment and management of the sclerosing bone dysplasias focus on treatment of specific symptoms of the condition. Management of patients with sclerosing bone dysplasias requires a comprehensive approach to characteristic clinical problems, including hematologic and metabolic abnormalities, fractures, bone deformities, back pain, bone pain, bone infection (osteomyelitis), hearing impairment, dental issues, short stature, and neurologic symptoms. Surgical intervention may be difficult and prolonged in affected individuals since standard equipment may be too short and not powerful enough to cut through the dense bone. In addition, bone regrowth occurs and may cause recurrence of symptoms after surgery.

Treatment of the hematologic issues found in the sclerosing bone dysplasias is focused on the correction of low blood iron (anemia) and low platelets. In some cases, a steroid, prednisone, may be used to treat both of these conditions. In other cases, transfusions to treat anemia and splenectomy to increase platelets may be recommended. Depending on the form of sclerosing bone dysplasia, treatment to correct hematologic issues may not be effective.

Medical treatment of sclerosis and hyperostosis in sclerosing bone dysplasias is based on efforts to stimulate host osteoclasts to break down bone or provide an alternative source of osteoclasts. Stimulation of osteoclasts has been attempted with calcium restriction and calcitriol, calcitonin therapy, steroids, parathyroid hormone therapy, and interferon. Bone marrow transplant has been used to treat infantile malignant osteopetrosis. Effective therapies for each type of sclerosing bone dysplasia need to be individualized. Many people affected by a sclerosing bone dysplasia will not respond to treatment.

Most treatment protocols for sclerosing bone dysplasias are focused upon the correction of the frequent bone fractures, using splints, casts, and braces. Orthopedic surgery may be needed to correct internal fractures.

Since hearing loss is a common feature of the sclerosing bone dysplasias, formal audiological evaluation is recommended at diagnosis. Hearing loss associated with the sclerosing bone dysplasias can be addressed through sign language, use of hearing aids, and/or surgery. Some

QUESTIONS TO ASK YOUR DOCTOR

- What type of sclerosing bone dysplasia do I/does my child have?
- Can you recommend the necessary surgical specialists to treat my condition?
- What is the chance to have another child affected with the same condition?
- Is genetic testing available for my form of sclerosing bone dysplasia?
- Will my child's/my lifespan be affected by this condition?

individuals pursue exploratory tympanotomy, stapedotomy, placement of a total ossicular reconstruction prosthesis, cochlear implantation, insertion of a Wehr's prosthesis, decompression, and other surgical procedures. Widening of the external auditory canal is usually necessary to accommodate a hearing aid. Correction of hearing loss is difficult and only has limited success.

In forms of sclerosing bone dysplasias associated with short stature, most individuals make an effort to modify their environment to suit their height. For individuals who wish to treat their short stature, some progress in increasing height has been made by growth hormone (GH) supplementation in affected children. However, hormone supplementation can cause disproportionate growth, leading to longer arms and trunk and shorter legs.

Intracranial pressure is one of the main features of sclerosing bone dysplasias, and the most severe. The increase in intracranial pressure caused by the increase in bone size and density often leads to headaches, hearing loss, blindness, facial paralysis, facial nerve palsies, and death. Accordingly, management of intracranial pressure includes monitoring for increased pressure, sudden onset of headaches, and blurred vision that may result in the need for decompression craniectomy or other forms of surgical decompression. Total decompression can prevent future attacks of facial paralysis in some forms of sclerosing bone dysplasias. Given the progressive nature of the sclerosing bone dysplasias, bone regrowth will occur and may cause recurrence of symptoms after surgery.

The abnormal formation of the head and skull bones impacts the form and function of the face, jaws, and remainder of the craniofacial skeleton. Surgery to correct bony overgrowth and density in the forehead, nose, and jaw bones is an option for some patients. Given the

progressive nature of the sclerosing bone dysplasias, bone regrowth will occur and may cause recurrence of symptoms after surgery.

The objective of treatment for bone infection (osteomyelitis) in sclerosing bone dysplasias is to eliminate the infection and prevent the development of chronic infection. Intravenous antibiotics are started early and may later be changed, depending on culture results. Some new antibiotics can be very effective when given orally. In chronic infection, surgical removal of dead bone tissue is usually necessary.

Treatment of scoliosis depends upon the type of sclerosing bone dysplasias and the severity of the scoliosis. Treatment options may include observation, orthoAbnormal bone development.pedic braces, and surgery. In some cases, the progressive nature of the underlying condition makes correction of scoliosis difficult, if not impossible.

The treatment for clubfoot involves orthopedic surgery to correct the abnormal formation of the lower limbs. Correction of the abnormality may require multiple surgeries, and aftercare with casts, braces, and physical therapy.

Treatment of the myriad of dental issues associated with sclerosing bone dysplasias are managed best through comprehensive oral and dental care. A craniofacial team may be best suited to address the variety of issues. Mandible reduction is often performed for cosmetic reasons or if mouth closure is impaired as a result of overgrowth of the mandible. Tooth extraction may be difficult given the density of bone.

Individuals affected by sclerosing bone dysplasias may have pain from arthritis, neuralgia caused by pressure, dental pain, and other pain sources related to abnormal bone remodeling. Pain management for each of these sources is different. Severe pain resulting from nerve compression may be helped by nerve decompression surgery. Spinal cord decompression surgery may help alleviate back pain. A pain management specialist working with an individual's treatment team can determine the level of pain, determine the best medications to treat the pain, and evaluate the effectiveness of the medications.

Prognosis

The prognosis for individuals affected by sclerosing bone dysplasia varies greatly depending upon the type of sclerosing bone dysplasia and severity of symptoms. Individuals affected by delayed or adult-onset forms of sclerosing bone dysplasia may have mild to severe symptoms that do not reduce their lifespan. Individuals who present with symptoms at birth or soon after birth, like

malignant infantile osteopetrosis and sclerosteosis, have a progressive course of disease that leads to early death. Increased intracranial pressure may result from a combination of circumstances and may have led, in several instances, to sudden death from impaction of the brain stem in the foramen magnum. Surgical procedures such as total decompression may increase length and quality of life.

Resources

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"SOST-related Sclerosing bone dysplasia." MedlinePlus. <https://medlineplus.gov/genetics/condition/sost-related-sclerosing-bone-dysplasia/> (accessed June 19, 2021).

ORGANIZATIONS

AboutFace, 1057 Steeles Ave. W, PO Box 702, The Concourse, North York, ON Canada M2R 3X1, (416) 597-2229 or (800) 665- 3223, (416) 597-8494, info@aboutface.ca, <http://www.aboutface.ca>

American Society for Deaf Children, 800 Florida Ave. NE, No. 2047, Washington, DC 20002-3695, (800) 942-2732, (410) 795-0965, <http://www.deafchildren.org>

Children's Craniofacial Association, 13140 Coit Rd., Suite 517, Dallas, TX 75240, (214) 570-9099 or (800) 535-3643, (214) 570-8811, contactCCA@ccaskids.com, <http://www.ccaskids.com>

International Skeletal Dysplasia Registry, UCLA-OHRC, 615 Charles E. Young Dr. S., Rm. 410, Los Angeles, CA 90095-7358, (310) 825-8998, AZargaryan@mednet.ucla.edu, <http://ortho.ucla.edu/body.cfm?id=279>

National Association of the Deaf, 8630 Fenton St., Suite 820, Silver Spring, MD 20910, (301) 587-1788, (301) 587-1791, nad.info@nad.org, <http://www.nad.org>.

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Scoliosis

Definition

Scoliosis is a side-to-side curvature of the spine of 10 degrees or greater.

Description

When viewed from the rear, the spine usually appears to form a straight vertical line. Scoliosis is a lateral (side-to-side) curve in the spine, usually combined with a rotation of the vertebrae. The lateral curvature of scoliosis should not be confused with the normal set of front-to-back spinal curves visible from the side. While a small degree of lateral curvature does not cause any medical problems, larger curves can cause postural imbalance and lead to muscle fatigue and pain. More severe scoliosis can interfere with breathing and lead to arthritis of the spine (spondylosis).

Four out of five cases of scoliosis are *idiopathic*, meaning the cause is unknown. Children with idiopathic scoliosis appear to be otherwise entirely healthy and have not had any bone or joint disease early in life. Scoliosis is not caused by poor posture, diet, or carrying a heavy book bag exclusively on one shoulder.

Idiopathic scoliosis is further classified according to age of onset:

- **Infantile.** Curvature appears before age three. This type is quite rare in the United States, accounting for only 1% of idiopathic cases in North America, but is more common in Europe, where it is 4% of known idiopathic cases.
- **Juvenile.** Curvature appears between ages 3 and 10. This type may be equivalent to the adolescent type, except for the age of onset.
- **Adolescent.** Curvature appears between ages 10 and 13 near the beginning of puberty. This is the most common type of idiopathic scoliosis.
- **Adult.** Curvature begins after physical maturation is completed.

Causes are known for three other types of scoliosis:

- **Congenital scoliosis** is due to congenital birth defects in the spine, often associated with other structural abnormalities such as neural tube defects.
- **Neuromuscular scoliosis** is due to loss of control of the nerves or muscles that support the spine. The most common causes of this type of scoliosis are cerebral palsy and muscular dystrophy.



X-ray of a spine in a patient with scoliosis. (Tewan Banditrukkanka/Shutterstock)

- Degenerative scoliosis may be caused by degeneration of the discs that separate the vertebrae or arthritis in the joints that link them.

Genetic profile

Idiopathic scoliosis has long been observed to run in families. Twin and family studies have consistently indicated a genetic contribution to the condition. However, no consistent pattern of transmission has been observed in familial cases. Research published in 2014 suggests mutations in the following genes may contribute to idiopathic scoliosis: *POC5*, *TBX6*, and *SH3GL1*. While other data has shown that there may not be a genetic link to scoliosis via mutations of the *MESP2*, *HES7*, and *DUSP6* genes as previously suspected, an earlier study found data to suggest that a combination of genetic predisposition and fetal hypoxia may create the condition in which scoliosis may be triggered. However, no further data has been published to support this hypothesis. Examination of chromosomal anomalies in individuals with idiopathic scoliosis identified a duplication of chromosome 1q21.1 and rearrangements of chromosome 15q11.2 and 16p11.2, suggesting that copy number variation and chromosomal aneuploidy may contribute to the pathogenesis of adolescent idiopathic scoliosis.

There are several genetic syndromes that involve a predisposition to scoliosis, and several studies have

investigated whether or not the genes causing these syndromes may also be responsible for idiopathic scoliosis. Using this *candidate gene approach*, the genes responsible for Marfan syndrome (fibrillin), Stickler syndrome, and some forms of osteogenesis imperfecta (collagen types I and II) have not been shown to correlate with idiopathic scoliosis.

Attempts to map a gene or genes for scoliosis have not shown consistent linkage to a particular chromosome region. Most researchers have concluded that scoliosis is a complex trait. As such, there are likely to be multiple genetic, environmental, and potentially additional factors that contribute to the etiology of the condition. Complex traits are difficult to study due to the difficulty in identifying and isolating these multiple factors.

Demographics

The incidence of scoliosis in the general population is 2%–3%. Among adolescents, however, 10% have some degree of scoliosis (though less than 1% have curves that require treatment).

Scoliosis is found in both boys and girls, but a girl's spinal curve is much more likely to progress than a boy's. Girls require scoliosis treatment about five times as often. The reason for these differences is not known but may relate to increased levels of estrogen and other hormones.

Signs and symptoms

Scoliosis causes a noticeable asymmetry in the torso when viewed from the front or back. The first sign of scoliosis is often seen when a child is wearing a bathing suit or underwear. A child may appear to be standing with one shoulder higher than the other, or to have a tilt in the waistline. One shoulder blade may appear more prominent than the other due to rotation. In girls, one breast may appear higher than the other, or larger if rotation pushes that side forward.

Curve progression is greatest near the adolescent growth spurt. Scoliosis that begins early on is more likely to progress significantly than scoliosis that begins later in puberty.

More than 30 states have screening programs in schools for adolescent scoliosis, usually conducted by trained school nurses or gym teachers.

Diagnosis

Diagnosis for scoliosis is done by an orthopedist. A complete medical history is taken, including questions about family history of scoliosis. The physical examination includes determination of pubertal development in adolescents, a neurological exam (which may reveal a

KEY TERMS

Aneuploidy—The state of having an abnormal number of chromosomes.

Cobb angle—A measure of the curvature of scoliosis, determined by measurements made on x-rays.

Pathogenesis—The process by which biophysical and biochemical reactions cause disease.

Scoliometer—A tool for measuring trunk asymmetry; it includes a bubble level and angle measure.

Spondylosis—Arthritis of the spine.

neuromuscular cause), and measurements of trunk asymmetry. Examination of the trunk is done while the patient is standing, bending over, and lying down, and involves both visual inspection and use of a simple mechanical device called a scoliometer.

If a curve is detected, one or more x-rays will usually be taken to define the curve or curves more precisely. An x-ray is used to document spinal maturity, any pelvic tilt or hip asymmetry, and the location, extent, and degree of curvature. The curve is defined in terms of where it begins and ends, in which direction it bends, and by an angle measure known as the Cobb angle. The Cobb angle is found by projecting lines parallel to the vertebrae tops at the extremes of the curve; projecting perpendiculars from these lines; and measuring the angle of intersection. To properly track the progress of scoliosis, it is important to project from the same points of the spine each time.

Occasionally, magnetic resonance imaging (MRI) is used, primarily to look more closely at the condition of the spinal cord and nerve roots extending from it if neurological problems are suspected.

Treatment and management

Treatment decisions for scoliosis are based on the degree of curvature, the likelihood of significant progression, and the presence of pain, if any.

Curves less than 20 degrees are not usually treated, except by regular follow-up for children who are still growing. Watchful waiting is usually all that is required in adolescents with curves of 20–25 degrees, or adults with curves up to 40 degrees or slightly more, as long as there is no pain.

For children or adolescents whose curves progress to 25 degrees, and who have a year or more of growth left, bracing may be required. Bracing cannot correct

curvature, but may be effective in halting or slowing progression. Bracing is rarely used in adults, except where pain is significant and surgery is not an option, as in some elderly patients.

There are two different categories of braces, those designed for nearly 24-hour use and those designed for night use. The full-time brace styles are designed to hold the spine in a vertical position, while the night-use braces are designed to bend the spine in the direction opposite the curve.

The Milwaukee brace is a full-time brace that consists of metal uprights attached to pads at the hips, rib cage, and neck. Other types of full-time braces, such as the Boston brace, involve underarm rigid plastic molding to encircle the lower rib cage, abdomen, and hips. Because they can be worn out of sight beneath clothing, the underarm braces are better tolerated and often leads to better compliance. The Boston brace is currently the most commonly used. Full-time braces are often prescribed to be worn for 22–23 hours per day, though some clinicians believe that recommending brace use of 16 hours leads to better compliance and results.

Night-use braces bend the patient's scoliosis into a correct angle, and are prescribed for 8 hours of use during sleep. Some investigators have found that night-use braces are not as effective as the day-use types.

Bracing may be appropriate for scoliosis due to some types of neuromuscular disease, including spinal muscular atrophy, before growth is finished. Duchenne muscular dystrophy is not treated by bracing, since surgery is likely to be required, and since later surgery is complicated by loss of respiratory capacity.

Surgery for idiopathic scoliosis is usually recommended if:

- the curve has progressed despite bracing
- the curve is greater than 40–50 degrees before growth has stopped in an adolescent
- the curve is greater than 50 degrees and continues to increase in an adult
- there is significant pain

Orthopedic surgery for neuromuscular scoliosis is often done earlier. The goals of surgery are to correct the deformity as much as possible, to prevent further deformity, and to eliminate pain as much as possible. Surgery can usually correct 40%–50% of the curve, and sometimes as much as 80%. Surgery cannot always completely eliminate pain.

The surgical procedure for scoliosis is called *spinal fusion*, because the goal is to straighten the spine as much

QUESTIONS TO ASK YOUR DOCTOR

- How do the four types of scoliosis differ from each other?
- Can scoliosis be prevented and, if so, how?
- What kinds of treatment are available for scoliosis, and how successful is each type of treatment?
- How does scoliosis affect a person's lifespan or the quality of life for that person?

as possible, and then to fuse the vertebrae together to prevent further curvature. To achieve fusion, the involved vertebra are first exposed, and then scraped to promote regrowth. Bone chips are usually used to splint together the vertebrae to increase the likelihood of fusion. To maintain the proper spinal posture before fusion occurs, metal rods are inserted alongside the spine, and are attached to the vertebrae by hooks, screws, or wires. Fusion of the spine makes it rigid and resistant to further curvature. The metal rods are no longer needed once fusion is complete, but are rarely removed unless their presence leads to complications.

Spinal fusion leaves the involved portion of the spine permanently stiff and inflexible. While this leads to some loss of normal motion, most functional activities are not strongly affected, unless the very lowest portion of the spine (the lumbar region) is fused. Normal mobility, exercise, and even contact sports are usually all possible after spinal fusion. Full recovery takes approximately six months.

Prognosis

The prognosis for a person with scoliosis depends on many factors, including the age at which scoliosis begins and the treatment received. Most cases of mild adolescent idiopathic scoliosis need no treatment, do not progress, and do not cause pain or functional limitations. Untreated severe scoliosis often leads to spondylosis, and may impair breathing.

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National Scoliosis Foundation, 5 Cabot Place, Stoughton, MA 02072, (781) 341-6333, nsf@scoliosis.org, <http://www.scoliosis.org>.

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Seckel syndrome

Definition

Seckel syndrome is an extremely rare inherited recessive disorder characterized by low birth weight, dwarfism, a very small head, intellectual disability, and unusual characteristic facial features, including a "beak-like" protrusion of the nose, large eyes, a narrow face, low ears, and an unusually small jaw. Common signs also include abnormalities of bones in the arms and legs.

Description

Seckel syndrome is one of the microcephalic primordial dwarfism syndromes—a category of disorders characterized by profound growth delay. It is characterized by dwarfism, a small head, developmental delay, and intellectual disability and abnormalities may also be found in the cardiovascular, hematopoietic, endocrine, and central nervous systems. Children with the disorder are often hyperactive and easily distracted; about half have IQs below 50. Individuals with Seckel syndrome are able to live for an extended period of time.

Seckel syndrome is also known as "bird-headed dwarfism," Seckel-type dwarfism, and nanocephalic

KEY TERMS

Autosomal recessive disorder—A genetic disorder that requires two mutated forms of a gene to be inherited for the traits of a disorder to develop.

Microcephalic primordial dwarfism syndromes—A group of disorders characterized by profound growth delay and small head size.

dwarfism. The disorder was named after Helmut G.P. Seckel, a German pediatrician who came to the United States in 1936. Dr. Seckel did not discover the syndrome but he authored a publication describing the disorder's symptoms based on two of his patients.

Genetic profile

Seckel syndrome displays an autosomal recessive pattern of inheritance. This means that both parents of a child with the disorder carry a copy of the Seckel gene—but the parents appear entirely normal. When both parents carry a copy of the Seckel gene, their children face a one in four chance of developing the disorder.

There are eight types of Seckel syndrome, each linked to mutations in different genes within the genome. The first type is caused by a mutation in the ataxia-telangiectasia and Rad3-related protein (*ATR*) gene and is the best characterized. The *ATR* gene codes for a phosphatidylinositol 3-linked kinase protein, which is an enzyme involved in sensing DNA damage and controlling the cell cycle. It is possible that mutations in this gene affect how well cells can monitor and manage DNA damage during replication.

Demographics

Seckel syndrome is extremely rare and appears to affect both men and women equally. Between 1960—the year that Dr. Seckel defined the disorder—and 2005, more than 100 cases have been reported.

Signs and symptoms

Prenatal signs of Seckel syndrome include cranial abnormalities and intrauterine growth delays that result in low birth weight. Postnatal growth delays result in dwarfism. Other physical features associated with the disorder include a very small head, often more severely affected than even the height; abnormalities of bones in the arms and legs; malformation of the hips; a permanently bent fifth finger; failure of the

QUESTIONS TO ASK YOUR DOCTOR

- How common is Seckel syndrome and what groups, if any, are at special risk for the disorder?
- How is Seckel syndrome diagnosed?
- What information can a genetic counselor give me about Seckel syndrome?
- What organizations can I contact for additional information about Seckel syndrome?

testes to descend into the scrotum in males; and unusual characteristic facial features, including a “beak-like” protrusion of the nose, large eyes, a narrow face, low ears, and an unusually small jaw. Children with the disorder not only have a small head but also a smaller brain, which leads to developmental delay and intellectual disability. Seizures have also been reported in some cases.

Diagnosis

Several forms of primordial dwarfism exhibit characteristics similar to those of Seckel syndrome, and it can be challenging for physicians to differentiate true Seckel syndrome from other, similar dwarfisms. Physicians do have a set of primary diagnostic criteria to follow—the criteria were first defined by Dr. Seckel in 1960 and later revised in 1982 to prevent overdiagnosis of cases.

Most of the primary diagnostic features of Seckel syndrome, including severe intrauterine growth restriction, a small head, a characteristic “bird-like” face, and intellectual disability, are well suited for prenatal sonographic diagnosis. The use of ultrasound examinations to evaluate fetal growth and the careful evaluation of the fetal face and cranial anatomy has proven effective at detecting Seckel syndrome.

Treatment and management

There is no cure for Seckel syndrome but certain medications may be prescribed to address other symptoms associated with the disorder.

Prognosis

Children affected with Seckel syndrome can live for an extended period of time although they are often faced with profound mental and physical deficits.

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ORGANIZATIONS

- Human Growth Foundation, 997 Glen Cove Ave., Glen Head, NY 11545, (800) 451-6434, (516) 671-4055, <http://www.hgfound.org>
- National Organization for Rare Disorders (NORD), PO Box 8923, New Fairfield, CT 06812-8923, (203) 746-6518 or (800) 999-6673, (203) 746-6481, <http://www.rarediseases.org>

Michelle Lee Brandt
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Seckel-type dwarfism see **Seckel syndrome**
Seemanova syndrome see **Nijmegen breakage syndrome**

Selfish gene theory

Definition

The selfish gene theory is a reinterpretation of the theory of natural selection from the standpoint of the genes within a genome. It postulates that there is an increased frequency of genes whose phenotypic effects in turn increase their replication success. Genes do this in cooperation with or to the detriment of other genes by building an organism that can effectively transmit them to future generations. The term “selfish gene” is the

popularized term for what is considered a gene-centered view on evolution.

Description

The selfish gene theory is a gene-centric rewriting of the theory of natural selection. In the original theory developed by Charles Darwin, evolution occurs when environmental pressures select for phenotypes or traits found within a population that provide a better reproductive benefit. Over several generations, these traits are preserved because they provide an advantage to those individuals within their environment. In other words, adaptations and genetic variance are the *phenotypic effects* of genes maximizing their heritable success. The selfish gene theory puts natural selection into a gene-centered perspective. It argues that adaptation happens by way of genes competing with each other such that those that produce phenotypic traits that promote their propagation increase their allelic frequency within a population. Ultimately, the theory states that evolution and natural selection act upon genes rather than populations of organisms because they inherit genetic information almost exclusively from DNA. The biologist Richard Dawkins developed the term and theory in 1976 as an extension of George C. Williams's book *Adaptation and Natural Selection*, which discussed altruism as a result of selection at the level of genes rather than on the level of a group. The selfish gene theory is used to investigate the possible genetic contributions to behavior, particularly altruism. It helps to postulate that altruism is, in part, a combination of kinship and recognition of shared phenotypes; in both cases preserving relatives or those with a similar trait has a positive cost-benefit ratio to the survival of common genes.

Along with contributing to the genetic understanding of altruistic behavior, the selfish gene theory also adds to the explanation of the existence of deceit, the preservation of characteristics that benefit the few at the cost of the population as a whole. In both cases, the passage of the gene over time through generations takes precedence over the transmission vehicle (i.e., the organism).

Applications of the selfish gene theory

Genetic combinations that help an organism survive or reproduce also improve a gene's own chances of being replicated. While this would classically be considered an outcome of natural selection on a population with genetic variation, gene-centric evolutionary theory interprets this as genetic success on the side of the gene, rather than reflecting on the benefit to the organism or the population.

KEY TERMS

Allele—One version of a gene that occurs at the same position (locus) on a chromosome.

Diploid—Having two copies of each gene within a genome.

Gamete—Reproductive cells of an organism that fuse together during fertilization.

Gene—The molecular unit of heredity. A gene is a specific sequence of DNA that is found at particular positions in the genome and codes for a particular protein product.

Genome—An organism's complete collection of genetic material.

Haploid—Having just one copy of each gene within a genome.

Intragenomic—Pertaining to components of one genome.

Locus—A specific position of a gene within a genome.

Meiosis—The process of cell division to produce haploid gametes.

Meiotic driver—A gene that affects or modifies the processes that control meiosis.

Natural selection—The evolutionary pressure that affects the survival and reproduction of individuals based on their differing phenotypes within a population.

Phenotype—The physical manifestation of the genetic composition of an organism.

Recombination—The production of genetic combinations in offspring that are different from those of the parents. This process occurs during meiosis.

As a matter of course, this requires that the reproduction or replication of a gene can be at the expense of the organism. The selfish gene theory is often utilized to postulate the molecular contributions to behavior that increases reproductive fitness over mortality, to rationalize the persistence of "junk DNA" within genomes that is not selected for but is nonetheless transmitted to future generations, and to explain intragenomic conflict and non-Mendelian genetic inheritance patterns.

Female meiotic drive

During meiosis in females, one functional egg and three non functional polar bodies are produced. Only genes that make it into the egg will be passed on to the next

generation, providing a condition for gene competition. Based on the Mendelian rule of random assortment, each genetic allele has a 50% chance of being passed on to the next generation; however, because only one egg is produced this chance is decreased. Female meiotic drive occurs when there is preferential segregation that favors the transmission of some genes over others.

Meiotic drivers are alleles that can increase their transmission frequency through the exploitation of the asymmetric cell division that occurs during meiosis. These genes are called “drivers” because they modify the rate of recombination during meiosis. Genetic recombination is a crucial part of providing genetic differences between parents and their offspring; it essentially scrambles the parental genome to create new allelic combinations in the next generation and can also affect inheritance rates of genes. If genes can modulate or alter the rate of recombination they can impact the potential of their inheritance. In this way, the ability to control recombination can be an evolutionary gain for meiotic drivers. Oftentimes this control comes at the expense of fertility in that organism. A recently discovered example of a meiotic driver in mice is the gene *r2d2* that is passed on to the next generation more than 50% of the time.

Intragenomic conflict

Female meiotic drive is an example of intragenomic conflict. This arises when genes in the same genome are not transmitted to the next generation with the same efficiency, especially when one gene inhibits the transmission or replication of another gene for its own replicative benefit.

Criticism

While Dawkins’s book *The Selfish Gene* and the gene-centric view of evolution have been and continue to be important in the theoretical investigation of biology and behavior, several scientists and philosophers have criticized the theories and their applications. Notably, Stephen Jay Gould, an influential evolutionary biologist, argued that genes cannot directly affect natural selection and that the selfish gene theory oversimplifies the relationship between genes and their organisms. Where Dawkins calls the gene the fundamental unit of selection, more traditional interpretations of evolution consider the phenotype to be the unit of selection because it is the relation of phenotypic variation and a population’s environment that allows for evolutionary pressure. In this view, genetic differences merely register the changes that occur with evolution—they do not cause evolutionary changes within a population. Biologist Niles Eldredge describes the argument as the difference between genes having a causal versus a passive recording role in evolution.

The gene-centric view of evolution conflicts with some population genetics models, and many critics suggest that from a sociobiological perspective, the selfish gene theory relies too heavily on animal behavior examples to describe human behavior models. Additionally, opponents state that there are moral and ethical issues with the theory in its description of altruistic behavior as an ultimately selfish response and that this justifies anti-social behavior or behavior that operates against communal benefit. Dawkins does, however, conclude that human intellect and free will can outweigh the genetic component of behavior.

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Emily R. Larson, PhD

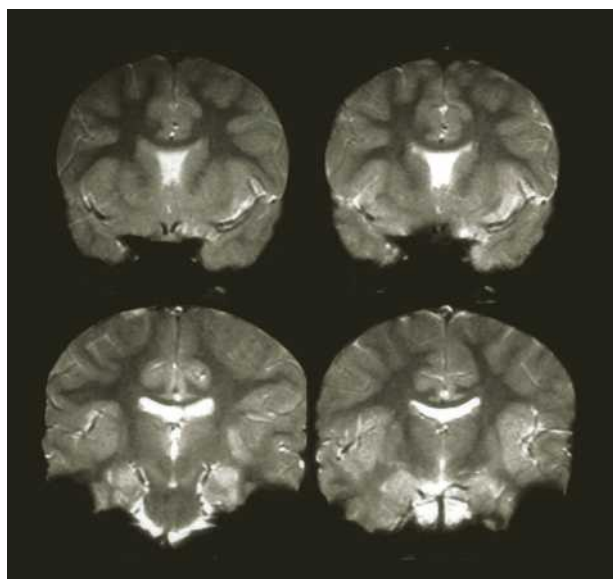
Septo-optic dysplasia

Definition

Septo-optic dysplasia (SOD) is a rare congenital disorder that includes underdevelopment of the nerves at the back of the eye(s), absence of the septum pellucidum and/or corpus callosum in the brain, and dysfunction of the pituitary gland that produces hormones in the body.

Description

SOD is also known as DeMorsier’s syndrome and is commonly recognized as the association of three features: underdevelopment of the optic nerves (optic nerve hypoplasia), absence of midline structures of the brain (most often the septum pellucidum), and problems with the functioning of the pituitary gland in the brain that controls hormone production in the body. These three



Septo-optic dysplasia is a disorder that includes absence of a part of the brain called the septum pellucidum and/or corpus callosum. (Living Art Enterprises, LLC/Science Source)

features of SOD most often cause partial or complete blindness and mild to severe visual problems, difficulty with coordination of mental and muscular activities, such as walking, and short stature. Individuals with SOD may have normal intelligence, or learning problems that can range from mild to severe.

Genetic profile

Most often, SOD occurs sporadically and is not inherited. For most individuals with SOD, there is no family history of the condition. However, there have been a few familial cases reported. These families raise the possibility that there is a form of SOD that is inherited in an autosomal recessive pattern. In autosomal recessive inheritance, two unaffected parents both carry a mutation in a single copy of a gene for a condition. When both parents pass the mutated gene on to a child, the child with two copies of the gene mutation is affected with the condition. People who are related by blood are more likely to be carriers of mutations in the same gene since they inherit their genes from a common ancestor.

Mutations in a gene called *HESX1*, located on the upper short arm of chromosome 3, have been identified in some people with SOD. The brother and sister whose parents were related were both found to have mutations in both copies of their *HESX1* genes. A 2001 study of 228 individuals with SOD or features of SOD revealed that three had a mutation in one copy of their *HESX1* gene. One Japanese individual with features of SOD was also found to have a mutation in one copy of his

HESX1 gene. Therefore, it is likely that *HESX1* is fully or partially causative in a small subset of individuals with SOD. The product of the *HESX1* gene is expressed in the brain in early development and has been shown to be involved in the development of structures that give rise to the pituitary gland. In 1998, a strain was created in mice with mutations in the *HESX1* gene so that no product was made from the gene. These mice had features similar to individuals with SOD, including pituitary gland dysfunction as well as structural changes in the brain and eyes.

Other causes of SOD are thought to be related to viral infections, diabetes, antiseizure medications, alcohol, and illicit drug use during pregnancy. In addition, a 2004 study suggested that amniotic bands may be responsible for SOD in some patients. Amniotic bands are formed when the inner membrane of the sac holding the fluid around a fetus tears. Pieces of the amnion may wrap around various parts of the fetus and restrict blood flow to those areas. Limb malformations have been shown to be caused by amniotic bands in some cases. However, in 2004 it was suggested that limb malformations are a recurrent feature of SOD, rather than SOD being caused by amniotic bands.

Demographics

The condition is considered to be rare, with an estimated incidence of 1 in 10,000 people. SOD does not occur more often in males or females and is not known to occur more or less frequently in any racial or ethnic group. SOD may become apparent during infancy, childhood, or in adolescence.

Signs and symptoms

A variety of changes in the structure and function of the eye(s) can occur as part of SOD. Most commonly, individuals have optic nerve hypoplasia, meaning that the nerves from the back of the eye to the brain are underdeveloped. The nerves may be small, and there are usually far fewer nerves connecting the eye to the brain than usual. The optic disk (the front surface of the optic nerve) may also be smaller than usual. Infants with SOD may have rapid, involuntary eye movements called nystagmus. Other changes in the structure of the eye may occur, such as strabismus (the eyes cannot focus on the same object at the same time), coloboma (notch-like area of absent tissue), and microphthalmia (small openings of the eyes). The optic features of SOD may affect one or both eyes, so that an individual with the condition may have good vision in one eye, or may have decreased or no vision in both eyes.

There can also be a variety of structural changes to the brain in people with SOD. Most often, a membrane in the midline of the brain called the septum pellucidum is absent. This membrane separates the fluid-filled cavities on each side of the brain. Another midline structure, the corpus callosum, may also be absent or underdeveloped. The corpus callosum is the thick band of nerve fibers that connects the two hemispheres of the brain. In addition, the region of the brain that controls voluntary movement, the cerebellum, may be underdeveloped. Other structural brain malformations have been reported in individuals with SOD.

Additional structures in the brain that can be affected in individuals with SOD include the hypothalamus and the pituitary gland. These parts of the brain control the production and release of hormones in the body. Individuals with SOD may not produce enough growth hormone and may exhibit short stature. There may be problems with low blood sugar, dehydration, seizures, and the production of hormones needed for sexual development.

Various other conditions have been reported in individuals with SOD. These include cleft lip and/or palate; limb anomalies, including fusion of fingers or toes and underdevelopment of fingernails or toenails; and apnea (difficulty breathing).

Patients affected with SOD can present at any age depending on the severity of the symptoms. Signs and symptoms, including failure to thrive, prolonged jaundice (yellow color to the skin caused by extra amounts of bile in the blood), difficulty controlling body temperature, decreased blood sugar, small genitalia, or low muscle tone, can herald the diagnosis of SOD in newborns. Older children may complain of visual difficulties, or have the inability to fixate on an object.

Many individuals with SOD have normal intelligence. However, there is a range of intelligence reported, including those with mild learning delays and those with significant mental retardation. Learning delays and mental retardation may be the result of structural changes in the brain or hormone disorders. Unrecognized visual problems or lack of education appropriate for those with visual impairment may also cause learning delays.

Diagnosis

SOD is often suspected when a child with visual impairment also has growth delay. When a diagnosis of SOD is suspected, a person is referred to several specialists who each perform tests to verify the diagnosis. An ophthalmologist can perform vision testing and examinations of the structure of the eye for features of SOD. In individuals with SOD, the optic nerves appear small and gray or pale in color and can be surrounded by a double

KEY TERMS

Computerized tomography (CT)—A technique that uses a beam of radiation and a computerized analysis to produce an image of a body structure, often the brain.

Corpus callosum—A band of nerve fibers that connects the right and left hemispheres of the brain.

Magnetic resonance imaging (MRI)—A technique that uses a magnetic field to produce images of various body structures.

Mutation—A permanent change in the DNA code of a gene that disrupts the gene from making its product, such as a protein or enzyme.

Optic nerve—A nerve at the back of the eyes that conducts impulses that cause sight.

Pituitary gland—A gland at the base of the brain that controls hormone production in the body; the hormones produced by the pituitary gland control growth, reproduction, and other bodily processes.

Septum pellucidum—A membrane made of nerve tissue that separates areas of fluid in the left and right sides of the brain.

pigmented ring or margin. In addition, stimulation testing of the optic nerves can be performed. A neurologist (brain specialist) can perform imaging studies of the brain, such as magnetic resonance imaging (MRI) or computerized tomography (CT) scan of the brain, focusing on the visual pathways, the septum pellucidum, hypothalamus-pituitary region, and other midline structures. An endocrinologist can perform blood tests to determine if there are problems with various hormones in the body.

There has been a report of prenatal diagnosis of SOD by an ultrasound that revealed absence of the septum pellucidum. Subsequent blood and urine tests on the mother revealed low levels of the hormone estriol, indicating a problem with the fetal pituitary gland. The diagnosis was confirmed after birth.

Treatment and management

SOD is treated symptomatically. Vision may be improved with corrective lenses, surgery, or other treatment. Seizures may be controlled with medication. Hormone deficiencies are managed with hormone replacement therapy, such as growth hormones or thyroid supplements. Hormone problems may arise at different ages, so even if not present initially, a person with SOD should be followed by an endocrinologist over time.

Children with SOD should receive early assessments of learning and development so that any supportive therapies, such as physical, speech, or educational therapy, can be initiated. Children with SOD may benefit from an individualized educational plan (IEP) in school, which is a plan created by a child's teachers, therapists, and other individuals who have performed developmental testing and designed techniques best suited to the child's needs. Families may consider placing a child with SOD in a school for visually impaired children. The child's pediatrician can monitor a child for any special needs and refer additional specialists as needed. Individuals and families with SOD may benefit from talking with a genetic counselor about possible patterns of inheritance and recurrence risks for SOD in the family. Families should also be introduced to the appropriate local and national support organizations, such as the American Foundation for the Blind, for further help and assistance.

Prognosis

Prognosis is variable, depending on the number and severity of features present. Most individuals with SOD have significant visual impairment, and many are legally blind. Patients with severe visual impairment may have difficulty obtaining a driver's license or gainful employment. Lifespan is most often normal, however, cortisol deficiency can lead to life-threatening episodes brought about by infection or stress.

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ORGANIZATIONS

MAGIC Foundation, 6645 W. North Ave., Oak Park, IL 60302, (708) 383-0808, ContactUs@magicfoundation.org, <http://www.magicfoundation.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

NIH Neurological Institute, PO Box 5801, Bethesda, MD 20824, (800) 352-9424, <http://www.ninds.nih.gov>

Seronegative spondyloarthropathies see
Ankylosing spondylitis

Severe combined immunodeficiency

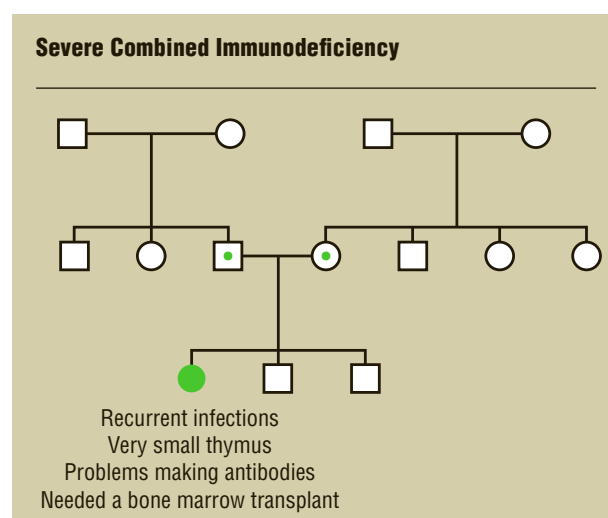
Definition

Severe combined immunodeficiency (SCID) is a group of rare, life-threatening diseases present at birth that impair the immune system. Without a healthy immune system the body cannot fight infections and individuals can easily become seriously ill from common infections.

Description

SCID is considered to be the most severe of the 70 forms of primary immunodeficiency diseases (PID). Primary immunodeficiency diseases describe conditions where a component of the immune system—either an organ or cells of the immune system—are missing or defective in their functions. There is a wide spectrum in the severity of symptoms associated with PIDs.

SCID is also known as the "boy in the bubble" syndrome because living in a normal environment can be



Severe Combined Immunodeficiency: pedigree chart analysis (Gale)

fatal to those affected, requiring them to be contained in a controlled, clean environment. SCID initially was called Swiss agammaglobulinemia because it was first described in Switzerland in 1961. Any exposure to germs or pathogens can pose a risk for infection including bacterial, viral, and fungal infections. In the first few months of life children with SCID become very ill with infections such as pneumonia (infection of the lungs that prevents oxygen from reaching the blood, making breathing difficult), meningitis (infection of the covering of the brain and spinal cord), sepsis (infection in the bloodstream), and viruses. Such infections can be fatal within the first year of life due to their compromised immune system.

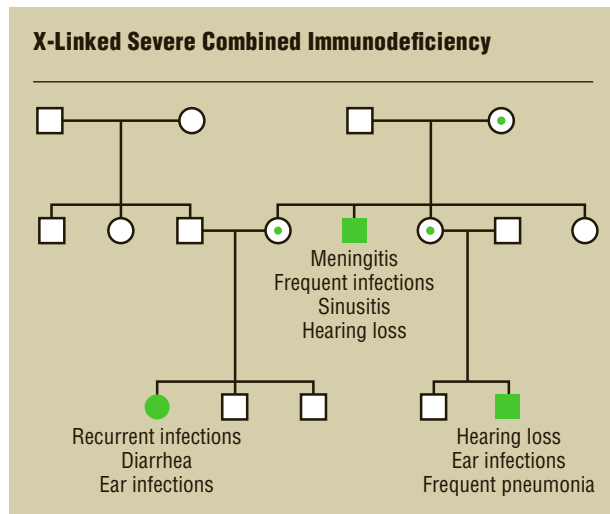
Children with SCID do not respond to medications like other children because their immune system does not function properly. They may also have an underdeveloped thymus gland. Medication usually stimulates a person's immune system to fight infection but in the case of SCID the immune system is unable to respond. The immune system is a complex network of cells and organs that protect the body from infection. The thymus and lymphatic system (lymph nodes and lymphatic vessels) house and transport two very important cells that fight infection called B and T cells. The bone marrow produces cells that become blood cells as well as cells that compose the immune system. One type of cell called lymphocytes, or white blood cells, mature in the bone marrow to form B cells, while others mature in the thymus to become T cells. B and T cells are the two major groups of lymphocytes that recognize and attack infections. Children with SCID have either abnormal or absent B and T cells.

Other infections can be seen in children with SCID including skin infections, yeast infections in the mouth and diaper area, diarrhea, and infection of the liver. Children with SCID fail to gain weight and grow normally. Treatment for SCID is available; however, many children with SCID are not diagnosed in time and die before their first birthday.

A diagnosis of SCID needs to be made quickly since common infections can prove fatal. In addition, permanent damage can result in the ears, lungs, and other organs.

Genetic profile

Genetic information is carried in tiny packages called chromosomes. Each chromosome contains thousands of genes and each gene contains the information for a specific trait. All human cells, except for cells involved in reproduction, contain 23 pairs of chromosomes for a total of 46 chromosomes. One of each pair of chromosomes is inherited from the mother and the other is inherited from the father. SCID is usually inherited in one of two ways: X-linked recessive or autosomal recessive. Recessive



X-Linked Severe Combined Immunodeficiency: pedigree chart analysis (Gale)

means that two copies of the gene are necessary to express the condition. Autosomal recessive means that the gene for the disease or trait is located on one of the first 22 pairs of chromosomes, or autosomes. Males and females are equally likely to have an autosomal recessive disease or trait. Therefore, a child inherits one copy of the gene from each parent, who is called a carrier because they have only one copy of the gene. Since carriers do not express the gene, parents usually do not know they carry the SCID gene until they have an affected child. Carrier parents have a 1-in-4 chance (or 25%), with each pregnancy to have a child with SCID.

The last pair of human chromosomes, either two X's (female) or one X and one Y (male)—determines gender. X-linked means the gene causing the disease or trait is located on the X chromosome. X-linked recessive diseases are most often seen in males because they only have one X chromosome. Therefore, if a male inherits a particular gene on the X chromosome, he expresses the gene because he only has a single copy of it. Females, on the other hand, have two X chromosomes and can carry a mutated gene on one of their X chromosomes yet not express any symptoms because their second X chromosome works normally. A mother usually carries the gene for SCID unknowingly and has a 50/50 chance with each pregnancy to transmit the gene. If the child is male, he will have SCID; if the child is female, she will be a carrier for SCID like the mother.

SCID is a group of inherited disorders caused by the inheritance of different mutated genes. About half of the cases are due to a gene on the X chromosome called *IL2RY*, which is important for proper immune cell development. The second most common form of SCID is

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman’s abdomen and into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Amniotic fluid—The fluid that surrounds a developing baby during pregnancy.

Autosomal recessive inheritance—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Bone marrow—A spongy tissue located in the hollow centers of certain bones, such as the skull and hip bones. Bone marrow is the site of blood cell generation.

Bone marrow transplant (BMT)—A medical procedure used to treat some diseases that arise from defective blood cell formation in the bone marrow. Healthy bone marrow is extracted from a donor to replace the marrow in an ailing individual. Proteins on the surface of bone marrow cells must be identical or very closely matched between a donor and the recipient.

Boy in the bubble—A description for SCID since these children need to be isolated from exposure to germs, until they are treated by bone marrow transplantation or other therapy.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother’s vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Failure to thrive—Significantly reduced or delayed physical growth.

Gene therapy—Replacing a defective gene with a normal copy.

Immune system—A major system of the body that produces specialized cells and substances that interact with and destroy foreign antigens that invade the body.

Lymphatic system—Lymph nodes and lymphatic vessels that transport infection-fighting cells around the body.

Lymphocytes—Also called white blood cells, lymphocytes mature in the bone marrow to form B cells, which fight infection.

Meningitis—An infection of the covering of the brain and spinal cord.

Pneumonia—An infection of the lungs.

Primary immunodeficiency disease (PID)—A group of approximately 70 conditions that affect the normal functioning of the immune system.

Sepsis—An infection of the bloodstream.

Severe combined immunodeficiency (SCID)—A group of rare, life-threatening diseases present at birth that cause a child to have little or no immune system. As a result, the child’s body is unable to fight infections.

Sporadic—Isolated or appearing occasionally with no apparent pattern.

Thymus gland—An endocrine gland located in the front of the neck that houses and transports T cells, which help to fight infection.

X-linked recessive inheritance—The inheritance of a trait by the presence of a single gene on the X chromosome in a male, passed from a female who has the gene on one of her X chromosomes, who is referred to as an unaffected carrier.

responsible for 15% of the cases and is caused by a mutation in the gene *ADA*, which codes for adenosine deaminase, an enzyme required for lymphocyte proliferation. Lymphocytes are crucial for a functional immune system and without them the immune system is compromised. The remaining 35% of SCID cases are caused by either an unknown autosomal recessive gene or are the result of a new mutation. New mutations—alterations in the DNA of the gene—can cause disease. In these cases neither parent has the disease-causing mutation. This may occur

because the mutation in the gene happened for the first time only in the egg or sperm for that particular pregnancy. New mutations are thought to happen by chance and are therefore referred to as “sporadic,” meaning by chance.

Demographics

It is estimated that about 400 children a year are born with some type of primary immunodeficiency disease. Approximately 1 in 100,000 children are born with SCID

each year regardless of the part of the world the child is from or the ethnic background of the parents. This disease can affect both males and females depending on its mode of inheritance.

Signs and symptoms

Babies with SCID fail to thrive, are frail, and do not grow well. They have numerous and serious life-threatening infections that usually begin in the first few months of life. Because they do not respond to medications like other children they may be on antibiotics for one or two months with no improvement before a physician considers a diagnosis of SCID. The types of infections typically include chronic skin infections, yeast infections in the mouth and diaper area, diarrhea, infection of the liver, pneumonia, meningitis, and sepsis. They can also have serious sinus and ear infections, as well as a swollen abdomen. Sometimes deep abscesses occur, which are pockets of pus that form around infections in the skin or in the body organs.

Diagnosis

About half of children who see a doctor for frequent infections are normal; another 30% may have allergies, 10% have some other type of serious disorder, and 10% have a primary or secondary immunodeficiency. A diagnosis of SCID is usually made based on a complete medical history and physical examination in addition to multiple blood tests and chest x-rays. The gene in X-linked recessive SCID is called the interleukin receptor gamma chain gene or *IL2RG*. The autosomal recessive forms of SCID are caused by a variety of different genes; one of the more common is called the adenosine deaminase gene or *ADA*. Since newborns do not routinely have a test to count white blood cells, SCID is not usually suspected and the diagnosis does not happen until the child develops his or her first infection. A pattern of recurrent infections suggests an immunodeficiency.

Once a couple has had a child with SCID and they have had the genetic cause identified by DNA studies, prenatal testing for future pregnancies may be considered on a research basis for some types of SCID, although prenatal testing may not be possible if a mutation cannot be identified. Prenatal diagnosis is available via either CVS (chorionic villus sampling) or amniocentesis. CVS is a biopsy of the placenta performed in the first trimester or the first 12 weeks of pregnancy under ultrasound guidance. Ultrasound uses sound waves to visualize the locations of the developing fetus and the placenta. The genetic makeup of the placenta is identical to the fetus and, therefore, the presence or absence of one of the SCID genes can be determined from this tissue. Amniocentesis is a procedure

QUESTIONS TO ASK YOUR DOCTOR

- A relative has a child affected by SCID. Is there any way of knowing if I am at risk for this condition?
- What are the most common symptoms associated with this disorder?
- Can bone marrow transplants be rejected? What are the complications associated with transplants in SCID patients?

performed under ultrasound guidance where a long thin needle is inserted through the mother's abdomen and into the uterus to withdraw amniotic fluid surrounding the developing baby. The SCID genes can be studied using cells from the amniotic fluid. Other genetic tests, such as a chromosome analysis may also be performed on either a CVS or amniocentesis. A small risk of miscarriage is associated with amniocentesis and CVS.

Treatment and management

The best treatment for SCID is a bone marrow transplant (BMT). A bone marrow transplant involves taking cells that are normally present in bone marrow and injecting them into the SCID patient. The goal of BMT is to infuse healthy bone marrow cells into a person after his or her own unhealthy bone marrow has been eliminated. BMT helps to strengthen the immune system of a child with SCID.

Other treatment for SCID includes treating each infection promptly and accurately. Injections are also available to help boost a child's immune system.

In the year 2000, gene therapy was first reported to be successful in two French patients with SCID. The goal behind gene therapy is to replace an abnormal gene with a normal copy. In SCID, bone marrow is removed to isolate the patient's stem cells. Stem cells are special cells in the bone marrow that produce lymphocytes. In a laboratory the normal gene is added to the genome of the abnormal stem cells. The genetically altered stem cells now have the normal gene and are transplanted back into the patient. Once the functioning stem cells with the normal gene enter the bone marrow, they reproduce quickly and replace stem cells that have the abnormal gene. The patient with SCID can now produce B and T cells normally and can fight off infections without antibiotics or other treatment. The long-term effects of gene therapy

are unknown since the children treated are still very young and the research is ongoing.

Prognosis

When SCID is diagnosed early, successful bone marrow transplantation usually corrects the problem and the child lives a normal life. This means children can go to school, mix with playmates, and take part in sports. However, the quality of life for individuals with severe cases of SCID can be greatly impaired if they do not receive a bone marrow transplant. Children with SCID may not live long if they do not receive the proper treatment or if their disease goes undiagnosed.

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ORGANIZATIONS

American Academy of Allergy, Asthma & Immunology, 555 E. Wells St., Ste. 1100, Milwaukee, WI 53202-3823, (414) 272-6071, <http://www.aaaai.org>

Immune Deficiency Foundation, 110 West Rd., Ste. 300, Towson, MD 21204, (800) 296-4433, info@primaryimmune.org, <http://primaryimmune.org>

Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

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Short-rib thoracic dysplasia with or without polydactyly

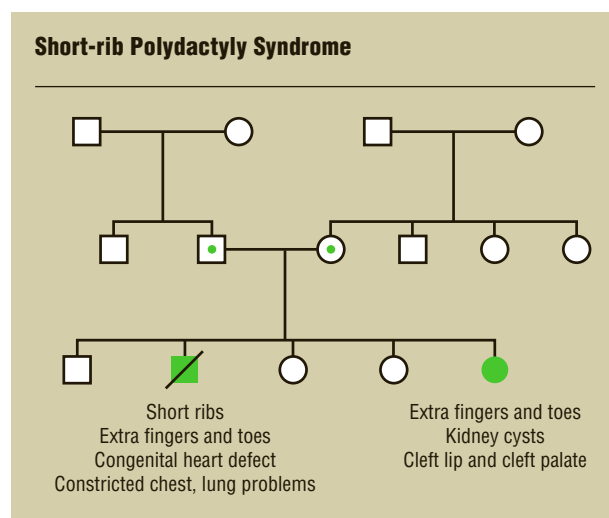
Definition

Short-rib thoracic dysplasia (SRTD) with or without polydactyly is a group of skeletal ciliopathies consisting of short ribs, short limbs, extra fingers or toes, and various internal organ abnormalities present at birth.

Description

In 1972, R. M. Saldino and C. D. Noonan first described two siblings with a dwarfism syndrome and symptoms of extremely shortened limbs, short ribs, small chest, abnormal bone formation, extra fingers, and internal organ damage. Since then, 15 additional SRTD subtypes have been identified. While each subtype has distinguishing features, there is a great amount of overlap between them.

The SRTD syndromes also include dwarfism syndromes such as asphyxiating thoracic dysplasia (Jeune syndrome) and Ellis-van Creveld syndrome. These syndromes, like the SRP types, have shortened limbs and ribs, small chest, and extra fingers or toes. As of 2015, the genetic causes for 14 types of SRTD had been identified, with multiple genetic mutations occurring in several forms. The cause of these syndromes is related to the abnormal function of cilia. Because cilia are integral to the structure of most cells, mutations in the genes responsible for the structure and function of cilia result in skeletal dysplasias or shortened bones in the arms, legs, and ribcage. The ribcage is also



Short-rib polydactyly syndrome: pedigree analysis chart
(Gale)

constricting, leaving very little room for lung growth. Development can also be abnormal in the internal organs, including the heart, kidneys, liver, and pancreas. The cause of death for newborns with this disorder is usually inability to breathe due to severely underdeveloped lungs.

Genetic profile

All types of SRTD with or without polydactyly are inherited in an autosomal recessive manner. An autosomal recessive condition is caused by two mutations in a gene responsible for SRTD. An affected individual will inherit one mutation for this condition from each parent. When both parents are carriers for mutations that cause SRTD with or without polydactyly, there is a 25% chance they will have an affected child. The parent who carries the gene mutation for this condition is not affected with symptoms of the syndrome.

Demographics

It is believed that SRTD with or without polydactyly occurs in 1 in 100,000 to 1 in 130,000 live births. Due to the rarity of the SRP syndromes, an exact incidence is unknown.

Signs and symptoms

There is much overlap of symptoms between the SRTD subtypes, and it is often difficult to distinguish between them. All present with extremely shortened bones of the arms, legs, and ribs. They all also include a small, constricted chest.

Saldino-Noonan (type I) is considered the most severe type. Features reported with this type include spur formation on the bones, abnormal vertebrae (bones of the spinal column), and decreased ossification (hardening of the bones). Heart defects are common. Cysts are often seen on the kidneys and pancreas. Extra fingers and/or toes (polydactyly) are a classic feature and are usually on the same side of the hand/foot as the “pinkie” finger/little toe (postaxial). Sex reversal has also been reported. This means that the baby is genetically male but has visible female genitalia.

Majewski (type II) also has cystic kidneys and post-axial polydactyly. This type can also have preaxial polydactyly, in which the extra fingers/toes are on the same side of the hand/foot as the thumb/big toe. Other distinguishing features include cleft lip and palate and liver damage. The tibia (one of the bones of the lower leg) is often oval shaped and shorter than the fibula (the other bone of the lower leg). The ends of the bones may also appear smooth on an x-ray.

KEY TERMS

Ciliopathies—Genetic disorders caused by a mutation in genes responsible for making proteins that maintain the integrity and role of cilia.

Dwarfism—Any condition that results in extremely shortened limbs.

Skeletal dysplasia—A group of syndromes consisting of abnormal prenatal bone development and growth.

Verma-Naumoff (type III) has much overlap with Saldino-Noonan (type I) and may be a milder variant. Internal organ involvement is less common. The ends of the bones may appear jagged and widened on an x-ray. The vertebrae are often small and flat. Polydactyly is also common in this type. Visible genitalia may be ambiguous (not clearly male or female).

Beemer-Langer (type IV), like Majewski, can have cleft lip and palate and liver damage. Cysts on the kidneys and pancreas are common. Polydactyly is usually absent but has been reported. A distinguishing feature of this type is bowed or curved bones.

Diagnosis

Diagnosis of the SRTD syndromes can be difficult. A careful examination of internal organs and x-ray evaluation is needed to distinguish SRTD syndromes from Jeune syndrome and Ellis-van Creveld syndrome. When SRTD syndrome is suspected, x-rays and internal organ involvement can also help to determine the particular type.

The main features of SRTD syndromes (short bones, short ribs, small chest) can be seen on prenatal ultrasound. Genetic testing is available for many of the different types of SRTD syndromes.

Treatment and management

There is no treatment or cure for the SRTD syndromes. The abnormal prenatal bone development is irreversible. The chest is usually too small to allow for lung growth after birth. Internal organs with cysts may not be functional.

Infants born with SRTD syndromes are given minimum care for warmth and comfort. Due to the poor prognosis, extreme measures to prolong life are rarely taken.

QUESTIONS TO ASK YOUR DOCTOR

- Is genetic testing available for short-rib thoracic dysplasia with or without polydactyly syndrome?
- Can SRTD with or without polydactyly be diagnosed prenatally and, if so, what are the risks and benefits from having such a test?
- Are there treatments available that will extend the life of an infant born with short-rib thoracic dysplasia with or without polydactyly?
- Where can I read more about this genetic disorder?

Prognosis

The prognosis for infants born with SRTD syndromes is quite poor. These babies usually die within hours or days of birth due to underdeveloped lungs. Some babies who survive infancy develop liver disease and renal failure.

Resources

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ORGANIZATIONS

- Compassionate Friends, PO Box 3696, Oak Brook, IL 60522, (630) 9900-0010 or (877) 969-0010, (630) 9900-0246, <https://www.compassionatefriends.org/home.aspx>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

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Shprintzen-Goldberg craniosynostosis syndrome

Definition

Shprintzen-Goldberg craniosynostosis syndrome (SGS) is a disorder of the connective tissue, featuring craniosynostosis and marfanoid body type with an alteration in intellectual function.

Description

SGS, also known as marfanoid craniosynostosis syndrome, is one of a group of disorders characterized by craniosynostosis and marfanoid body type. It is a condition that involves craniofacial, skeletal, and other abnormalities. SGS is caused by genetic mutations (changes affecting the structure and function of the gene) in a gene that contributes to the formation of connective tissue.

Connective tissue plays a major role in the structure of the body. Its major function is to support, connect, suspend, and separate tissues and organs in the body. It is the foundation of blood cells, immune cells, lymphatic tissue, fat cells, cartilage, and bone. If connective tissue is not formed correctly, as seen in SGS, the structure and the function of the body will be disrupted.

Clinical features of SGS are widespread; however, skeletal changes are often the hallmark sign. Marfanoid characteristics include elongated features due to hyperlordism, scoliosis, pectus excavatum, and pes planus. Other skeletal characteristics include camptodactyly (bent fingers) and a hypoplastic mandible and maxilla. The clinical features that distinguish SGS from Marfan syndrome, which is an inherited genetic disorder of the connective tissue that involves the eye, heart, aorta, and skeletal system, are craniosynostosis and intellectual disability. Due to the fact that connective tissue is found throughout the body, the structural integrity of tissues and organs is also compromised, as seen in clinical symptoms such as mitral valve prolapse, aortic aneurysm, hernias, decreased fat cells that function as cushions between organs, translucent skin, and an overall appearance of being "stretched out."

Genetic profile

SGS is associated with abnormalities of the elastic fibers of connective tissue. Elastic fibers are complex in structure and are composed of at least 19 different proteins. Mutations in three of the genes that encode the majority of these 19 proteins cause abnormalities in several body systems, including the skeletal system, blood vessels, and eye.

SGS shares characteristics with Marfan syndrome, which is caused by mutations in the fibrillin-1 (*FBNI*) gene that is located on chromosome 15. Since SGS is similar in many ways to Marfan syndrome, studies of the *FBNI* gene have been conducted on SGS patients to see if they also had mutations in this gene. There were indeed abnormalities found in the *FBNI* genes of persons with SGS. Researchers think that these mutations predispose a person to develop SGS but that other factors are required in addition to the mutation in the gene to develop the disease.

Studies have determined that SGS is not primarily due to an *FBNI* gene abnormality, separating it even more from Marfan syndrome. Instead, a mutation in the *SKI* gene on the short arm of chromosome 1 is the underlying cause of SGS. One study determined that a frameshift mutation in exon 1 of the *SKI* gene causes SGS due to its role in mediating TGF-beta. TGF-beta is a cytokine growth factor that controls the proliferation and differentiation of most cells in the body and has a high link to Marfan syndrome and other connective tissue disorders with an alteration in TGF-beta activity. Another study also concluded that an alteration of *SKI* may be the underlying cause of SGS but also suggested that both *SKI* and *FBNI* mutations may cause a Marfan-like syndrome with craniosynostosis and intellectual dysfunction as seen in SGS.

The mutations appear to be sporadic in nature (not inherited) and autosomal dominant (only one mutation is necessary for a person to be predisposed to the disease). Sporadic genetic mutations in the sperm occur (in any gene, not just *FBNI*) at a higher rate in older men (over 45 years), and there is in fact one case report of a child with SGS in which the father was 49 years old. The father of another child with SGS reportedly had chemotherapy and radiation treatment prior to conception of the child. The recurrence risk for siblings is probably low, although such data are not available.

Demographics

There were approximately 29 reported cases as of 2013, with the first case being described in 1981. The ratio of females to males is 10:5, making females affected twice as often as males. Ethnicities would be expected to be affected equally with sporadic mutations, although

KEY TERMS

Aortic root—The location where the aorta (main heart blood vessel) inserts in the heart. Enlargement of the aortic root can cause it to rupture.

Camptodactyly—A condition characterized by the bending of one or more fingers.

Craniosynostosis—Premature, delayed, or otherwise abnormal closure of the sutures of the skull.

Marfanoid—Term for a body type that is similar to that of people with Marfan syndrome. Characterized by tall, lean body with long arms and long fingers.

Pectus excavatum—An abnormality of the chest in which the sternum (breastbone) sinks inward; sometimes called “funnel chest.”

Pes planus—Flat feet.

data regarding SGS specifically is limited. There is difficulty determining current demographics due to the overlapping symptoms between SGS and Marfan syndrome.

Signs and symptoms

Findings in SGS include skeletal abnormalities, hydrocephalus, and intellectual disability. Most babies born with SGS are well nourished and have a relatively long birth length. The most frequently described craniofacial features of SGS include abnormal head shape (dolichocephaly), a high, prominent forehead, bulging eyes (ocular proptosis), widely spaced eyes (hypertelorism), downslanting eyes, strabismus (wandering eye), small jaw (maxillary hypoplasia), high narrow palate (roof of the mouth), and low-set ears.

The main skeletal findings in persons with SGS include long, thin fingers (arachnodactyly, or spider-like fingers), flat feet (pes planus), “bird” chest deformity (pectus deformity), scoliosis (curvature of the spine), and joint hypermobility (loose joints).

Other features can include clubfoot, enlarged aortic root, mitral valve prolapse (a floppy heart valve that allows flow of blood back into the chamber of the heart that it came from), low muscle tone (hypotonia), developmental delay, intellectual disability, very little body fat, and a small penis in males. Myopia (nearsightedness) and abdominal wall defects (a developmental problem that occurs during formation of the fetus in which parts of the intestine or other organs can protrude outside of the body; it is usually surgically correctable) can also occur.

Radiologic findings include hydrocephalus (water on the brain), certain brain malformations (Chiari-I malformation or dilatation of the lateral ventricles), abnormalities in the first and second cervical vertebrae (vertebrae in the neck), square-shaped vertebrae, thin ribs, thinning of the bones, and craniofacial abnormalities.

Diagnosis

There are more than 75 syndromes associated with craniosynostosis. There are also a number of different syndromes associated with both craniosynostosis and marfanoid body type. X-ray evaluation can be helpful in determining whether a person has SGS, as they tend to have abnormal first and second cervical vertebrae, hydrocephalus (water on the brain), and certain brain abnormalities.

SGS must be differentiated from other syndromes with craniosynostosis and marfanoid body type. Two such syndromes include Idaho syndrome II and Antley-Bixler syndrome. Idaho syndrome II has less severe craniofacial problems than SGS and has abnormal leg bones and absent patellae (knee caps). Antley-Bixler syndrome is an inherited syndrome with craniofacial abnormalities, abnormal arm and leg bones, and fractures in the femurs (thigh bones). These characteristics are different from SGS. A clinical geneticist is a physician who has special training in recognizing and diagnosing rare genetic conditions and is a good resource for differentiating among these complicated and similar conditions.

A true diagnosis can be made via genetic testing. This will help differentiate SGS from other connective tissue disorders such as Marfan syndrome and Loeys-Dietz syndrome. Genetic testing may be done in laboratories utilizing deletion/duplication analysis with PCR and Sanger Sequence Analysis.

Treatment and management

Cardiology evaluation is important since several children have been reported to have severe cardiac disease with SGS. Aortic root must be evaluated and measured routinely to minimize the risk for rupture. Enlarged aortic roots may need to be surgically repaired.

Patients should have an ophthalmologic evaluation, since mutations in the *FBR1* gene are associated with abnormalities in the eyes.

Surgical correction of craniofacial problems or pectus are sometimes necessary or desirable. Shunting (surgical placement of a shunt to drain the accumulated fluid in the brain to the abdominal cavity to relieve pressure) may be required for patients with hydrocephalus. Orthopedic devices may be required for scoliosis or other bone deformities.

QUESTIONS TO ASK YOUR DOCTOR

- What does the term “marfanoid body type” mean?
- How is Shprintzen-Goldberg craniosynostosis syndrome diagnosed, and at what age can a reliable diagnosis be made?
- What kinds of treatments are recommended for the medical problems related to Shprintzen-Goldberg craniosynostosis syndrome?
- What is the prognosis for a child diagnosed with this genetic disorder?
- How often should cardiovascular function and integrity be assessed?

Special education for intellectually disabled individuals or individuals with developmental delay is recommended.

Genetic counseling is recommended for persons with relatives diagnosed with SGS.

Prognosis

SGS does not alter lifespan, although complications from associated abnormalities such as intellectual disability or respiratory problems can cause problems.

Resources

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ORGANIZATIONS

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Sialidosis

Definition

Sialidosis, previously known as neuraminidase deficiency, is a rare inherited metabolic disorder with multiple symptoms that can include skeletal abnormalities and progressive neurological degeneration.

Description

Nomenclature

Neuraminidase deficiency is caused by a mutation, or change, in the *NEU1* gene that codes for the lysosomal enzyme alpha-N-acetyl-neuraminidase, or neuraminidase for short. This enzyme sometimes is referred to as sialidase. It is also sometimes called N-acetyl-neuraminic acid hydrolase. The disorder is manifested in one of two forms, known as sialidosis types I and II. Sialidosis type I is the milder form of the disorder, with symptoms typically appearing during adolescence. It is known as the nondysmorphic or normophormic form of sialidosis. Sialidosis type II is the more severe form of neuraminidase deficiency, with symptoms developing in the fetus, at birth, or during infancy or early childhood. It is known as the dysmorphic form of sialidosis.

Over the years, this disorder has been called by a number of different names, in addition to neuraminidase deficiency, alpha-neuraminidase deficiency, sialidase deficiency, and sialidosis. It sometimes is known as cherry-red spot and myoclonus syndrome, cherry-red spot myoclonus epilepsy syndrome, or myoclonus and cherry-red spot syndrome, in reference to characteristic symptoms of the disorder. Other names include glycoprotein neuraminidase deficiency, *NEUG* deficiency, *NEU* or *NEU1* deficiency, and neuraminidase 1 deficiency. Sialidosis type I sometimes is referred to as juvenile sialidosis and type II as infantile sialidosis, in reference to the age of onset.

Lysosomal storage diseases

Lysosomes are membrane-bound spherical compartments or vesicles within the cytosol, the semi-fluid areas of cells. Lysosomes contain more than 50 different enzymes that are responsible for digesting, or hydrolyzing, large molecules and cellular components. These include proteins; polysaccharides, which are long, linear, or branched chains of sugars; and lipids, which are large insoluble biomolecules that are usually built from fatty acids. The smaller breakdown products from the lysosomes are recycled to the cytosol.

Neuraminidase deficiency is one of at least 41 genetically distinct lysosomal storage diseases. These disorders result from mutations in the genes encoding the hydrolytic enzymes of the lysosome. In these disorders, some of the macromolecules in the lysosomes cannot be degraded and they, or their partial-breakdown products, accumulate there. The lysosomes swell to the point where cellular function is disrupted.

Neuraminidase deficiency, particularly sialidosis type II, commonly has been classified as the lysosomal storage disease called mucopolysaccharidosis type I (ML I), formerly lipomucopolysaccharidosis. This is because the symptoms of neuraminidase deficiency are similar to various mucopolysaccharidosis disorders. However, mucopolysaccharidoses are characterized by the accumulation of large and complex lipid-polysaccharides. In contrast, neuraminidase deficiency leads to the accumulation of specific types of short chains of sugar called oligosaccharides and of certain proteins with oligosaccharides attached to them, called glycoproteins. Thus, it may be more appropriate to classify neuraminidase deficiency as an oligosaccharide storage disease, since it leads to the accumulation of excess oligosaccharides in various tissues throughout the body and the excretion of oligosaccharides.

Neuraminidase

Neuraminidase, or sialidase, is a type of enzyme known as an exoglycosidase because it cleaves terminal sugar units, or residues, off oligosaccharides. Specifically, neuraminidase cleaves, or hydrolyzes, terminal sialic acid residues. Sialic acid, also known as N-acetylneuraminic acid, is a type of sugar molecule that often is at an end of an oligosaccharide. The oligosaccharides with sialic acid residues may be attached to proteins (glycoproteins). Therefore, neuraminidase deficiency prevents the proper breakdown of oligosaccharides and glycoproteins that contain sialic acid, and the disorder is characterized by the accumulation and excretion of these substances.

In addition to interfering with the lysosomal breakdown of sialic acid compounds, neuraminidase deficiency can lead to abnormal proteins. Following protein

synthesis, some lysosomal enzymes reach the lysosome in an inactive form and require further processing for activation. One such processing step is the neuraminidase-catalyzed removal of sialic acid residues from oligosaccharides on the enzymes. Lysosomal hydrolases that require further processing by neuraminidase include acid phosphatase, alpha-mannosidase, arylsulfatase B, and alpha-glucosidase.

Under conditions of neuraminidase deficiency, sialyloligosaccharides accumulate in various cells, including lymphocytes (white blood cells that produce antibodies), fibroblasts (connective tissue cells), bone marrow cells, Kupffer cells of the liver, and Schwann cells, which form the myelin sheaths of nerve fibers. Furthermore, proteins with sialic acid attachments accumulate and can be detected in fibroblasts and in the urine.

Neuraminidase exists in the lysosome in a high-molecular-weight complex with three other proteins: the enzyme beta-galactosidase, the enzyme N-acetylgalactosamine-6-sulfate sulfatase (GALNS), and a multi-functional enzyme called protective protein/cathepsin A (PPCA). Neuraminidase must be associated with PPCA in order for the neuraminidase to reach the lysosome. Once inside the lysosome, PPCA mediates the association of as many as 24 neuraminidase molecules to form active neuraminidase. The active enzyme remains associated with PPCA and beta-galactosidase, which appear to be necessary for protecting and stabilizing the neuraminidase activity. A distinct lysosomal storage disease, neuraminidase deficiency with beta-galactosidase deficiency, or galactosialidosis, results from mutations in the gene encoding PPCA. In this disorder, both neuraminidase and beta-galactosidase are deficient.

Genetic profile

Inheritance of sialidosis

Sialidosis is an autosomal recessive disorder that can be caused by any one of a number of different mutations in the *NEU1* gene encoding the lysosomal neuraminidase. The disorder is autosomal because the *NEU1* gene is located on chromosome 6, rather than on the X or Y sex chromosomes. The disorder is recessive because it only develops when both genes encoding neuraminidase, one inherited from each parent, are defective; however, the two defective *NEU1* genes do not need to carry the same mutations. If the two mutations are identical, the individual is a homozygote. If the two mutations are different, the affected individual is called a compound heterozygote. Individuals with one defective gene and one normal gene encoding neuraminidase may have reduced levels of the active enzyme, but they do not have symptoms of neuraminidase deficiency.

All of the offspring of two parents with neuraminidase deficiency will inherit the disorder. All of the offspring of one parent with neuraminidase deficiency and one parent with a single defective *NEU1* gene will inherit at least one defective *NEU1* gene. They will have a 50% chance of inheriting two defective genes and, therefore, developing neuraminidase deficiency. The offspring of one parent with neuraminidase deficiency and one parent with normal *NEU1* genes will inherit a defective gene from the affected parent but will not develop neuraminidase deficiency. The offspring of parents who both carry one defective *NEU1* gene have a 50% chance of inheriting one defective *NEU1* gene and a 25% chance of inheriting two genes and developing neuraminidase deficiency. Finally, the children of one parent with a single defective *NEU1* gene and one parent with normal *NEU1* genes will have a 50% chance of inheriting the defective gene but will not develop neuraminidase deficiency.

Mutations in the NEU1 gene, type I sialidosis and type II sialidosis

Roughly 50 different mutations that can cause sialidosis have been identified in the *NEU1* gene. The type of neuraminidase deficiency, sialidoses types I or II, as well as the severity of the symptoms, depends on the specific mutation(s) that are present. Some mutations change one amino acid out of the 415 amino acids that compose a single neuraminidase molecule. Other identified mutations result in a shortened enzyme. Many of the identified mutations are clustered in one region on the surface of the protein. These mutations result in a sharp reduction in the activity of the enzyme and lead to the rapid degradation of neuraminidase inside the lysosome.

Some mutations in the *NEU1* gene lead to a complete absence of neuraminidase activity, with little or no neuraminidase enzyme present in the lysosomes. These mutations usually result in the severe, infantile-onset type II sialidosis. Other mutations result in an inactive protein that is present in the lysosome. These mutations generally result in juvenile-onset type II sialidosis, with symptoms of intermediate severity. Some mutations significantly reduce, but do not obliterate, neuraminidase activity in the lysosome. Individuals with at least one mutated gene of this type are not completely neuraminidase-deficient and have mild type I sialidosis. Occasionally, individuals have multiple mutations in the *NEU1* gene, leading to more severe forms of neuraminidase deficiency.

Demographics

Sialidosis is an extremely rare disorder. Because of its similarities to many other disorders, it has been difficult to determine its frequency. In the United States, it is

estimated to occur in 1 out of every 250,000 live births. In Australia, the estimate is 1 out of 4.2 million. Since sialidosis is an autosomal rather than a sex-linked disorder, it occurs equally in males and females.

As an autosomal recessive disorder, sialidosis requires two copies of the defective gene, one inherited from each parent. Thus, it is much more common in the offspring of couples who are related to each other (consanguineous marriages), such as first or second cousins.

Sialidosis type I appears to be more common among Italians. Type 2 sialidosis seems to occur more frequently among Japanese.

Signs and symptoms

The clinical symptoms of neuraminidase deficiency are similar to the symptoms of the mucopolidoses, including I-cell disease (mucopolidosis II) and pseudo-Hurler polydystrophy (mucopolidosis III). Furthermore, the clinical distinctions between sialidoses types I and II may not be clearly defined.

Sialidosis type I

The symptoms of sialidosis type I do not appear until the second decade of life. Infants and children with this form of sialidosis may have a normal appearance and grow normally until adolescence. At that time, the appearance of red spots in both eyes, known as cherry-red macules or cherry-red macular spots, may be one of the first symptoms of neuraminidase deficiency. Eventually, color and/or night blindness may develop. Cataracts may occur, and vision may deteriorate gradually into blindness. Atrophy of the brain may also occur.

Other symptoms of sialidosis type I include myoclonus. These are sudden involuntary muscle contractions that may eventually develop into myoclonic seizures. The myoclonus may become debilitating, even in sialidosis type I. Individuals with this form of sialidosis may have increased deep tendon reflexes (hyperreflexia) and may develop tremors and various other neurological conditions. There may be a progressive loss of muscle coordination, called ataxia, and walking and standing may become increasingly difficult. Speech problems, such as slurring, may develop.

These symptoms also may occur in sialidosis type II. However, in addition to the age of onset, type I can be distinguished from type II by the absence of skeletal and facial abnormalities. Furthermore, individuals with this form of neuraminidase deficiency have normal intelligence.

KEY TERMS

Dysostosis multiplex—A variety of bone and skeletal malformations.

Fibroblast—Cells that form connective tissue fibers like skin.

Glycoprotein—A protein with at least one carbohydrate group.

Heterozygote—Having two different versions of the same gene.

Homozygote—Having two identical copies of a gene or chromosome.

Lipid—Large, complex biomolecule, such as a fatty acid, that will not dissolve in water. A major constituent of membranes.

Lysosome—Membrane-enclosed compartment in cells, containing many hydrolytic enzymes; where large molecules and cellular components are broken down.

Myoclonus—Twitching or spasms of a muscle or an interrelated group of muscles.

Oligosaccharide—Several monosaccharide (sugar) groups joined by glycosidic bonds.

Polysaccharide—Linear or branched macromolecule composed of numerous monosaccharide (sugar) units linked by glycosidic bonds.

Recessive—Genetic trait expressed only when present on both members of a pair of chromosomes, one inherited from each parent.

Sialic acid—N-acetylneuraminic acid, a sugar that is often at the end of an oligosaccharide on a glycoprotein.

Vacuolation—The formation of multiple vesicles, or vacuoles, within the cytosol of cells.

Sialidosis type II

Sialidosis type II has three forms: congenital or neonatal, with symptoms present at or before birth; infantile, with symptoms developing at birth or during the first year of life; and juvenile, with symptoms developing between the ages of 2 and 20.

Symptoms of sialidosis type II vary from mild to severe but are always more severe than in type I sialidosis. With neonatal onset, infants may be born with ascites (accumulation of fluid in the abdominal cavity), swollen liver and spleen (hepatosplenomegaly), hernia of the umbilicus or the groin, and other abnormalities. With

severe forms of the disorder, children may die in infancy. With milder forms, they may show no symptoms for the first 10 years of life. Thus, ascites, hepatosplenomegaly, and hernias may develop later. Children with sialidosis may grow abnormally fast. Cherry-red macules, myoclonus, and other neurological abnormalities, including tremors, may be present. The myoclonus may progress into a form of epilepsy. These children may have mild to severe intellectual disability.

Sialidosis type II is characterized by a variety of skeletal malformations (dysostosis multiplex). Obvious symptoms may include distinctive, coarse facial features (called coarse facies), a short trunk with relatively long legs and arms, and a prominent breast bone (pectus carinatum). In addition, there may be a lack of muscle tone and strength (hypotonia) and the progressive wasting of muscular tissue.

Hearing may be affected in sialidosis type II. Individuals may have difficulty breathing (dyspnea). Cardiac problems may develop, and severe congenital sialidosis type II apparently can result in severely dilated coronary arteries. Loose bowel movements are common with this form of neuraminidase deficiency.

Diagnosis

Neuraminidase activity

Typically, sialidosis is diagnosed by measuring the activity of the enzyme in cultures of fibroblast cells that have been grown from cells obtained via a skin biopsy. Lysosomal neuraminidase also can be measured in leukocytes (white blood cells). However, human cells have two other types of neuraminidase, encoded by different genes. One of these enzymes is present in the cell membrane, and the other is in the cytosol of various cells, including leukocytes. These enzymes are not deficient in sialidosis, and their activities can interfere with the measurement of lysosomal neuraminidase.

Neuraminidase activity usually is measured by testing the ability of fibroblast cell preparations to hydrolyze, or cleave, a synthetic compound such as 4-methylumbelliferyl-D-N-acetylneuraminic acid. Hydrolysis by neuraminidase liberates 4-methylumbelliferone, which is a compound with a fluorescence that can be measured accurately. Neuraminidase is an unstable enzyme, and special precautions are needed to test for its activity. The normal range of neuraminidase activity in fibroblasts is 95–653 picomoles per minute per milligram of protein. In leukocytes, the normal range is 6–60 picomoles per minute per milligram of protein. Levels of active neuraminidase are much lower in sialidosis type II as compared to type I.

QUESTIONS TO ASK YOUR DOCTOR

- What type of sialidosis do I have?
- What is my prognosis?
- How often should I be screened for progression of my disorder?
- Are there support groups for me and my family?
- How accurate is the genetic testing for me to screen any future children I may have?

Urine tests

Sialidosis may be diagnosed by screening the urine for the presence of sialyloligosaccharides using chromatography to separate the components of the urine on the basis of size and charge. In unaffected individuals, sialyloligosaccharides are cleaved by neuraminidase and, therefore, are present in the urine in only very low amounts. With sialidosis, urine levels of sialyloligosaccharides may be three to five times higher than normal. Sialyloligosaccharides or partially degraded proteins with sialyloligosaccharides still attached, also can be detected in the urine under conditions of sialidosis. A study published in 2014 proposed the use of mass spectrometry for the diagnosis of sialidosis and other lysosomal diseases for urinary screening of oligosaccharides.

Histology

Sialidosis and other lysosomal storage diseases interfere with the normal lysosomal breakdown of cellular components. As a result, the lysosomes may fill up with large molecules that are only partially digested. In the case of sialidosis, the lysosomes fill up with sialyloligosaccharides and sialylglycopeptides. These swollen lysosomes may form inclusion bodies and give cells a vacuolated appearance that is diagnostic of lysosomal storage disease. Sialidosis may be diagnosed by histological, or microscopic, examination of a number of different types of cells that may show this cytosolic vacuolation. These cells include the Kupffer cells of the liver, lymphocytes, bone marrow cells, epithelial skin cells, and fibroblasts.

Sialidosis type II

Infants with sialidosis type II often have visual symptoms of the disorder at birth, including facial and skeletal abnormalities. Skeletal x-rays may be used to diagnose the dysostosis multiplex of this type of sialidosis.

Magnetic resonance imaging (MRI) may be used to determine brain atrophy.

Prenatal diagnosis

Sialidosis may be diagnosed prenatally. In at-risk fetuses, cultured fetal cells from the amniotic fluid, obtained by amniocentesis, or cultured chorionic villus cells, obtained by chorionic villus sampling in the early weeks of pregnancy, may be tested for neuraminidase activity. Since carriers of a single mutated *NEU1* gene do not have symptoms of neuraminidase deficiency, it may be difficult to recognize an at-risk fetus unless there is a family history of the disorder.

Treatment and management

At present, there is no treatment for sialidosis. Rather, attempts are made to manage individual symptoms. Myoclonic seizures in particular are very difficult to control. A study published in 2013, however, did report that some mutations associated with sialidosis type I may respond well to gene therapy specific to structure and function of lysosomes. This study was performed on mice models, indicative of the need for more research on this topic.

Prognosis

Individuals with sialidosis type I may have a near-normal life expectancy. However, the myoclonus may be progressively debilitating, and myoclonic seizures can be fatal. Children with neonatal-onset sialidosis type II usually are stillborn or die at a young age. Those with infantile-onset sialidosis type II rarely survive through adolescence.

Resources

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PERIODICALS

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WEBSITES

"Sialidosis." MedlinePlus. August 18, 2020. <https://medlineplus.gov/genetics/condition/sialidosis/> (accessed June 20, 2021).

"Sialidosis." NORD. <https://rarediseases.org/rare-diseases/sialidosis/> (accessed June 20, 2021).

ORGANIZATIONS

Canadian Society for Mucopolysaccharide and Related Diseases, #218-2055 Commercial Dr., Vancouver, BC Canada V5N 0C7, (604) 924-5130 or (800) 667-1846, info@mpssociety.ca, <http://www.mpssociety.ca>

National MPS Society, PO Box 14686, Durham, NC 27709-4686, (919) 806-0101 or (877) MPS-1001, info@mpssociety.org, <http://www.mpssociety.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

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Sickle cell disease

Definition

Sickle cell disease describes a group of inherited blood disorders characterized by chronic anemia, painful events, and various complications due to associated tissue and organ damage.

Description

The most common and well-known type of sickle cell disease is sickle cell anemia, also called SS disease. All types of sickle cell disease are caused by a genetic change in hemoglobin, the oxygen-carrying protein inside the red blood cells. The red blood cells of affected individuals contain a predominance of a structural variant of the usual adult hemoglobin. This variant hemoglobin, called sickle hemoglobin, has a tendency to develop into rod-like structures that alter the shape of the usually flexible red blood cells. The cells take on a shape that resembles the curved blade of a sickle, an agricultural tool. Sickle cells have a shorter lifespan than normally shaped red blood cells. This results in chronic anemia characterized by low levels of hemoglobin and decreased numbers of red blood cells. Sickle cells are also less flexible and more sticky than normal red blood cells, and can become trapped in small blood vessels, preventing blood flow. This compromises the delivery of oxygen, which can result in pain and damage to associated tissues and organs. Sickle cell disease presents with marked variability, even within families.

Demographics

Carriers of the sickle cell gene are said to have sickle cell trait. Unlike sickle cell disease, sickle cell trait does

not cause health problems. In fact, sickle cell trait is protective against malaria, a disease caused by blood-borne parasites transmitted through mosquito bites. According to a widely accepted theory, the genetic mutation associated with the sickle cell trait occurred thousands of years ago. Coincidentally, this mutation increased the likelihood that carriers would survive malaria infection. Survivors then passed the mutation on to their offspring, and the trait became established throughout areas where malaria was common. As populations migrated, so did the sickle cell trait. Today, approximately 1 in 12 African Americans has sickle cell trait.

It has been estimated that in the United States, 70,000 to 80,000 people have sickle cell disease. Sickle cell disease primarily affects people of African, Mediterranean, Middle Eastern, and eastern Indian ancestry. In the United States, sickle cell disease is most often seen in African Americans, in whom the disease occurs in 1 out of every 500 births. The disease has been described in individuals from several different ethnic backgrounds and is also seen with increased frequency in Latino Americans—particularly those of Caribbean, Central American, and South American ancestry. Approximately 1 in every 1,000–1,400 Latino births is affected.

Genetic profile

Humans normally make several types of the oxygen-carrying protein hemoglobin. An individual's stage in development determines whether he or she makes primarily embryonic, fetal, or adult hemoglobins. All types of hemoglobin are made of three components: heme, alpha (or alpha-like) globin, and beta (or beta-like) globin. Sickle hemoglobin is the result of a genetic change in the beta globin component of normal adult hemoglobin. The beta globin gene is located on chromosome 11. The sickle cell form of the beta globin gene results from the substitution of a single DNA nucleotide, or genetic building block. The change from adenine to thymine at codon (position) 6 of the beta globin gene leads to insertion of the amino acid valine—instead of glutamic acid—at this same position in the beta globin protein. As a result of this change, sickle hemoglobin has unique properties in comparison to the usual type of adult hemoglobin.

Most individuals have two normal copies of the beta globin gene, which make normal beta globin that is incorporated into adult hemoglobin. Individuals who have sickle cell trait (called sickle cell carriers) have one normal beta globin gene and one sickle cell gene. These individuals make both the usual adult hemoglobin and sickle hemoglobin in roughly equal proportions, so they do not experience any health problems as a result of having the trait. Although traces of blood in the urine and difficulty



The lower leg of this man has ulcerated tissue due to sickle cell anemia. (Sue Ford/Science Source)

in concentrating the urine can occur, neither represents a significant health problem as a result of sickle cell trait. Of the millions of people with sickle cell trait worldwide, a small handful of individuals have experienced acute symptoms. In these very rare cases, individuals were subject to very severe physical strain.

When both members of a couple are carriers of sickle cell trait, there is a 25% chance in each pregnancy for the baby to inherit two sickle cell genes and have sickle cell anemia, or SS disease. Correspondingly, there is a 50% chance the baby will have sickle cell trait and a 25% chance that the baby will have the usual type of hemoglobin.

Other types of sickle cell disease include SC disease, SD disease, and S/beta thalassemia. These conditions are caused by the co-inheritance of the sickle cell gene and another altered beta globin gene. For example, one parent may have sickle cell trait and the other parent may have hemoglobin C trait (another hemoglobin trait that does not cause health problems). For this couple, there would be a 25% chance of SC disease in each pregnancy.

Signs and symptoms

Normal adult hemoglobin transports oxygen from the lungs to tissues throughout the body. Sickle hemoglobin can also transport oxygen. However, once the oxygen is released, sickle hemoglobin tends to polymerize (line up) into rigid rods that alter the shape of the red blood cell. Sickling of the red blood cell can be triggered by low oxygen, such as occurs in organs with slow blood flow. It can also be triggered by cold temperatures and dehydration.

Sickle cells have a decreased lifespan in comparison to normal red blood cells. Normal red blood cells survive for approximately 120 days in the bloodstream; sickle cells last only 10–12 days. As a result, the bloodstream is chronically short of red blood cells and hemoglobin, and the affected individual develops anemia.

Sickle cells can create other complications. Due to their shape, they do not fit well through small blood vessels. As an aggravating factor, the outside surfaces of sickle cells may have altered chemical properties that increase the cells' "stickiness." These sticky sickle cells are more likely to adhere to the inside surfaces of small blood vessels, as well as to other blood cells. As a result of the sickle cells' shape and stickiness, blockages form in small blood vessels. Such blockages prevent oxygenated blood from reaching areas where it is needed, causing pain as well as organ and tissue damage.

The severity of symptoms cannot be predicted based solely on the genetic inheritance. Some individuals with sickle cell disease develop health- or life-threatening problems in infancy, but others may have only mild symptoms throughout their lives. Individuals may experience varying degrees of health at different stages in the life cycle. For the most part, this clinical variability is unpredictable, and the reasons for the observed variability cannot usually be determined. However, certain types of sickle cell disease (i.e., SC disease) tend to result in fewer and less severe symptoms on average than other types of sickle cell disease (i.e., SS disease). Some additional modifying factors are known. For example, elevated levels of fetal hemoglobin in a child or adult can decrease the quantity and severity of some symptoms and complications. Fetal hemoglobin is a normally occurring hemoglobin that usually decreases from more than 90% of the total hemoglobin to less than 1% during the first year of life. This change is genetically determined, although some individuals may experience elevated levels of fetal hemoglobin due to variation in the genes that control fetal hemoglobin production. Such individuals often experience a reduction in their symptoms and complications due to the ability of fetal hemoglobin to prevent the

polymerization of sickle hemoglobin, which leads to sickling of the red blood cell.

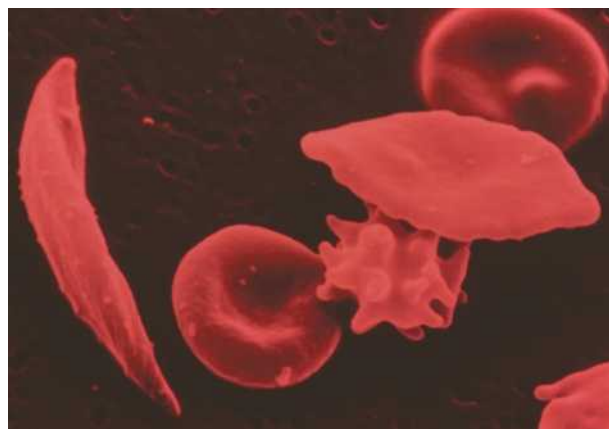
There are several symptoms that warrant immediate medical attention, including the following:

- signs of infection (fever 101°F or 38.3°C, frequent cough or breathing trouble, unusual crankiness, feeding difficulties)
- signs of severe anemia (pale skin or lips, yellowing of the skin or eyes, very tired, very weak)
- signs indicating possible dehydration (vomiting, diarrhea, fewer wet diapers)
- other signs (pain or swelling in the abdomen, swollen hands or feet, screams when touched).

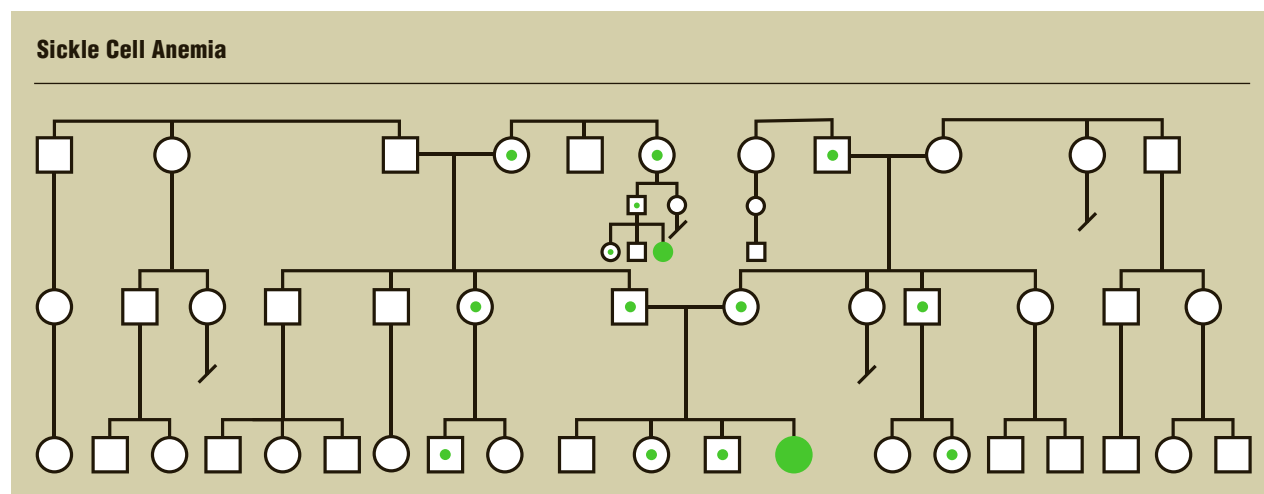
These can be signs of various complications that occur in sickle cell disease.

Infections and effects on the spleen

Children with sickle cell disease who are under age three are particularly prone to life-threatening bacterial infections. *Streptococcus pneumoniae* is the most common offending bacteria, and invasive infection from this organism leads to death in 15% of patients. The spleen, an organ that helps to fight bacterial infections, is particularly vulnerable to the effects of sickling. Sickle cells can impede blood flow through the spleen, causing organ damage, which usually results in loss of spleen function by late childhood. The spleen can also become enlarged due to blockages and/or increased activity of the spleen. Rapid enlargement of the spleen may be a sign of another complication called *splenic sequestration*, which occurs mostly in young children and can be life threatening. Widespread sickling in the spleen prevents adequate blood flow from the organ, removing increasing volumes



Colored scanning electron micrograph of a deformed red blood cell (left) taken from a person with sickle cell disease. (Jackie Lewin/Royal Free Hospital/Science Source)



Sickle cell anemia: pedigree analysis chart (Gale)

of blood from the circulation and leading to accompanying signs of severe anemia.

Painful events

Painful events, also known as *vaso-occlusive events*, are a hallmark symptom of sickle cell disease. The frequency and duration of the pain can vary tremendously from person to person and over an individual's life cycle. Painful events are the most common cause of hospitalizations in sickle cell disease. However, only a small portion of individuals with sickle cell disease experience frequent and severe painful events. Most painful events can be managed at home. Pain results when small blood vessel blockages prevent oxygen from reaching tissues. Pain can affect any area of the body, although the extremities, chest, abdomen, and bones are frequently affected sites. There is some evidence that cold temperatures or infection can trigger a painful event, but most events occur for unknown reasons. The hand-foot syndrome, or *dactylitis*, is a particular type of painful event. Most common in toddlers, dactylitis results in pain and swelling in the hands and feet, sometimes accompanied by a fever.

Anemia

Sickle cells have a high turnover rate leading to a deficit of red blood cells in the bloodstream. Common symptoms of anemia include fatigue, paleness, and a shortness of breath. A particularly severe form of anemia—aplastic anemia—occurs following infection with parvovirus. Parvovirus causes extensive destruction of the bone marrow, bringing production of new red blood cells to a halt. Bone marrow production resumes after seven to ten days; however, given the short lives of sickle

cells, even a brief shutdown in red blood cell production can cause a rapid decline in hemoglobin concentrations.

Delayed growth

The energy demands of the bone marrow for red blood cell production compete with the demands of a growing body. Children with sickle cell anemia may have delayed growth and reach puberty at a later age than normal. By early adulthood, they catch up on growth and attain normal height; however, weight typically remains below average.

Stroke

Children with sickle cell disease have a significantly elevated risk of having a stroke, which can be one of the most concerning complications of sickle cell disease. Approximately 11% of individuals with sickle cell disease will have a recognizable stroke by the age of 20. Magnetic resonance imaging studies have found that 17% of children with sickle cell anemia have evidence of a previous stroke or clinically “silent” stroke-like events called *transient ischemic events*. Stroke in sickle cell disease is usually caused by a blockage of a blood vessel, but about one-quarter of the time may be caused by a hemorrhage (or rupture) of a blood vessel.

Strokes result in compromised delivery of oxygen to an area of the brain. The consequences of stroke can range from life threatening, to severe physical or cognitive impairments, to apparent or subtle learning disabilities, to undetectable effects. Common stroke symptoms include weakness or numbness that affects one side of the body, sudden behavioral changes, loss of vision, confusion, loss of speech or the ability to understand spoken

KEY TERMS

Amino acid—Organic compounds that form the building blocks of protein. There are 20 types of amino acids (eight are “essential amino acids” which the body cannot make and must therefore be obtained from food).

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Bilirubin—A yellow pigment that is the end result of hemoglobin breakdown. This pigment is metabolized in the liver and excreted from the body through the bile. Bloodstream levels are normally low; however, extensive red cell destruction leads to excessive bilirubin formation and jaundice.

Bone marrow—A spongy tissue located in the hollow centers of certain bones, such as the skull and hip bones. Bone marrow is the site of blood cell generation.

Bone marrow transplantation—A medical procedure used to treat some diseases that arise from defective blood cell formation in the bone marrow. Healthy bone marrow is extracted from a donor to replace the marrow in an ailing individual. Proteins on the surface of bone marrow cells must be identical or very closely matched between a donor and the recipient.

Globin—One of the component protein molecules found in hemoglobin. Normal adult hemoglobin has a pair each of alpha-globin and beta-globin molecules.

Heme—The iron-containing molecule in hemoglobin that serves as the site for oxygen binding.

Hemoglobin—Protein-iron compound in the blood that carries oxygen to the cells and carries carbon dioxide away from the cells.

Hemoglobin A—Normal adult hemoglobin that contains a heme molecule, two alpha-globin molecules, and two beta-globin molecules.

Hemoglobin electrophoresis—A laboratory test that separates molecules based on their size, shape, or electrical charge.

Hemoglobin S—Hemoglobin produced in association with the sickle cell trait; the beta-globin molecules of hemoglobin S are defective.

Hydroxyurea—A drug that has been shown to induce production of fetal hemoglobin. Fetal hemoglobin has a pair of gamma-globin molecules in place of the typical beta-globins of adult hemoglobin. Higher-than-normal levels of fetal hemoglobin can prevent sickling from occurring.

Impotence—The inability to have a penile erection, which can be due to tissue damage resulting from sickling within the penis (priapism).

Iron overload—A side effect of frequent blood transfusions in which the body accumulates abnormally high levels of iron. Iron deposits can form in organs, particularly the heart, and cause life-threatening damage.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Narcotics—Strong prescription medication that can be effective in treating pain, but have the potential to be habit-forming if their use is not supervised correctly.

Nucleic acid—A type of chemical used as a component for building DNA. The nucleic acids found in DNA are adenine, thymine, guanine, and cytosine.

Ophthalmology—The medical specialty of vision and the eye.

Placenta—The organ responsible for oxygen and nutrition exchange between a pregnant mother and her developing baby.

Red blood cell—Hemoglobin-containing blood cells that transport oxygen from the lungs to tissues. In the tissues, the red blood cells exchange their oxygen for carbon dioxide, which is brought back to the lungs to be exhaled.

Screening—Process through which carriers of a trait may be identified within a population.

Sickle cell—A red blood cell that has assumed an elongated shape due to the presence of hemoglobin S.

words, dizziness, headache, seizures, vomiting, or even coma.

Approximately two-thirds of the children who have a stroke will have at least one more. Transfusions have been shown to decrease the incidence of a second stroke. A recent study showed that children at highest risk to experience a first stroke were ten times more likely to stroke if untreated when compared to high-risk children treated with chronic blood transfusion therapy. High-risk children were identified using transcranial Doppler ultrasound technology to detect individuals with increased blood flow speeds due to constricted intracranial blood vessels.

Acute chest syndrome

Acute chest syndrome (ACS) is a leading cause of death for individuals with sickle cell disease, and recurrent attacks can lead to permanent lung damage. Therefore, rapid diagnosis and treatment is of great importance. ACS can occur at any age and is similar but distinct from pneumonia. Affected persons may experience fever, cough, chest pain, and shortness of breath. ACS seems to have multiple causes including infection, sickling in the small blood vessels of the lungs, fat embolisms in the lungs, or a combination of factors.

Priapism

Males with sickle cell anemia may experience priapism, a condition characterized by a persistent and painful erection of the penis. Due to blood vessel blockage by sickle cells, blood is trapped in the tissue of the penis. Priapism may be short in duration or it may be prolonged. Priapism can be triggered by low oxygen (hypoxemia), alcohol consumption, or sexual intercourse. Since priapism can be extremely painful and result in damage to this tissue causing impotence, rapid treatment is essential.

Kidney disease

The environment in the kidney is particularly prone to damage from sickle cells. Signs of kidney damage can include blood in the urine, incontinence, and enlarged kidneys. Adults with sickle cell disease often experience insufficient functioning of the kidneys, which can progress to kidney failure in a small percentage of adults with sickle cell disease.

Jaundice and gallstones

Jaundice is indicated by a yellow tone in the skin and eyes, and alone it is not a health concern. Jaundice may occur if bilirubin levels increase, which can occur with high levels of red blood cell destruction. Bilirubin is the final product of hemoglobin degradation, and is typically removed from the bloodstream by the liver. Therefore,

jaundice can also be a sign of a poorly functioning liver, which may also be evidenced by an enlarged liver. Increased bilirubin also leads to increased chance for gallstones in children with sickle cell disease. Treatment, which may include removal of the gall bladder, may be selected if the gallstones start causing symptoms.

Retinopathy

The blood vessels that supply oxygen to the retina—the tissue at the back of the eye—may be blocked by sickle cells, leading to a condition called retinopathy. This is one of the only complications that is actually more common in SC disease as compared to SS disease. Retinopathy can be identified through regular ophthalmology evaluations and effectively treated in order to avoid damage to vision.

Joint problems

Avascular necrosis of the hip and shoulder joints, in which bone damage occurs due to compromised blood flow due to sickling, can occur later in childhood. This complication can affect an individual's physical abilities and result in substantial pain.

Diagnosis

Inheritance of sickle cell disease or trait cannot be prevented, but it may be predicted. Screening is recommended for individuals in high-risk populations. In the United States, African Americans and Latino Americans have the highest risk of having the disease or trait. Sickle cell is also common among individuals of Mediterranean, Middle Eastern, and Eastern Indian descent.

A complete blood count (CBC) will describe several aspects of an individual's blood cells. A person with sickle cell disease will have a lower than normal hemoglobin level, together with other characteristic red blood cell abnormalities. A hemoglobin electrophoresis is a test that can help identify the types and quantities of hemoglobin made by an individual. This test uses an electric field applied across a slab of gel-like material. Hemoglobins migrate through this gel at various rates and to specific locations, depending on their size, shape, and electrical charge. Although sickle hemoglobin (Hb S) and regular adult hemoglobin (called Hb A) differ by only one amino acid, they can be clearly separated using hemoglobin electrophoresis. Isoelectric focusing and high-performance liquid chromatography (HPLC) use similar principles to separate hemoglobins and can be used instead of or in various combinations with hemoglobin electrophoresis to determine the types of hemoglobin present.

Another test, called the sickledex, can help confirm the presence of sickle hemoglobin, although this test

cannot provide accurate or reliable diagnosis when used alone. When Hb S is present, but there is an absence or only a trace of Hb A, sickle cell anemia is a likely diagnosis. Additional beta globin DNA testing, which looks directly at the beta globin gene, can be performed to help confirm the diagnosis and establish the exact genetic type of sickle cell disease. CBC and hemoglobin electrophoresis are also typically used to diagnose sickle cell trait and various other types of beta globin traits.

Diagnosis of sickle cell disease can occur under various circumstances. If an individual has symptoms that are suggestive of this diagnosis, the above-described screening tests can be performed followed by DNA testing, if indicated. Screening at birth using HPLC or a related technique offers the opportunity for early intervention. More than 40 states include sickle cell screening as part of the usual battery of blood tests done for newborns. This allows for early identification and treatment. Hemoglobin trait screening is recommended for any individual of a high-risk ethnic background who may be considering having children. When both members of a couple are found to have sickle cell trait, or other related hemoglobin traits, they can receive genetic counseling regarding the risk of sickle cell disease in their future children and various testing options.

Sickle cell disease can be identified before birth through the use of prenatal diagnosis. Chorionic villus sampling (CVS) can be offered as early as ten weeks of pregnancy and involves removing a sample of the placenta made by the baby and testing the cells. CVS carries a risk of causing a miscarriage that is between one-half to one percent.

Amniocentesis is generally offered between 16 and 18 weeks of pregnancy, but can sometimes be offered earlier. Two to three tablespoons of the fluid surrounding the baby is removed. This fluid contains fetal cells that can be tested. This test carries a risk of causing a miscarriage, which is less than 1%. Pregnant women and couples may choose prenatal testing in order to prepare for the birth of a baby that may have sickle cell disease.

Preimplantation genetic diagnosis (PGD) is a relatively new technique that involves in vitro fertilization followed by genetic testing of one cell from each developing embryo. Only the embryos unaffected by sickle cell disease are transferred back into the uterus. PGD is currently available on a research basis only, and is relatively expensive.

Treatment and management

There are several practices intended to prevent some of the symptoms and complications of sickle cell disease. These include preventive antibiotics, good hydration,

QUESTIONS TO ASK YOUR DOCTOR

- What are the risks and benefits of having a prenatal screening for sickle cell anemia?
- If my wife is a carrier of the gene for sickle cell anemia, what is the probability that one of our children will develop the disease?
- What is the genetic basis for sickle cell anemia?
- What is the status of current research on sickle cell anemia, and is a cure for the disease in the foreseeable future?

immunizations, and access to comprehensive care. Maintaining good health through adequate nutrition, avoiding stresses and infection, and getting proper rest is also important. Following these guidelines is intended to improve the health of individuals with sickle cell disease.

Penicillin

Infants are typically started on a course of penicillin that extends from infancy to age six. Use of this antibiotic is meant to ward off potentially fatal infections. Infections at any age are treated aggressively with antibiotics. Vaccines for common infections, such as pneumococcal pneumonia, are also recommended.

Pain management

Pain is one of the primary symptoms of sickle cell anemia, and controlling it is an important concern. The methods necessary for pain control are based on individual factors. Some people can gain adequate pain control through over-the-counter oral painkillers (analgesics). Other individuals, or painful events, may require stronger methods, which can include administration of narcotics. Alternative therapies may be useful in avoiding or controlling pain, including relaxation, hydration, avoiding extremes of temperature, and the application of local warmth.

Blood transfusions

Blood transfusions are not usually given on a regular basis but are used to treat individuals with frequent and severe painful events, severe anemia, and other emergencies. In some cases blood transfusions are given as a preventive measure, for example to treat spleen enlargement or prevent a second stroke (or a first stroke in an individual shown to be at high risk).

Regular blood transfusions have the potential to decrease formation of hemoglobin S, and reduce associated symptoms. However, there are limitations and risks associated with regular blood transfusions, including the risk of blood-borne infection and sensitization to proteins in the transfused blood that can make future transfusions very difficult. Most importantly, chronic blood transfusions can lead to iron overload. The body tends to store excess iron, such as that received through transfusions, in various organs. Over time, this iron storage can cause damage to various tissues and organs, such as the heart and endocrine organs.

Some of this damage can be prevented by the administration of a medication called desferoxamine that helps the body eliminate excess iron through the urine. Alternately, some individuals receive a new, nonstandard treatment called erythrocytapheresis. This involves the automated removal of sickle cells and is used in conjunction with a reduced number of regular transfusions. This treatment helps to reduce iron overload.

Hydroxyurea

Emphasis is being placed on developing drugs that treat sickle cell anemia directly. The most promising of these drugs since the late 1990s has been hydroxyurea, a drug that was originally designed for anticancer treatment. Hydroxyurea has been shown to reduce the frequency of painful crises and acute chest syndrome in adults, and to lessen the need for blood transfusions. Hydroxyurea, and other related medications, seem to work by inducing a higher production of fetal hemoglobin. The major side effects of the drug include decreased production of platelets, red blood cells, and certain white blood cells. The effects of long-term hydroxyurea treatment are unknown.

Bone marrow transplantation

Bone marrow transplantation has been shown to cure sickle cell anemia in some cases. This treatment is reserved primarily for severely affected children with a healthy donor whose marrow proteins match those of the recipient, namely a brother or sister who has inherited the same tissue type. Indications for a bone marrow transplant are stroke, recurrent acute chest syndrome, and chronic unrelieved pain.

Bone marrow transplantations tend to be the most successful in children; adults have a higher rate of transplant rejection and other complications. There is approximately a 10% fatality rate associated with bone marrow transplants done for sickle cell disease. Survivors face potential long-term complications, such as chronic graft-versus-host disease (an immune-mediated attack by

the donor marrow against the recipient's tissues), infertility, and development of some forms of cancer. A relatively recent advance in transplantation involves the use of donor stem cells obtained from cord blood, the blood from the placenta that is otherwise discarded following the birth of a new baby. Cord blood cells, as opposed to fully mature bone marrow cells, appear to be less likely to result in graft-versus-host disease in the recipient. This increases the safety and efficacy of the transplant procedure.

Surgery

Certain surgical interventions are utilized in the treatment of specific sickle cell-related complications. Removal of a dysfunctional gallbladder or spleen can often lead to improvements in health. Investigations are currently under way to establish the efficacy of hip coring surgery, in which a portion of affected bone is removed to treat avascular necrosis of the hip. The hope is that this may provide an effective treatment to alleviate some pain and restore function in the affected hip.

Psychosocial support

As in any lifelong, chronic disease, comprehensive care is important. Assistance with the emotional, social, family-planning, economic, vocational, and other consequences of sickle cell disease can enable affected individuals to better access and benefit from their medical care.

Prognosis

Sickle cell disease is characteristically variable between and within affected individuals. Predicting the course of the disorder based solely on genes is not possible. Several factors aside from genetic inheritance determine the prognosis for affected individuals, including the frequency, severity, and nature of specific complications in any given individual. The availability and access of comprehensive medical care also plays an important role in preventing and treating serious, acute complications, which cause the majority of sickle cell-related deaths. For those individuals who do not experience such acute events, life-expectancy is probably substantially greater than the average for all people with sickle cell disease. The impact of recent medical advances supports the hypothesis that current life expectancies may be significantly greater than those estimated in the early 1990s. At that time, individuals with SS disease lived to the early- to mid-40s, and those with SC disease lived into the upper 50s on average. With early detection and comprehensive medical care, most people with sickle cell disease are in fairly good health most of the time. Most individuals can be expected to live well into adulthood,

enjoying an improved quality of life including the ability to choose a variety of education, career, and family-planning options for themselves.

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Sickle Cell Disease Association of America, Inc, 3700 Koppers St., Suite 570, Baltimore, MD 21227, (800) 421-8453, scdaa@sicklecelldisease.org, <http://sicklecelldisease.org>.

Jennifer Bojanowski, MS, CGC

Silver-Russell syndrome see **Russell-Silver syndrome, Primordial dwarfism**

Simpson dysmorphia syndrome (SDYS) see **Simpson-Golabi-Behmel syndrome**

Simpson-Golabi-Behmel syndrome

Definition

Simpson-Golabi-Behmel syndrome (SGBS) is a rare X-linked recessive inherited condition. It causes general

overgrowth in height and weight. Individuals with SGBS also have characteristic facial features in childhood that tend to become less obvious in adulthood.

Description

SGBS is also known as Simpson dysmorphia syndrome (SDYS), bulldog syndrome, Golabi-Rosen syndrome, and dysplasia gigantism syndrome X-linked (DGSX). SGBS is a rare X-linked recessive inherited condition. Individuals with this condition have increased height and weight for their age; a broad, stocky appearance; a large protruding jaw; a short, broad nose; incomplete closure of the roof of the mouth (cleft palate); and broad, short hands and fingers. Individuals with SGBS are usually taller than average. The characteristic features usually become less apparent in adulthood. There are at least two genes for SGBS. Both genes are located on the X chromosome.

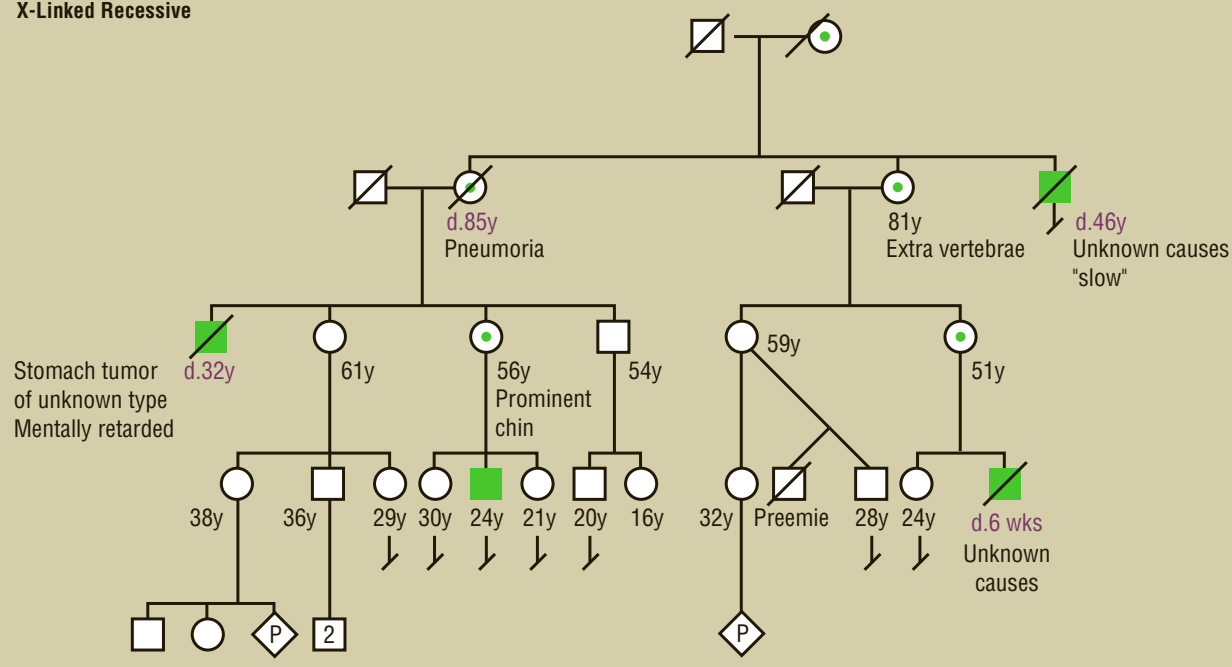
Genetic profile

SGBS is caused by an alteration (mutation) in one of two genes on the X chromosome. Chromosomes are units of hereditary material passed from a parent to a child through the egg and sperm. The information on the chromosomes is organized into units called genes. Genes contain information necessary for normal human growth and development. Each cell in the body usually contains 46 chromosomes, arranged as 23 pairs. Twenty-two pairs of chromosomes are the same in males and females. The twenty-third pair is the sex chromosomes: females have two X chromosomes and males have an X and a Y chromosome. There are two genes on the X chromosome that can cause SGBS. The first gene is responsible for making a protein called glypican-3 (GPC3). The exact role of GPC3 is not known but it is thought to play a role in growth and development. When the gene for GPC3 is altered, the signs and symptoms of SGBS result. A second candidate gene, which causes a more severe form of SGBS, is also located on the X chromosome. The function of this second gene is not known. Generally, individuals who have SGBS due to a gene alteration in the *GPC3* gene are said to have SGBS type 1 (SGBS1) and individuals who have SGBS due to an alteration in the second gene on the X chromosome are said to have SGBS type 2 (SGBS2).

SGBS is inherited as an X-linked recessive condition. With X-linked recessive conditions, males are usually more severely affected than females. Females have two copies of the *SGBS* gene (because they have two X chromosomes) while males have one copy of the *SGBS* gene (because they have one X chromosome). Females who have an alteration in one copy of the *SGBS* gene are said to be carriers of

Simpson-Golabi-Behmel Syndrome

X-Linked Recessive



Simpson-Golabi-Behmel syndrome: pedigree analysis chart (Gale)

SGBS. Generally, carriers show minimal or no effects of the altered gene because they have a second normal copy of the gene that is able to compensate for the altered copy. Since males have only one working copy of the *SGBS* gene to start, if that gene is altered, they will develop SGBS. When carrier females have children, they are at risk to have a child with SGBS. In each pregnancy, carrier females have a 25% chance of having a child (always a son) with SGBS and a 25% chance of having a child (always a daughter) whom is a carrier of SGBS. Males who are affected with SGBS cannot pass this condition to their sons (because their sons inherit the Y chromosome); however, all daughters of a male affected with SGBS will be carriers for the condition.

Demographics

SGBS is a rare inherited condition that primarily affects males from all ethnic groups. Female carriers for SGBS may show subtle features of the condition. The exact prevalence of SGBS remained unknown as of 2015, by which time only 130 people globally had been diagnosed with the condition.

Signs and symptoms

The spectrum of clinical features in SGBS is broad, ranging from very mild forms in carrier females to forms

that are lethal in the newborn male. SGBS affects the face, hands, chest, abdomen, genitals, internal organs, and overall growth.

Individuals with SGBS are larger than average at birth in height, weight, and head size. This overgrowth continues into adulthood, with affected males being taller than average. Final height in males ranges from 74 in. to 83 in. (188 cm to 210 cm). There are typical facial characteristics in affected males including widely spaced eyes, short nose, large mouth, large tongue, a groove in the lower lip, and teeth that do not align properly. Incomplete closure of the lip (cleft lip) and/or the roof of the mouth (cleft palate) can also occur. The large tongue and improperly aligned teeth can be a cause of speech difficulties.

The hands and feet of males with SGBS tend to be short and broad. Other hand abnormalities such as small nails, webbing of the skin between the fingers, and extra fingers/toes, is also common. Males with SGBS have extra nipples and some may have undescended testicles.

The internal organs are larger than average, particularly the liver, spleen, and kidneys. The kidneys may also have many cysts on them. A few individuals have been known to have lung and diaphragm abnormalities. Heart abnormalities can also occur in SGBS1 and have been a

cause of death in several individuals under two years of age. These include conduction defects causing arrhythmias. The stomach and intestines can also be affected, which may cause digestive problems. The bones may also be affected. Some individuals have an abnormal curving and twisting of the spine (scoliosis), extra ribs, and/or problems with the structure of the bones of the spine. The bony changes can be seen on x-ray but may not cause any symptoms.

Despite their large size, newborns with SGBS tend to be floppy babies with decreased muscle tone. Due to this low muscle tone, there are several features that can result such as mouth breathing, a deformity of the chest wall (pectus excavatum), shoulders that droop, hernias, and undescended testicles.

There is an increased risk to develop tumors of the kidney (Wilms tumor) in SGBS in early childhood. This risk appears to be greatest in individuals under two years of age.

Most individuals with SGBS are of average intelligence, although some degree of mental impairment has been observed in males who are more severely affected. Individuals with SGBS may have psychological difficulties dealing with their distinctive facial appearance and speech difficulties, which often give the false impression that they are mentally impaired.

Diagnosis

The diagnosis of SGBS is based on the presence of certain clinical features and in some cases may be confirmed through genetic testing. Not all affected individuals will have all of the features associated with SGBS. SGBS should be considered in an individual who is large in height, weight, and head circumference both before and after birth. Features of the condition that are almost always present include overgrowth, extra nipples, chest deformity, low muscle tone, and characteristic facial features including widely spaced eyes, short nose, large tongue and mouth, central groove of the lower lip, and improperly aligned teeth.

It may be possible to confirm the diagnosis of SGBS through genetic testing. Genetic testing for mutations in the *GPC3* gene causing SGB1 is available. Genetic testing involves obtaining a blood sample from the affected individual in order to look for the specific disease-causing mutation in the *GPC3* gene. Since not all individuals with SGBS have mutations in the *GPC3* gene, it may not be possible to confirm the diagnosis through genetic testing in all individuals suspected of having this condition. Genetic testing for the SGBS can be done on the developing baby before birth through amniocentesis or chorionic villus sampling if a mutation in the gene for

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the early embryo. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

GPC3 is first identified in an affected family member. Prenatal testing for parents of an affected individual should only be undertaken after the SGBS carrier status of the parents has been confirmed and the couple has been counseled regarding the risks of recurrence.

Treatment and management

The heart function of individuals with SGBS should be carefully monitored because it can be a cause of early death. Individuals with SGBS should be regularly followed by a heart specialist (cardiologist).

Individuals with SGBS are at increased risk to develop kidney tumors. They should be screened for possible kidney tumor development or other tumors of infancy for at least the first five years of life. Screening usually involves an ultrasound (sound wave picture) of the abdomen, including the kidneys.

The large tongue and improperly aligned teeth may lead to speech difficulties. Some individuals may require surgery to reduce the size of the tongue to aid with speech development or for cosmetic reasons. Individuals with speech difficulties may benefit from speech therapy.

QUESTIONS TO ASK YOUR DOCTOR

- What signs and symptoms are characteristic of Simpson-Golabi-Behmel syndrome?
- What information about Simpson-Golabi-Behmel syndrome can a genetic counselor provide me?
- What is the projected lifespan for an infant diagnosed with Simpson-Golabi-Behmel syndrome, and what factors affect that prognosis?
- Where can I obtain additional information about this genetic disorder?

Individuals with SGBS may benefit from psychological support and social support to help them reach an adequate level of self-esteem. They may also benefit from genetic counseling, which may provide them with further information on the condition itself and recurrence risks for future pregnancies.

Prognosis

The spectrum of clinical manifestations in SGBS is broad, varying from very mild forms in carrier females to infantile lethal forms in affected males. As many as 50% of males affected with SGBS die in the newborn period. The cause of this high mortality is not known but may be related to heart defects. In one reported family with a severe form of SGBS causing death in the newborn period, the responsible gene was not glypican-3 but the second candidate gene on the X chromosome.

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National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, <http://www.rarediseases.org>

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Single genome sequencing

Definition

Single genome sequencing is an efficient method of sequencing the DNA of a single cell. Single genome sequencing is used to determine the variance between the cells of an individual and the cells of the norm for the indication of genetic-related pathologies such as cancers and autoimmune diseases.

Description

Since the completion of the Human Genome Project, more and more genome studies have been performed. The Human Genome Project mapped the blueprint of the code of human DNA (deoxyribonucleic acid). Any possible variance in a person's DNA can now be sequenced and compared to the normal genome, which can lead to an increased number of correct diagnoses, more effective treatment methods, and a better understanding of the relationship between DNA and genes and the interrelationship between genes themselves. As the need for information about and understanding of the human genome increases, so does the need for more time-efficient, cost-effective, and accurate methods of sequencing. Such methods include whole genome sequencing, next-generation sequencing, genome-wide association studies, Sanger sequencing (an older method), and a newer method known as single genome sequencing. These are all methods of sequencing that amplify DNA of cells, typically from blood or saliva, to determine the sequence of nucleotides that make up a string of DNA. This sequence is then compared to a normal sequence, and any variation can be linked to certain genes. Thus, an alteration in the structure or function of the human body can be pathologically identified.

Single genome sequencing is the sequencing of the genome of one cell using linear amplification. This

decreases the amount of bias that may arise in the non-linear sequencing seen in other sequencing methods and in turn increases the accuracy of the sequencing. Being able to sequence a single genome—the genome of a single cell—is extremely important in prenatal testing, when the zygote is only made up of a small number of cells relative to the size of a full-term fetus; for meiosis research; for the sequencing of a small number of tumor cells to determine possible treatment options; for studying the pathogenesis of cancer; and for testing a small amount of DNA in forensic analysis.

Studies have been done on mouse models between the three germ layers of the developing embryo with very good results. In the future this could prove instrumental for the sequencing of human embryos, as well as for further understanding of germ layers in embryology and potential genetic testing at early gestation. Single genome sequencing is also being used for assessing the frequency of drug resistance in patients with HIV-1. In addition to the use of single cell genome sequencing in the human body, single cell sequencing has also proven useful for the study of smaller organisms such as bacteria and archaea. Sequencing organisms such as these can give scientists a much better understanding on how they live and interact and of the evolutionary linkage between organisms.

Techniques

Single genome sequencing is currently performed using a technique developed in 2012 by Harvard University chemical biologist Sunney Xie and is termed MALBAC, which stands for multiple annealing and looping-based amplification cycles. MALBAC was developed after the false-positive and/or false-negative rates of previous methods such as single-nucleotide sequencing (SNS) were found to be too high due to high bias and the evaluation of incorrect strands of mRNA. Multiple displacement amplification (MDA), like MALBAC, was developed based on the mistakes of SNS.

A 2014 study investigated the differences between MALBAC and MDA and determined that MALBAC is the most useful technique because it has less bias and more coverage of the genome, making it the current technique of choice. MALBAC replicates a strand of DNA using color-coded primers (a separate primer for all four nucleotides—adenine, guanine, cytosine, and thymine). These primers are then separated by weight using a gel electrophoresis method to determine the sequence of the strand of DNA. This is typical of most genome sequencing methods. The single genome sequencing method differs from other methods because of the use of primers with two parts. The first part is an 8-nucleotide sequence that binds to the DNA being examined, starting the

KEY TERMS

Chromosome—A microscopic thread-like structure found within each cell of the body and consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

De novo mutation—A genetic mutation that is seen for the first time in the affected person, not inherited from the parents.

DNA—Deoxyribonucleic acid, the main component in chromosomes and the substance that carries all genetic material.

Gene sequencing—The process of mapping the order of DNA or genetic material in an organism.

Genome—The entire DNA sequence of a cell or organism.

Human Genome Project—An international effort begun in 1990 and completed in 2003 to locate and identify the 100,000 genes on the 46 human chromosomes.

Nucleotide—A small molecule composed of three parts: a nitrogen base (a purine or pyrimidine), a sugar (ribose or deoxyribose), and phosphate; they serve as the building blocks of nucleic acids (DNA and RNA).

replication process, and the second part of the primer is a 27-nucleotide sequence with stop codons (a portion of the sequence that tells the DNA to stop replicating). The stop sequence cuts down on the amount of replications performed, decreasing the amount of time needed for the sequencing and also causing the DNA to loop back on itself. This prevents overcopying and major amplification and, therefore, makes it faster and easier to determine the sequence of the DNA being examined because only one original DNA sequence is replicated and coded. MALBAC is also used to see how quickly mutations accumulate, and the technique can determine variations in genes and chromosomes in the cells of an individual, helping researchers to understand *de novo* and other types of mutations and their impact on certain cells.

The MALBAC technique is an efficient technique for single genome sequencing, but it does have some drawbacks. The technique, although it allows for the most amount of duplication compared to other sequencing techniques (at 93%), only detects 66% of single-

nucleotide variants. In addition, the primer is error prone, potentially copying the original DNA incorrectly and presenting an increased number of single-nucleotide variants, such as in the event of a false positive. This is due to the fact that each cell has thousands of copies of each mRNA molecule but only two chromosomes.

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ORGANIZATIONS

- National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Dr., MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, <https://www.genome.gov/about-nhgri/Contact>

Taryn Terry, DC

Sirenomelia

Definition

Sirenomelia is a lethal birth defect of the lower body characterized by apparent fusion of the legs into a single lower limb. Other birth defects are always associated with sirenomelia, most commonly abnormalities of the kidneys, large intestines, and genitalia.

Description

This pattern of birth defects is believed to be associated with abnormal umbilical cord blood vessels. The normal fetus develops two umbilical arteries, which pump blood from the fetus to the placenta, and one umbilical vein, which returns blood from the placenta to the fetus. The umbilical arteries branch off the iliac

arteries in the pelvis. The iliac arteries supply the legs and pelvic organs such as the genitalia. Most babies with sirenomelia have only one umbilical artery and one vein. Rarely, a baby with sirenomelia can have the typical two arteries and one vein with occlusion (blockage) of one artery.

In sirenomelia, the one functional artery is larger than normal and branches from the aorta high in the abdomen. Below this umbilical artery, the aorta becomes abnormally narrow. This type of single umbilical artery is known as a vitelline artery because it is thought to arise from the primitive vitelline arteries early in the life of the embryo. The vitelline arteries normally fuse a few weeks after conception to form the arteries that supply the gastrointestinal system and genitourinary system (superior mesenteric, inferior mesenteric, and celiac arteries). If the normal umbilical arteries do not form correctly as branches from the iliac arteries, then a vitelline artery might persist.

The vitelline umbilical artery steals blood and nutrition from the lower body and diverts it to the placenta. This results in a small aorta and variable absence of the arteries that supply the kidneys, large intestine, and genitalia (renal, inferior mesenteric, and celiac arteries). Because of the loss of nutrition and blood flow, the lower limbs fail to form as separate limbs, the kidneys do not form or are malformed, the large intestine ends blindly in the abdominal cavity, the anus is imperforate, and the internal and external genitalia are absent or malformed.

The typical malformation of the lower limbs seen in babies with sirenomelia consists of apparent fusion of the legs. There is a spectrum of severity, with severe cases having one lower limb that tapers to a point with the absence of foot structures. In these severe cases there are only two bones present in the entire limb (a femur and presumably a tibia). On the mild end of the spectrum are babies with fusion of the skin of the lower limbs only. In these infants the feet may be fully formed with fusion at the ankles. All bones are fully formed and separate. Normally there are three bones in each leg—the femur in the upper leg (thigh) and the tibia and fibula in the lower leg (calf).

Other birth abnormalities of the upper body involving the heart, lungs, spine, brain, and arms can also be seen in this syndrome, but not in every affected individual. It is unknown at this time why a single umbilical artery could cause these changes.

Single umbilical artery occurs in about 1% of all live-born infants. In most of these infants the one umbilical artery is normally formed and not of vitelline origin. In these cases, the risk of other birth defects is low (about 8%). All infants born with a vitelline umbilical artery will

have other malformations, the most common being sirenomelia.

Genetic profile

All cases of sirenomelia have occurred in families as isolated cases, and there is no known genetic cause. It is possible that sirenomelia is an autosomal dominant condition and because it is lethal, all cases represent a new mutation. Alternatively, it might be a multifactorial trait in which multiple genes and environmental factors come together to cause this pattern of malformations. The fact that all cases have been isolated does not support this possibility. Sirenomelia is more common in monozygotic (identical) twin pregnancies. This may be indicative of an environmental cause.

Demographics

Sirenomelia is very rare, estimated to occur once in every 60,000 to 100,000 births. While the exact incidence in different populations is not known, sirenomelia has been reported worldwide in a variety of ethnic groups. It is known to be more common in monozygotic twin pregnancies (when compared to dizygotic (fraternal) twins) and in babies born to mothers with diabetes mellitus.

Signs and symptoms

Abnormalities associated with sirenomelia include the following:

- absence of the kidneys or malformed nonfunctioning kidneys
- blind ending colon and imperforate anus
- small, absent, fused, or poorly formed pelvic bones
- small, absent, or poorly formed internal and external genitalia
- fusion of the lower limbs along the inner leg, from skin only to complete fusion with the appearance of only one leg
- death from underdeveloped and immature lungs caused by oligohydramnios
- occasional birth defects in the upper body, including abnormalities in the heart, lungs, arms, spine, and brain

Diagnosis

The diagnosis is obvious at birth on examination of a baby, but prenatal diagnosis often occurs in the second trimester (weeks 13 through 26 of a pregnancy) by an ultrasound.

KEY TERMS

Aorta—The main artery located above the heart that pumps oxygenated blood out into the body. Many congenital heart defects affect the aorta.

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a nonsex chromosome is required for a disease or inherited trait to develop in an individual.

Iliac arteries—Arteries that supply blood to the lower body including the pelvis and legs.

Imperforate anus—Also known as anal atresia. A birth defect in which the opening of the anus is absent or obstructed.

Mermaid syndrome—Alternate name for sirenomelia, often used in older references.

Mutation—An inherited or de novo change in the DNA sequence of the genome.

Oligohydramnios—Reduced amount of amniotic fluid. Causes include nonfunctioning kidneys and premature rupture of membranes. Without amniotic fluid to breathe, a baby will have underdeveloped and immature lungs.

Stillbirth—The birth of a baby who has died sometime during the pregnancy or delivery.

Teratogenic—Any agent that can cause birth defects or intellectual disability in a developing fetus. Common teratogens are medications or other chemicals, but they also include infections, radiation, maternal medical condition, and other agents.

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.

Treatment and management

Babies born alive with functioning kidneys may survive with appropriate surgical management. Operations to reconstruct the urinary and gastrointestinal outlet tracts are almost always needed. Other procedures and treatments depend on the extent of other birth defects. It appears that if a baby does survive, he or she will not have any mental delays.

Prognosis

Because of the birth defects involving the gastrointestinal tract and kidneys, sirenomelia is almost always fatal. About 50% of babies are stillborn (the baby has died before delivery) and 50% are live-born with survival

QUESTIONS TO ASK YOUR DOCTOR

- What is the cause of sirenomelia?
- What are the chances of survival for a baby born with sirenomelia?
- Can sirenomelia be detected by prenatal tests, such as ultrasound or chorionic villus sampling?
- What kind of information about sirenomelia is available from a genetic counselor?

lasting a few minutes to a few days. There have been at least two reported cases of sirenomelia patients that have survived beyond the first month of life. These infants had normal-functioning kidneys during their development.

Resources

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ORGANIZATIONS

- Fetal Health Foundation, 9786 S. Holland St., Littleton, CO 80127, (303) 932-0553 or (877) 789-HOPE, info@fetalhealthfoundation.org, <http://www.fetalhealthfoundation.org>
- March of Dimes, 1275 Mamoroneck Ave., White Plains, NY 10605, (914) 997-4488, <http://www.marchofdimes.com>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Randall Stuart Colby, MD
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Sjögren-Larsson syndrome

Definition

Sjögren-Larsson syndrome is an inherited disorder characterized by ichthyosis (scaly skin), speech abnormalities, mental retardation, and spasticity (a state of increased muscle tone with heightened reflexes). Severity is variable.

Description

Sjögren-Larsson syndrome is a rare genetic disorder inherited in an autosomal recessive fashion. First characterized by Swedish psychiatrist Torsten Sjögren in 1956 (and by Sjögren and Tage Larsson in 1957); they suggested that all Swedes with the syndrome are descended from one ancestor in whom a mutation (a genetic change) occurred about 600 years ago. The highest incidence of the disease occurs in northern Sweden.

In infancy, development of various degrees of scaling and reddened skin occurs, often accompanied by hyperkeratosis (thickening of the skin) on the outer skin layer. After infancy, skin on the arms, legs, and abdomen often is dark, scaly, and lacking redness. Seizures and speech abnormalities may accompany skin symptoms. About half of children affected with the syndrome experience degeneration of the pigment in the retina of the eye.

Sjögren-Larsson syndrome is also sometimes known as SLS; congenital ichthyosis-mental retardation-spasticity syndrome; ichthyosis-spastic neurologic disorder-oligophrenia syndrome; fatty aldehyde dehydrogenase deficiency (FALDH deficiency); fatty aldehyde dehydrogenase 10 deficiency (FALDH10 deficiency); or disorder of cornification 10 (Sjögren-Larsson Type). Sjögren-Larsson syndrome is not to be confused with Sjögren syndrome; it is sometimes called the T. Sjögren syndrome to distinguish it from Sjögren syndrome (characterized by dry eyes and mouth), which was described by Swedish ophthalmologist Henrick Sjögren.

Genetic profile

Inheritance of Sjögren-Larsson syndrome is autosomal recessive. In autosomal recessive inheritance, a single abnormal gene on one of the autosomal chromosomes (one of the first 22 "nonsex" chromosomes) from both parents can cause the disease. Both of the parents must be carriers in order for the child to inherit the disease since recessive genes are expressed only when both copies in the pair have the same recessive instruction. Neither of the parents has the disease (since it is recessive).

A child with both parents who carry the disease has a 25% chance of having the disease; a 50% chance of being a carrier of the disease (but not affected by the disease, having both one normal gene and one gene with the mutation for the disorder); and a 25% chance of receiving both normal genes, one from each parent, and being genetically normal for that particular trait.

The gene for the Sjögren-Larsson syndrome, *FALDH*, is located on chromosome number 17 in band 17p11.2. The gene mutation that is responsible for the disorder is located near the center of the chromosome and is strongly associated with the gene markers called D17S805 and ALDH10.

Demographics

Sjögren-Larsson syndrome is a rare disorder. The highest incidence occurs in northern Sweden. In Sweden, the prevalence of this syndrome is 1 in 250,000. All Swedes with the syndrome are believed to be descendants of one ancestor in whom a genetic change occurred about 600 years ago. (The phenomenon wherein everyone is descended from one person within what was once a tiny group of people is called founder effect.) The disease also occurs in members of families of other European, Arabic, and Native American descent, but is less prevalent. Sjögren-Larsson syndrome affects both males and females.

Signs and symptoms

There are several signs and symptoms of Sjögren-Larsson syndrome. The major features of the disorder are the following:

- **Skin:** In infancy, development of various degrees of scaling and reddened skin occurs (ichthyosis), often accompanied by hyperkeratosis (thickening of the skin) on the outer skin layer. After infancy, skin on the arms, legs, and abdomen is often dark and scaly and lacking redness. Bruises are present at birth or soon after.
- **Hair:** Hair may be brittle.
- **Extremities:** Joint contracture and hypertonia cause resistance of joints to movement and of muscles to stretching. Most individuals with the syndrome never walk.
- **Eyes:** About half of the individuals with this syndrome have retinitis pigmentosa (pigmentary degeneration of the retina). Glistening white or yellow-white dots on the retina (ocular fundus) are characteristic. They may be an early sign of the disease, presenting at age one to two, and may increase with age.

KEY TERMS

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Diplegia—Paralysis affecting like parts on both sides of the body, such as both arms or both legs.

Hypertonia—Excessive muscle tone or tension, causing resistance of muscle to being stretched.

Ichthyosis—Rough, dry, scaly skin that forms as a result of a defect in skin formation.

Retinitis pigmentosa—Progressive deterioration of the retina, often leading to vision loss and blindness.

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

Tetraplegia—Paralysis of all four limbs. Also called quadriplegia.

- **Nervous system:** Spastic diplegia or tetraplegia (paralysis) affecting arms and/or legs. About half of the individuals with this disorder have seizures.
- **Urogenital system:** Kidney diseases may be associated with this syndrome.
- **Growth and development:** Individuals with the disorder tend to be unusually short in stature. Mental retardation is characteristic. Speech disorders may be present.

Speech abnormalities, mental retardation, and seizures usually occur during the first two or three years of life.

Diagnosis

The clinical features of Sjögren-Larsson syndrome are often distinctive, and a pattern of anomalies may suggest the diagnosis. In addition to ichthyosis and spasticity at birth, glistening white or yellow-white dots on the retina may be an early sign of the disease, presenting in the first or second year of life. If they occur, speech abnormalities, mental retardation, and seizures present during the first two or three years of life.

Laboratory findings are important in diagnosing Sjögren-Larsson syndrome. A laboratory test for deficiency of an enzyme (a protein that catalyzes chemical reactions in the human body) called fatty aldehyde dehydrogenase 10 (*FALDH10*) will determine presence of the disease. Sjögren-Larsson is due to a deficiency of *FALDH10*, and the gene for the Sjögren-Larsson syndrome is the same as the *FALDH10* gene.

Positive laboratory results for Sjögren-Larsson will include the following findings:

- hexadeconal elevated in fibroblasts
- fatty alcohol NAD+ deficient in Sjögren-Larsson syndrome fibroblasts
- fatty aldehyde dehydrogenase (FALDH) deficiency

Genetic counseling

Individuals with a family history of Sjögren-Larsson syndrome may benefit from genetic counseling to learn about the condition including treatments, inheritance, testing, and options available to them so that they can make informed decisions appropriate to their families. A child with both parents who carry the Sjögren-Larsson gene mutation has a 25% chance of having the disorder. Couples who have had one affected child have a 25% risk of having another child with the disorder in each pregnancy.

Prenatal testing

Families at risk to have a child with Sjögren-Larsson syndrome may have the option of prenatal diagnosis. DNA can be extracted from fetal cells obtained by either chorionic villus sampling (usually done at 12 weeks gestation) or amniocentesis (usually done at 16–18 weeks gestation) and tested to determine if the altered gene in the family is present. These techniques usually require that the alteration in the gene has been identified previously in an affected family member.

Chorionic villus sampling is a procedure to obtain chorionic villi tissue for testing. Chorionic villi are microscopic, finger-like projections that emerge from the chorionic membrane and eventually form the placenta. The cells of the chorionic villi are of fetal origin so laboratory analysis can identify a number of genetic abnormalities of the fetus. Because the villi are attached to the uterus, however, there is a chance that maternal tissue may be analyzed rather than the fetal cells. If the sample is too small, it may be necessary to repeat the procedure. In addition, the quality of the chromosome analysis is usually not as good with chorionic villus sampling as with amniocentesis. The chromosomes may not be as long, and so it may not be possible to identify some of the smaller bands on the chromosomes.

Amniocentesis is a procedure that involves inserting a thin needle into the uterus, into the amniotic sac, and withdrawing a small amount of amniotic fluid (a liquid produced by the fetal membranes and the fetus that surrounds the fetus throughout pregnancy). DNA can be extracted from the fetal cells contained in the amniotic

QUESTIONS TO ASK YOUR DOCTOR

- How common is Sjögren-Larsson syndrome in the general public outside of Sweden?
- What are the most common signs and symptoms associated with Sjögren-Larsson syndrome?
- What treatments are available to reduce the severity of this disorder?
- What is the prognosis for an infant diagnosed with Sjögren-Larsson syndrome?

fluid and tested for the specific mutation known to cause Sjögren-Larsson syndrome.

Treatment and management

Individuals with Sjögren-Larsson syndrome should be under routine health supervision by a physician who is familiar with the disorder, its complications, and its treatment. Supportive resources for individuals with Sjögren-Larsson syndrome and their families should be provided. Some clinical improvement has been reported to occur with fat restriction in the diet and supplementation with medium-chain triglycerides.

Other treatment of the disorder is generally symptomatic.

- For dermatologic symptoms, various skin-softening ointments are useful in reducing symptoms. Plain petroleum jelly may be effective, especially when applied while the skin is still moist, such as after bathing. Salicylic acid gel may also be effective. When using the ointment, skin is covered at night with an airtight, waterproof dressing. Lactate lotion is another effective treatment for the dermatologic symptoms.
- For ocular symptoms, regular care from a qualified ophthalmologist is important.
- To control seizures, anticonvulsant medications may be helpful.
- Speech therapy and special education services may be helpful.

Prognosis

Prognosis is variable depending upon the severity of the disease. Sjögren-Larsson syndrome does not generally lead to shortened lifespan.

Resources

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ORGANIZATIONS

- Foundation for Ichthyosis and Related Skin Types (FIRST), 2616 N. Broad St., Colmar, PA 18915, (215) 997-9400, info@firstskinfoundation.org, <http://www.firstskinfoundation.org>
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), 1 AMS Circle, Bethesda, MD 20892, (301) 495-4484, NIAMSinfo@mail.nih.gov, <http://www.nih.gov/niams>

Jennifer F. Wilson, MS

Skeletal dysplasia

Definition

Skeletal dysplasias, also called osteochondrodysplasias, are a group of congenital abnormalities of the bone and cartilage that are characterized by short stature. There are more than 350 known types of skeletal dysplasia.

Description

Skeletal dysplasia, sometimes called dwarfism, is a disorder of short stature defined as height that is three or more standard deviations below the mean height for age,

race, and gender. Although all skeletal dysplasias involve disproportionately short stature, there are many other associated conditions.

Skeletal dysplasia may also have additional skeletal abnormalities, including:

- short arms and trunk, bowlegs, and a waddling gait
- skull malformations, such as a large head, cloverleaf skull, craniosynostosis (premature fusion of the bones in the skull), and wormian bones (abnormal thread-like connections between the skull bones)
- anomalies of the hands and feet, including polydactyly (extra fingers), "hitchhiker" thumbs, and abnormal fingernails and toenails
- chest anomalies, such as pear-shaped chest and narrow thorax

Other anomalies that may be present in individuals with skeletal dysplasia include:

- anomalies of the eyes, mouth, and ears, such as congenital cataract, myopia (nearsightedness), cleft palate, and deafness
- brain malformations, such as hydrocephaly, porencephaly, hydranencephaly, and agenesis of the corpus callosum
- heart defects, such as atrial septal defect (ASD), patent ductus arteriosus (PDA), and transposition of the great vessels (TGV)
- developmental delays and intellectual disability

Skeletal dysplasia encompasses more than 350 different specific diagnoses. Researchers and clinicians are still working to develop a consistent method of categorizing these disorders. In 1997, a standardized method for naming and classifying the skeletal dysplasias was proposed using information about the etiology of each disorder based on the genetic mutation or protein defect involved. Disorders that originate from similar or identical gene mutations were grouped together, and other categories were renamed in an attempt to create a more logical classification system. With so many unique disorders, categorizing the skeletal dysplasias will continue to evolve as new genetic mutations are identified. This system is still under consideration with clinicians attempting to choose between categories based on genetics and categories based on phenotype or clinical presentation.

Genetic profile

Skeletal dysplasia refers to a group of disorders characterized by abnormalities of bone and cartilage with similar modes of transmission: autosomal dominant and recessive and X-linked dominant and recessive.

KEY TERMS

Agenesis of the corpus callosum—An absence of the structure in the brain that connects the two hemispheres of the brain.

Atrial septal defect (ASD)—An abnormal opening between the two upper chambers of the heart (atria).

Autosomal—Genetic trait found on a chromosome that is not involved in determining sex.

Calcification—The process by which tissue becomes hardened by the depositing of calcium in the tissue.

Cleft palate—An abnormal opening, or cleft, between the roof of the mouth and the nasal cavity.

Cloverleaf skull—An abnormal, or cloverleaf, appearance to the skull caused by premature fusion of the bones in the skull of an infant.

Computed tomography (CT) scan; 3D CT scan—A diagnostic imaging procedure in which x-ray and computer technology are used to generate slices or cross-sectional images of the body; 3D CT scan produces three-dimensional images.

Congenital—Present at birth.

Congenital cataract—Clouding of the lens in the eye that is present at birth.

Craniosynostosis—An abnormal premature fusion of the bones of the skull in an infant.

Developmental delay—Not reaching the milestones of childhood development as expected.

Dominant—A genetic trait that is expressed when only one copy of it is present.

Echocardiogram (ECHO)—A diagnostic procedure that uses sound waves to produce images of the heart.

Epiphyses—Areas at the tip of the long bones that allow them to grow.

Gene mutation—A permanent change in genetic material that is transmittable.

Histological studies—Laboratory tests performed on tissue samples and cells.

“Hitchhiker” thumbs—A congenital anomaly of the thumb in which it is abnormally positioned at a right angle to the first joint.

Hydranencephaly—Congenital enlargement of the head and brain.

Hydrocephaly—An increase of cerebrospinal fluid in the brain.

Hypoplasia/hypoplastic—Small.

Kyphosis—Anomaly of the spine in which it curves backward.

Long bones—The femur in the leg and the humerus in the arm.

Lordosis—An abnormal curvature of the spine in which the lumbar, or lower section, is excessively curved.

Magnetic resonance imaging (MRI)—A diagnostic procedure that uses a combination of high-powered magnets, radio frequencies, and computers to generate detailed images of structures within the body.

Molecular analysis—Evaluation of molecules, tests that may identify single gene mutations.

Myopia—Nearsightedness.

Patent ductus arteriosus (PDA)—A congenital anomaly of the heart occurring when the ductus arteriosus (the temporary fetal blood vessel that connects the aorta and the pulmonary artery) does not close at birth.

Polydactyly—Extra fingers or toes.

Porencephaly—A congenital anomaly of the brain in which there are abnormal holes or cavities in the brain.

Prenatal ultrasound—An imaging test using high-frequency sound waves to create images of internal organs. Prenatal indicates the test is *performed on the* fetus while still in the womb.

Recessive—A genetic trait that is only expressed when another identical recessive gene is present.

Scapula—Shoulder blade.

Scoliosis—Abnormal curvature of the spine in which the spine curves to the side.

Short stature—Height of less than three standard deviations from the mean for age, race, and gender.

Short trunk—An abnormally short torso or body.

Sleep apnea—A potentially life-threatening condition in which the individual has episodes during sleep in which breathing temporarily stops.

Thorax—Chest cavity.

Transposition of the great vessels (TGV)—A congenital heart defect in which the major vessels of the heart are attached to the wrong chambers of the heart.

Wormian bones—A condition of the bones and cartilage in which growing bones are abnormally connected by thin string-like structures.

X-linked—A genetic trait that is carried on the X chromosome.

X-ray—An imaging test that uses beams of energy to create images of structures within the body.

There are approximately 350 different types of skeletal dysplasia; all have one or more unique genetic causes.

The most common forms of skeletal dysplasia and the genetic mutations that cause them include:

Achondrogenesis

This is a lethal form of skeletal dysplasia that is actually a group of disorders, type 1A, type 1B, and type 2. They are caused by mutations in the *TRIP11*, *SLC26A2*, and *COL2A1* genes, respectively. The features of these disorders include a small body, short limbs, and other skeletal abnormalities.

Achondroplasia

This is the most commonly reported type of skeletal dysplasia. It is caused by mutations in the *FGFR3* gene and is inherited through an autosomal dominant pattern. Individuals with this condition have an average height of 131 centimeters or 4.3 feet. Other features of this disorder include an average-size trunk, short arms and legs, an enlarged head (macrocephaly) with a prominent forehead, short fingers, and trident-appearing hands.

Diastrophic dysplasia

This type of skeletal dysplasia is caused by mutations in the *SLC26A2* gene, which has an autosomal recessive pattern of inheritance. A rare form of dwarfism, diastrophic dysplasia has characteristic features including short stature, very short arms and legs (mesomelic shortening), early-onset osteoarthritis, and joint contractions, which restrict movement. These joint problems can make it hard to walk and will worsen with age. Other features are clubfoot, scoliosis, cleft palate, and “hitchhiker thumb” (thumbs positioned at an angle).

Multiple epiphyseal dysplasia

This type of skeletal dysplasia is caused by mutations of the *COMP*, *COL9A1*, *COL9A2*, *COL9A3*, or *MATN3* genes and is most often inherited in an autosomal dominant pattern. In a few rare cases this disorder is transmitted in an autosomal recessive pattern, and the parents do not show symptoms. Features of the autosomal dominant type of multiple epiphyseal dysplasia include mild hip and knee disorders, arthritis (early-onset), and a waddling gait. Although most individuals with this disorder are of normal height, some may have mild short stature as adults. Most individuals are diagnosed during childhood; mild cases may not be diagnosed until adulthood. The recessive type is characterized by scoliosis and malformations of the hands, feet, and knees. About 50% of individuals with recessive multiple epiphyseal dysplasia are born with at least one additional abnormal

feature such as clubfoot, cleft palate, clinodactyly, ear swelling, or a double-layered patella (knee cap).

Pseudoachondroplasia

This type of skeletal dysplasia is caused by mutations in the *COMP* gene and is inherited in an autosomal dominant pattern. Individuals with this type have an average height of 116–120 centimeters or 3 feet 9 inches to 3 feet 11 inches. Other features include short arms and legs; a waddling walk; joint pain; osteoarthritis; hyperextensibility of the hands, knees, and ankles; limited range of motion at the elbows and hips; scoliosis; and normal facial features, head size, and intelligence.

Spondyloepiphyseal dysplasia (SED)

There are three types of this form of skeletal dysplasia:

- **X-linked spondyloepiphyseal dysplasia tarda** is caused by mutations in the *TRAPPC2* gene (aka *SEDL* gene) and has an X-linked inheritance pattern. It primarily affects boys and is characterized by normal growth until late childhood when growth is slowed and the features begin to develop. These features include shortened trunk and neck, unusually long arms, flattened vertebrae with hump-shaped bulges, and progressively thinning discs between vertebrae, scoliosis or kyphosis of the spine, hip abnormalities, curved legs, decreased movement in large joints, and early development of arthritis.
- **Spondyloepiphyseal dysplasia congenital** is a rare skeletal dysplasia that is caused by mutations in the *COL2A1* gene and is inherited in an autosomal dominant pattern. The short stature is present at birth, and other symptoms develop over time. Features are similar to X-linked spondyloepiphyseal dysplasia tarda with additional features that include mild abnormal facial features, vision and hearing impairment, and cleft palate.
- **CHST3-related skeletal dysplasia** (also called Larsen syndrome) caused by mutations in the *CHST3* gene with an unknown inheritance pattern. It is a rare condition with features similar to the other forms of spondyloepiphyseal dysplasia.

Thanatophoric dysplasia, type I and type II

This is a lethal form of skeletal dysplasia. It is caused by mutations in the *FGFR3* gene and is inherited in an autosomal dominant pattern. It is a severe skeletal disorder characterized by extremely short limbs and folds of extra skin on the arms and legs. Other features include a narrow chest, short ribs, underdeveloped lungs (pulmonary hypoplasia), and an enlarged head. There are two types, type I and type II. Type I is distinguished by curved thigh

bones and flattened bones of the spine (platyspondyly), while type II is characterized by straight thigh bones and a skull abnormality called a cloverleaf skull.

Demographics

Skeletal dysplasia is usually diagnosed at birth; however, some dysplasias may not be detected until much later. For this reason, it is difficult to determine the true incidence. The reported rate in the United States is 1 per every 4,000–5,000 births.

No one race is more likely to have skeletal dysplasia. The X-linked recessive disorders affect males almost exclusively, and X-linked dominant types are often lethal in males. Autosomal recessive and dominant transference affect males and females equally.

Signs and symptoms

The primary signs of skeletal dysplasia are abnormally shortened long bones in the legs and arms, short trunk, and abnormalities of the skull. In addition to the skeletal system, skeletal dysplasia disorders may also affect the heart, face, extremities, and joints. Some forms are lethal, and a significant number of fetuses with skeletal dysplasia die *in utero*.

Diagnosis

Many skeletal dysplasias can be diagnosed prenatally during routine prenatal ultrasound. If skeletal dysplasia is suspected, assessment and careful measurement of the extremities, thorax, spine, and facial structure can detect signs of the condition. Fetal movement may be decreased, and associated congenital heart and renal heart defects may be observed as well.

After birth, x-rays are the most effective diagnostic tool for evaluating the skeleton. A skeletal study includes views of the long bone, hands and feet, skull, chest, spine, and pelvis.

Abnormal x-ray results that may indicate a skeletal dysplasia include:

- dumbbell-shaped long bones
- bowing of the arms and legs
- oval-shaped translucencies in the femur and humerus
- scapula hypoplasia (small shoulder blades)
- abnormal pelvis
- vertebral abnormalities
- rib abnormalities, including cupping of the ends or shortening of the entire rib and stippled or spotted appearance to the cartilage

QUESTIONS TO ASK YOUR DOCTOR

- What type of skeletal dysplasia does my child have?
- What are the chances that we will have another child with skeletal dysplasia?
- Does my child need genetic testing?
- What are the most common symptoms of skeletal dysplasia?
- What treatments are recommended for this disorder?
- Are there organizations that provide support and information for families with skeletal dysplasia?

- epiphyses (growth centers of the long bones) abnormalities, including cone shape, stippled appearance, or an absence of calcification centers
- long bone fractures

Computed tomography (CT) scan and magnetic resonance imaging (MRI) are useful in assessing concurrent brain anomalies. MRI is useful in determining the extent and type of spinal abnormalities and compression present.

Three-dimensional CT scan is used to evaluate craniofacial anomalies prior to reconstructive surgery. MRI of the spine is also helpful in presurgical planning prior to surgical treatment of spinal and pelvic abnormalities.

Chromosome analysis may be performed to help determine the type of skeletal dysplasia an individual has. This is important so that other associated conditions can be diagnosed and treated as well.

Other diagnostic procedures that may be performed, including molecular analysis to identify single gene mutations, sleep studies to evaluate potentially life-threatening sleep apnea that is often a problem for individuals with skeletal dysplasia, histological studies to examine specific types of cells that identify some skeletal dysplasia forms, and an echocardiogram (ECHO) to evaluate the heart for defects.

Treatment and management

Treatment and management of children with skeletal dysplasia begins, in some cases, at birth. Neonatal resuscitation may be necessary for infants with certain more severe types of skeletal dysplasia in which the thoracic cavity is extremely small. This intervention can be life-saving.

The medical management of children with skeletal dysplasia begins at birth and continues into adulthood. Careful monitoring of height, weight, and head circumference is essential. Obesity is a risk for those with skeletal dysplasia. Excess weight can cause serious complications, including breathing difficulties such as sleep apnea, and may aggravate other spinal cord compression and joint instability found in many types of skeletal dysplasia.

Surgical treatment of skeletal dysplasia varies depending on the specific type present and the associated conditions. Sleep apnea may be treated by removal of the adenoids.

Spinal abnormalities, such as spinal cord compression, scoliosis, kyphosis, and lordosis, may be treated surgically. A spinal column fusion can relieve the stress on the spinal cord caused by malformations of the spinal column. In a spinal fusion, two or more vertebrae are fused together using bone grafts or metal rods.

In some individuals with short-limbed types of skeletal dysplasia, bone growth may be induced by a surgical bone-lengthening procedure. This procedure involves several surgeries and an extensive recovery period. The bone to be lengthened is cut. Leaving a narrow gap between the two pieces of bone, metal pins are inserted into the bone and the skin is closed. An external frame is attached to the pins and, gradually, the bone is pulled apart just enough to provide a small gap for the bone to grow into. As the bone grows, the space is widened and more bone grows. After the bone has healed, the pins are surgically removed. In some cases, as much as 6 in. (15 cm) has been added to leg length using this procedure.

Prognosis

While some skeletal dysplasias are lethal, most individuals with skeletal dysplasia have a normal life expectancy. The associated conditions may require medical and surgical treatment; however, these treatments are highly effective. Intelligence is usually normal. Most people with skeletal dysplasia have an excellent prognosis.

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ORGANIZATIONS

Human Growth Foundation, 997 Glen Cove Ave., Suite 5, Glenhead, NY 11545, (800) 451-6434, (516) 671-4055, <http://www.hgfound.org>

Little People of America, 250 El Camino Real, Suite 211, Tustin, CA 92780, (714) 368-3689 or (888) LPA-2001, (714) 368-3367, info@lpaonline.org, <http://www.lpaonline.org>

March of Dimes, 1275 Mamaroneck Ave., White Plains, NY 10605, (914) 997-4488, <http://www.marchofdimes.com>

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Sly syndrome (MPS VII) see **Mucopolysaccharidoses**

Smith syndrome see **Smith-Lemli-Opitz syndrome**

Smith-Fineman-Myers syndrome

Definition

Smith-Fineman-Myers syndrome (SFMS) is a rare and severe type of X-linked inherited intellectual impairment.

Description

Smith-Fineman-Myers syndrome is also known as Smith-Fineman-Myers-type intellectual impairment and Smith-Fineman-Myers-type X-linked intellectual impairment. SFMS results in severe intellectual impairment along with characteristic facial features and skeletal differences.

Genetic profile

Smith-Fineman-Myers syndrome is an X-linked disease. X-linked diseases map to the human X chromosome, a sex chromosome. Females have two X chromosomes, whereas males have one X chromosome and one Y chromosome. Because males have only one X chromosome, they require only one copy of an abnormal X-linked gene to display disease. Because females have two X chromosomes, the effect of one X-linked recessive disease gene is masked by the disease gene's normal counterpart on her other X chromosome.

In classic X-linked inheritance males are affected, presenting full clinical symptoms of the disease. Females are not affected. Affected fathers can never pass X-linked diseases to their sons. However, affected fathers always pass X-linked disease genes to their daughters. Females who inherit the faulty gene but do not show the disease are known as carriers. Female carriers of SFMS have a 50% chance to pass the disease-causing gene to each of their children. Each of a female carrier's sons has a 50% chance to display the symptoms of SFMS. None of a female carrier's daughters would display symptoms of SFMS.

Some patients with SFMS have been found to have a mutation in the *ATRX* gene, on the X chromosome at position Xq13.3. *ATRX* is also the disease gene for several other forms of X-linked intellectual impairment, such as X-linked alpha-thalassemia/intellectual impairment syndrome, Carpenter syndrome, Juberg-Marsidi syndrome, and X-linked intellectual impairment with spastic paraplegia. A 2008 report mapped the causative gene in a large Chinese family with SFMS to *Xq25*.

Demographics

SFMS affects only males and is very rare. As of 2015, fewer than 20 cases had been reported in the medical literature. SFMS has been reported in brothers of affected boys.

Signs and symptoms

SFMS visibly affects the skeletal and nervous systems and results in an unusual facial appearance. The genitals may also show effects ranging from mild (e.g., undescended testes) to severe (leading to female gender assignment).

Skeletal features

Boys with SFMS have short stature and a thin body build. Their heads are small and may also be unusually shaped. Scoliosis and chest abnormalities have been reported to occur with SFMS. X-rays may show that their

KEY TERMS

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

Tone—A term used to describe the tension of muscles. Increased tone is increased tension in the muscles.

bones have characteristics of the bones of people younger than they are. Hands are often short with unusual palm creases and short, unusually shaped fingers. Fingernails may be abnormal. Foot abnormalities and shortened or fused toes have also been reported.

Neurological features

Boys with SFMS exhibit severe intellectual impairment. Restlessness, behavior problems, seizures, and severe delay in language development are common. Boys with SFMS may be self-absorbed with reduced ability to socialize with others. Affected boys show reduced muscle tone as infants and young children. Later, muscle tone and reflexes are abnormally increased, causing spasticity.

Boys with SFMS may display cortical atrophy, or degeneration of the brain's outer layer, on brain imaging studies. Cortical atrophy is commonly found in older unaffected people. When cortical atrophy is found in younger people it is typically due to a serious brain injury. Brain biopsies of two patients with SFMS have been normal.

Facial features

SFMS is associated with unusual facial features including a large mouth with a drooping lower lip, prominent upper jaw and front teeth, and an underdeveloped chin. Cleft palate has been reported in one set of affected twins. Eyes are widely spaced with drooping eyelids. Skin may be lightly pigmented with multiple freckles.

Diagnosis

Assessment for any type of intellectual impairment should include a detailed family history and thorough physical exam. Brain and skeletal imaging through CT scans or x-rays may be helpful. A chromosome study and certain other genetic and biochemical tests help to rule out other possible causes of intellectual impairment.

Diagnosis of SFMS has traditionally been based on the visible and measurable symptoms of the disease. Until

QUESTIONS TO ASK YOUR DOCTOR

- I recently read about a child with Smith-Fineman-Myers syndrome. How common is this disease?
- Other than intellectual impairment, what symptoms are associated with this disorder?
- What is the lifespan of an individual with Smith-Fineman-Myers syndrome?
- Why do there not seem to be any clinical trials for the treatment of Smith-Fineman-Myers syndrome?

2000, SFMS was not known to be associated with any particular gene. Scientists do not yet know if other genes may be involved in some cases of this rare disease. Genetic analysis of the *ATRX* gene may, however, prove to be helpful in diagnosis of SFMS.

Treatment and management

Treatment for SFMS is based on the symptoms each individual displays. Seizures are controlled with anticonvulsants. Medications and behavioral modification routines may help to control behavioral problems.

Prognosis

Intellectual disability is severe, but it does not seem to get worse with age. Lifespan does not appear to be shortened.

Resources

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ORGANIZATIONS

- March of Dimes, 1275 Mamaroneck Ave., White Plains, NY 10605, (914) 997-4488, <http://www.marchofdimes.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Smith-Fineman-Myers type X-linked mental retardation see **Smith-Fineman-Myers syndrome**

Smith-Lemli-Opitz syndrome

Definition

Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessive syndrome characterized by microcephaly, intellectual disability, short stature, and major and minor malformations; it is caused by a mutation in the gene that encodes the enzyme 7-dehydrocholesterol reductase (*DHCR7*), which is required for cholesterol metabolism.

Description

David W. Smith, John M. Opitz, and Luc Lemli first characterized SLOS in 1964. The syndrome has variable characteristics marked mainly by short stature, intellectual disability, microcephaly, postaxial polydactyly (an extra digit on the little finger side of the hand or the little toe side of the foot), cleft palate, cardiovascular defects, genital malformations, and other abnormalities associated with altered cholesterol metabolism. In 1993, scientists discovered that children with SLOS have a metabolic disorder that prevents the synthesis of sufficient amounts of cholesterol to support normal growth and development.

Sometimes the severe form of the disease is called SLOS type II but research has shown that type II is not biochemically distinct from other forms of SLOS. Rather, it represents a more severe expression of the SLOS phenotype.

SLOS is also known as Smith syndrome, RSH syndrome, and RSH/Smith-Lemli-Opitz (RSH/SLO) syndrome. The designation RSH represents initials of the surnames of the first three patients in whom the syndrome was first observed.

Genetic profile

SLOS is inherited in an autosomal recessive manner. In autosomal recessive inheritance, mutated genes for *DHCR7* must be inherited from both parents for the traits associated with the disease to be present. Parents of children with SLOS are carriers of the disorder and are most often not affected themselves, as they have one functional and one mutated *DHCR7* gene.

A child with both parents as carriers for SLOS has a 25% chance of having the disease; a 50% chance of being a carrier of the disease; and a 25% chance of receiving both normal genes and being genetically normal for that particular trait.

The protein product of the *DHCR7* gene is required for cholesterol synthesis. Cholesterol is a major component of lipid membranes in animals that supports membrane integrity and fluidity. Additionally, cholesterol is a precursor substrate for steroid hormones that are required for sexual differentiation and development, as well as multiple functions in metabolic regulation.

Demographics

SLOS occurs in approximately 1 in 20,000 to 30,000 births in populations of northern and central European background. Evidence suggests that there is a higher frequency of SLOS in people of northern European ancestry and a lower frequency in people of Asian or African background.

Because of the presence of recognizable genital abnormalities, males are more likely than females to be evaluated for a diagnosis of SLOS. Therefore, the occurrence of the disease among females is less understood.

Signs and symptoms

The following are features of SLOS:

- Nearly 90% of people with SLOS have microcephaly.
- Nearly all people with SLOS have moderate to severe intellectual disability.
- Other neurologic findings are less common. These include seizures and muscle hypotonia.
- Characteristic facial features include narrowing at the temples, epicanthal folds (skin fold of the upper eyelid covering the inner corner of the eye), down-slanting eyes, drooping upper eyelids, anteverted nares (nostrils that tilt forward), and abnormal smallness of the jaw (micrognathia). Cleft palate is present in 40%–50% of people with SLOS, and about 20% have congenital cataracts. Strabismus, poor tracking, opsoclonus (impairment of eye movements), and optic nerve

KEY TERMS

Anomaly—Different from the normal or expected. Unusual or irregular structure.

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Congenital—Refers to a disorder that is present at birth.

Cryptorchidism—A condition in which one or both testes fail to descend normally.

Hypospadias—An abnormality of the penis in which the urethral opening is located on the underside of the penis rather than at its tip.

Hypotonia—Reduced or diminished muscle tone.

Microcephaly—An abnormally small head.

Polydactyly—The presence of extra fingers or toes.

Strabismus—An improper muscle balance of the ocular muscles resulting in crossed or divergent eyes.

Syndactyly—Webbing or fusion between the fingers or toes.

demyelination (deterioration) are other possible ophthalmologic manifestations.

- Cardiac abnormalities are present in about 35%–40% of patients with SLOS. Increased incidence of atrioventricular canal defects and anomalous pulmonary venous return is seen in people with SLOS.
- Urogenital anomalies are frequent. Kidney hypoplasia (smaller than normal kidneys) or dysplasia (abnormal development) of the kidneys occurs in about 40% of people with SLOS. Genital anomalies of variable severity may include hypospadias and/or bilateral cryptorchidism, which occur in about half of reported cases, and a small penis. Many biologically male individuals with severe manifestations of SLOS have undermasculinization of the external genitalia, resulting in female external genitalia (sex reversal). Abnormalities in the uterus and vagina have been noted in females.
- Syndactyly of the second and third toes occurs frequently. Postaxial polydactyly is present in 25%–50% of all cases. Other abnormalities affecting the hands and feet may be present.
- Short stature is common. Limbs and neck are shorter than normal.

Growth may be retarded prenatally, and children born with SLOS will often show failure to thrive, have abnormal sleep patterns, and have photosensitivity.

Diagnosis

The clinical features of SLOS are often distinctive, and a pattern of congenital anomalies can suggest a diagnosis. The diagnosis of SLOS relies on clinical suspicion and detection of abnormally elevated serum concentration of 7-dehydrocholesterol (7-DHC) or an elevated 7-dehydrocholesterol:cholesterol ratio. Serum concentration of cholesterol is usually low, with cholesterol levels less than 50 mg/dl (normal is greater than 100 mg/dl). Cholesterol is an essential building block of all cell membranes and the white matter of the brain; SLOS appears to be caused by abnormally low levels of the enzyme 7-DHC-reductase, which converts 7-DHC into cholesterol. Children with SLOS with the lowest cholesterol levels tend to have the most severe forms of the disorder and often die at birth or in the first few months. In about 10% of patients, cholesterol is in the normal range and is considered to be an unreliable marker for screening and diagnosis.

Molecular genetic testing of the *DHCR7* gene is not generally available, but since the molecular structure of the *DHCR7* has been identified, the possibility now exists for DNA-based testing for diagnosis and genetic counseling. Currently such testing is available on a research basis only.

Genetic counseling

Carrier detection is problematic using biochemical testing because carriers usually have normal 7-DHC and cholesterol levels. Although not widely available, carrier testing is possible by measurement of 7-DHC or enzyme levels in cultured cells. More accurate DNA testing for *DHCR7* mutations is not currently available but it is anticipated in the near future. Couples who have had one affected child have a 25% risk of having a child with SLOS in each pregnancy.

Prenatal testing

For couples known to be at 25% risk for having a baby with SLOS, testing is available to assist in prenatal diagnosis. Prior testing of family members is usually necessary for prenatal testing.

Either chorionic villus sampling (CVS) or amniocentesis may be performed for prenatal testing. Abnormal levels of 7-dehydrocholesterol in amniotic fluid or CVS are diagnostic of SLOS. CVS can be performed at 10–12 weeks gestation, while amniocentesis testing is performed after 15 weeks.

Abnormal concentration of 7-dehydrocholesterol levels in tissue obtained from CVS or in amniotic fluid is diagnostic in the prediction of prenatal cases of SLOS.

For low-risk pregnancies, in which there is no family history of SLOS, certain findings in the fetus might prompt consideration of the syndrome. The combination of low unconjugated estriol levels, low HCG, and low alpha-fetoprotein on routine maternal serum testing at 16–18 weeks gestation might suggest the possible diagnosis of SLOS. Findings on ultrasound examination such as cardiac defects, cleft palate, genital abnormalities, or growth retardation might be suggestive, prompting consideration of a 7-dehydrocholesterol assay of amniotic fluid.

Treatment and management

It is not known what role the elevated levels of 7-DHC and other sterol precursors—not usually present in significant concentrations in the plasma—play in the pathogenesis of SLOS. Children with SLOS should be under routine health supervision by a physician who is familiar with SLOS, its complications, and its treatment. Since a common complication of the syndrome is pneumonia, it should be treated with appropriate antibiotics when it occurs. Special education services and physical therapy may be recommended as needed.

Infant care

A physician familiar with the range of problems seen in infants with SLOS is important for appropriate health supervision and anticipatory guidance. Poor feeding and problems with weight gain are common in infants with SLOS; many infants have difficulties with sucking and/or swallowing and may require alternative feeding. A diagnosis of pyloric stenosis (caused by a thickening and spasm of the stomach outlet) should be considered for those with frequent vomiting or apparent gastroesophageal reflux. Particular attention should also be given to the stooling pattern, abdominal distention, or other signs of possible obstruction, particularly in children with more severe phenotype since these may indicate Hirschsprung disease (absence of nerves in the colon).

Surgical treatment

Surgical management of congenital anomalies such as cleft palate, congenital heart disease, and genital anomalies for the more severely affected infants need to be considered as they would in any other infant with a severe, usually lethal disorder. Even with vigorous intervention, children with multiple major manifestations of SLOS are believed to have decreased rates of survival.

QUESTIONS TO ASK YOUR DOCTOR

- Please explain the genetic basis of Smith-Lemli-Opitz syndrome.
- What are the most serious medical consequences of this genetic disorder?
- What is the prognosis for Smith-Lemli-Opitz syndrome?
- Where can I find additional information about this genetic disorder?

Dietary supplementation

Because SLOS is a cholesterol deficiency syndrome, research trials have recently included dietary cholesterol supplementation. An increase in total caloric intake and an increase in cholesterol intake hold promise for treatment of SLOS, but the research is still preliminary. Benefits reported in these studies include improved growth in children with SLOS, possible enhanced developmental progress, reduced dermatologic problems, and improved behavior. No harmful side effects of cholesterol supplementation have been documented.

Prognosis

Prognosis is variable depending upon the severity of the disease. Children with SLOS who have multiple major malformations are believed to have decreased rates of survival, even with vigorous intervention.

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ORGANIZATIONS

- The Arc, 1825 K St. NW, Suite 1200, Washington, DC 20006, (800) 433-5255, <http://www.thearc.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>
- Smith-Lemli-Opitz RSH Foundation, <http://www.smithlempiopitz.org>

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Smith-Magenis chromosome region see
Smith-Magenis syndrome

Smith-Magenis syndrome

Definition

Smith-Magenis syndrome (SMS) is a relatively rare genetic disorder characterized by a specific pattern of physical, behavioral, and developmental features. First described in 1982 by Ann C. M. Smith (a genetics counselor) and colleagues, the syndrome results from a deletion on chromosome 17, specifically referred to as deletion 17p11.2.

Description

Until the mid-1990s, SMS was not a well-known disorder, even among genetics experts; the chromosome deletion is small (a microdeletion) and difficult to detect. Most individuals are not diagnosed until they receive specialized genetic tests, usually in mid-childhood or adulthood.

Smith-Magenis syndrome causes multiple birth defects (congenital abnormalities) as well as moderate to severe intellectual disabilities. The clinical manifestations of SMS vary. However, a number of characteristic physical features, developmental delays, and behavioral problems occur in all patients with the disorder. According to some researchers, the extent of the chromosomal deletion may account for the variable severity of symptoms.

The most common and clinically recognizable features of those with SMS include mild to moderate brachycephaly (short, wide head), flat midface, intellectual disability, and short, broad hands. Common but less consistent physical abnormalities include a prominent forehead, protruding jaw, and low-set ears. The major clinical features and the specific abnormalities of SMS are the most obvious diagnostic clues to the disorder. Some experts believe that with more research on this syndrome, SMS may be determined to be a relatively common cause of intellectual disabilities.

Genetic profile

Although SMS is caused by a deletion of genetic material from a portion of chromosome 17, the syndrome usually does not run in families. In most cases, the deletion occurs accidentally at conception when an abnormal sperm or egg from one parent unites with a normal sperm or egg from the other parent. The abnormal sperm or egg contains the missing chromosomal material. These abnormal sperm or eggs are present in everyone; however, the risk of an abnormal conception increases significantly with the parents' ages.

Research has shown a random parental origin of deletion, suggesting that SMS is likely a contiguous gene deletion syndrome. Contiguous gene syndromes are conditions that occur as a result of microdeletions or microduplications involving several neighboring genes.

Demographics

Although the exact incidence of SMS is not known, the disorder is rare and estimated to occur in approximately 1 in 25,000–50,000 live births. Only about 150 cases have been identified worldwide from a diversity of ethnic groups. The ages of those affected ranges from neonates to individuals in their 70s. About an equal number of males and females are affected by the disorder.

Signs and symptoms

Although there are many features associated with SMS, not every individual exhibits all of these features. The following is a common list of traits that have been reported:

- distinct facial features: brachycephaly, flat midface area, prominent forehead, eyelid folds, broad nasal bridge, protruding jaw, and low-set ears
- brachydactyly (short fingers and toes)
- short stature
- hoarse, deep voice
- speech delay
- learning disabilities

KEY TERMS

Brachycephaly—An abnormal thickening and widening of the skull.

Brachydactyly—Abnormal shortness of the fingers and toes.

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Contiguous gene syndrome—Conditions that occur as a result of microdeletions or microduplications involving several neighboring genes.

FISH (fluorescent in situ hybridization)—Technique used to detect small deletions or rearrangements in chromosomes by attempting to attach a fluorescent (glowing) piece of a chromosome to a sample of cells obtained from a patient.

Melatonin—A sleep-inducing hormone secreted by the pineal gland.

Phenotype—The physical expression of an individual's genes.

Scoliosis—An abnormal, side-to-side curvature of the spine.

- chronic ear infections
- intellectual disabilities (typically in the 50–60 range for IQ)
- poor muscle tone and/or feeding problems in infancy
- eye disorders
- sleep disturbances
- insensitivity to pain
- behavioral problems: hyperactivity, head banging, hand/nail biting, skin picking, pulling off fingernails and toenails, explosive outbursts, tantrums, destructive and aggressive behavior, excitability, arm hugging/squeezing when excited

- engaging and endearing personality

Less common symptoms include:

- heart abnormalities
- scoliosis (curvature of the spine)
- seizures
- urinary tract abnormalities
- abnormalities of the palate, cleft lip

- hearing impairment

Diagnosis

Although SMS is generally believed to be underdiagnosed, with increased professional awareness and improved methods of testing, the number of individuals identified increases annually. In diagnosing the disorder, the characteristic behavioral features of SMS are usually recognized before the facial features, often leading to a delay in diagnosis.

Phenotype (physical features) identification

Facial abnormalities evolve over time and are more subtle in early childhood. Thus, diagnosis of SMS at birth or in infancy is infrequent and is usually made by chance when abnormal facial features suggest a diagnosis of Down syndrome (a more commonly known congenital abnormality caused by an extra chromosome 21) and chromosome testing reveals the SMS 17p11.2 deletion.

The phenotypic overlap of SMS with Down syndrome, particularly in early life, can be striking. Both conditions share a number of features, including brachycephaly, upward-slanting eyes, a short and broad nose, midface flattening, eye disorders, short stature, small hands and feet, and poor muscle tone. However, age evolves the somewhat coarse appearance of the face, and by young adulthood, the phenotype of the disorder is well developed and striking. Familiarity with the clinical manifestations of both genetic disorders improves the likelihood of early diagnosis and intervention.

High-resolution chromosome analysis

The diagnosis of SMS is often confirmed through a blood test called a high-resolution chromosome analysis, which is generally performed for the evaluation of developmental delays or congenital abnormalities. In the case of microdeletions, the chromosome deletions are so small that often they cannot be detected by chromosome analysis alone. In an older child, however, the phenotype is distinctive enough for a clinical diagnosis to be made by an experienced clinician prior to the chromosome analysis.

FISH analysis

If chromosome analysis is inconclusive, FISH (fluorescent in situ hybridization) is the test of choice to document the SMS deletion because it has a high degree of accuracy. In FISH analysis, which has become a standard molecular test, denatured DNA (DNA altered by a process that separates the complementary strands within the DNA double helix structure) is kept in place in the chromosome and is then hybridized (mixed) with RNA or DNA

QUESTIONS TO ASK YOUR DOCTOR

- How and at what stage in a child's life can Smith-Magenis syndrome be diagnosed?
- Are there medications or procedures that can be used to slow progress of the disease or otherwise keep it under control?
- What is the long-term prognosis for a child who has been diagnosed with Smith-Magenis syndrome?
- Are there organizations from which I can obtain more information about this genetic disorder?

(extracted from another source) to which a fluorescent tag has been attached. The advantage of maintaining the DNA in the chromosome is that the specific chromosome (or chromosomes) containing the gene of interest can be identified by observing, under a microscope, the location of the fluorescence. Combining FISH and standard chromosome analysis can characterize the structural rearrangements and marker chromosomes.

In SMS, predictive or prenatal screening is an unlikely outcome of identifying the flawed gene because the disease is so rare and does not run in families. Instead, researchers hope to determine how the extent of the microdeletion on chromosome 17 is related to the various signs and symptoms of SMS.

Treatment and management

There is no cure for SMS because the disorder is so complex and has received relatively little research attention. Therefore, managing symptoms becomes a priority in those diagnosed with the disorder.

A child with SMS typically displays self-injurious behavior as well as attention-seeking outbursts and aggressive behavior. Medications such as carbamazepine (an anticonvulsant) may be prescribed for severe behavioral problems associated with SMS. However, in most cases, drugs to help control or modify behavior or increase attention span have been found to be minimally effective. Any pharmacologic treatment of SMS remains individual, and several drugs may need to be tested to optimize results.

In addition to behavioral problems, children with SMS tend to have speech delays. Therefore, speech therapy, starting as early as possible, is typically beneficial. Most children learn to communicate verbally, and either with sign language or gestures.

Since children with SMS are often easily distracted, they tend to do better in small, focused classroom settings in which there are no more than five to seven children. If the classroom is larger, competition for the teacher's attention increases, along with the probability of behavioral problems. These children also seem to respond to consistency, structure, and routines; changes in routine can provoke behavioral outbursts and tantrums.

Children with SMS have problems with sequential processing, which makes counting, mathematical skills, and multi-step tasks especially difficult. They tend to learn best with visual cues (such as pictures illustrating tasks). Also, since they have a fascination with electronics, the use of computers and other technology may be effective teaching tools in these children. Generally very responsive to affection, praise, and other positive emotions, children with SMS usually enjoy interacting with adults. A parent or teacher's positive response can often motivate a child to learn.

More than half of children with SMS have sleep disturbances such as daytime sleepiness, difficulty falling asleep at night, nocturnal awakening, decreased sleep time, and abnormalities in REM (rapid eye movement) sleep. These disturbances are due to abnormal melatonin metabolism. Melatonin is a sleep-inducing hormone secreted by the pineal gland in the brain. Therefore, a locking mechanism on the door may be helpful in preventing the child from wandering out of his or her bedroom at night. Also, a night-time dose of melatonin has been recommended for some children and adults with SMS.

Some experts have suggested that every individual with SMS have annual examinations for thyroid function, scoliosis, and eye problems. If any of these tests is abnormal, intervention and further clinical evaluation is appropriate.

Prognosis

Although there is no medical prevention or cure for SMS, early diagnosis gives parents time to learn about and prepare for the challenges of the disease. Although there is insufficient data regarding the average life expectancy of those diagnosed with SMS, some individuals have lived well into their 70s.

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National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Genevieve T. Slomski, PhD

Sotos syndrome

Definition

Sotos syndrome is a genetic condition causing excessive growth and a distinctive head and facial appearance. It has in the past been known as cerebral gigantism. It is often accompanied by delayed development, low muscle tone, and impaired speech.

Description

Sotos syndrome was first described in 1964 and is primarily classified as an overgrowth syndrome, which means that the individual affected with it experiences rapid growth. A number of different symptoms occur in Sotos syndrome; however, it primarily results in rapid growth beginning in the prenatal period and continuing through the infancy and toddler years and into the elementary school years. It is also strongly associated with the bones developing and maturing more quickly (advanced bone age), in a distinctive-appearing face, and in developmental delay.

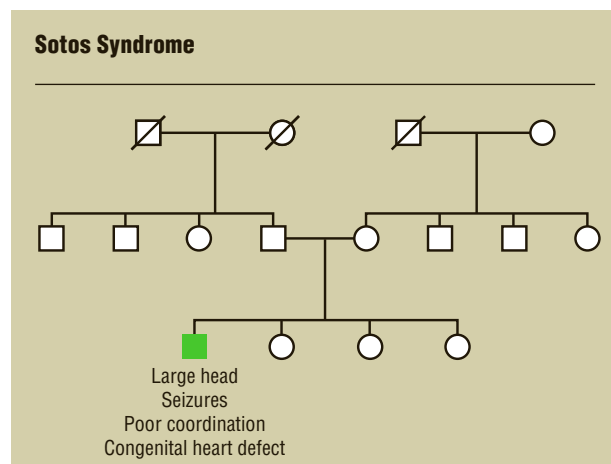
The excessive prenatal growth often results in the newborn being large with respect to length and head circumference; weight is usually average. The rapid growth continues through infancy and into the youth years with the child's length/height and head circumference often being above the 97th percentile, meaning that out of 100

children of the same age, the child is longer/taller and has a larger head than 97 of the children. The rate of growth appears to decrease in later childhood and adolescence and final heights tend to be within the normal ranges.

The facial features of individuals with Sotos syndrome change over time. In infants and toddlers, the face is round with the forehead being prominent and the chin small. As the child grows older and becomes an adolescent, the face becomes long with the chin being more prominent, usually with a pointed or square shape. In adults, faces are usually long and thin. The head remains large from birth through adulthood.

Hypotonia is present at birth in nearly every child with Sotos syndrome. Hypotonia means that there is significantly less tone in the muscles. Bodies with hypotonia are sometimes referred to as “floppy.” Muscle tone improves as the child grows older but even in adults, it is still present to some degree. Hypotonia affects many aspects of the baby’s development. It can cause difficulty in sucking and swallowing and many babies are diagnosed with failure to thrive in the newborn period. This, however, usually lasts for about three to four months and then goes away. Hypotonia makes attaining fine motor skills (grasping, playing with toys, babbling) and gross motor skills (rolling, crawling, walking) difficult and these developmental milestones are usually delayed. Speech is also affected by hypotonia but as the child grows older and the hypotonia resolves or goes away, speech improves. Although the child may have delayed development, intellect typically is borderline to normal. Special attention may be needed in certain subjects, such as reading comprehension and arithmetic. Severe mental retardation is rarely seen.

There are a number of other features that have been associated with Sotos syndrome including jaundice in



Sotos syndrome: pedigree analysis chart (Gale)

KEY TERMS

Advanced bone age—The bones, on x-ray, appear to be those of an older individual.

Congenital—Refers to a disorder that is present at birth.

Failure to thrive—Significantly reduced or delayed physical growth.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Karyotype—A standard arrangement of photographic or computer-generated images of chromosome pairs from a cell in ascending numerical order, from largest to smallest.

Tumor—An abnormal growth of cells. Tumors may be benign (noncancerous) or malignant (cancerous).

the newborn period, coordination problems, and a tendency for clumsiness. Behavioral problems and emotional immaturity are commonly reported. About half of the children with Sotos syndrome will experience a seizure associated with fever. Dental problems such as early eruption of teeth, excessive wear, discoloration, and gingivitis are common. Teeth may also be aligned incorrectly due to changes in the facial structure.

Infections tend to develop in the ear, upper respiratory tract, and urinary tract. In some children, hearing may be disrupted due to recurrent ear infections and in these situations, a referral to an otolaryngologist (a doctor specializing in the ear, nose, and throat) may be necessary for assessment of hearing. Urinary tract infections occur in about one out of five children with Sotos syndrome. These have been associated with structural problems of the bladder and ureters; consequently, if urinary tract infections occur, the child should undergo further evaluation.

Congenital heart problems and development of tumors have been reported in individuals with Sotos syndrome. However, the information regarding the actual risks of these problems is not definitive and medical screening for these conditions is not routinely recommended.

Genetic profile

Sotos syndrome is for the most part a sporadic condition, meaning that a child affected by it did not inherit it from a parent. In a very few families, autosomal dominant inheritance has been documented, which means that both a parent and his/her child is affected by Sotos syndrome.

A Japanese research team found that there is a fault in the *NSD1* gene in most children with Sotos syndrome. Other causes have not been identified.

Demographics

Sotos syndrome has been found to occur in between 1 in 10,000 and 1 in 14,000 newborns. Sotos syndrome occurs in both males and females and has been reported in several races and countries.

Signs and symptoms

A variety of clinical features are associated with Sotos syndrome:

- Newborns are large with respect to length and head circumference; weight is usually average. The rapid growth continues through infancy and into childhood with the child's length/height and head circumference often being above the 97th percentile. The rate of growth appears to decrease in later childhood and adolescence.
- Respiratory and feeding problems (due to hypotonia) may develop in the neonatal period.
- Infants have a round face with prominent forehead and small chin. As the child grows into adolescence and then adulthood the face becomes long and thin, and the chin becomes more prominent.
- Hypotonia is present at birth. This affects the development of fine and gross motor skills, and developmental milestones are usually delayed. Speech is also affected by hypotonia but as the child grows older and the hypotonia resolves or goes away, speech improves.
- Intellect typically is borderline to normal.
- Behavioral problems and emotional immaturity are commonly reported.
- Dental problems such as early eruption of teeth, excessive wear, discoloration, and gingivitis are common.

Diagnosis

Diagnosis of Sotos syndrome is based upon clinical examination, medical history, and x-ray data. There are no laboratory tests that can provide a diagnosis. The clinical criteria that are considered to be diagnostic for Sotos syndrome are excessive growth during the prenatal and postnatal period, advanced bone age, developmental delay, and a characteristic facial appearance. It should be noted that although features suggestive of Sotos syndrome may be present at birth or within 6–12 months after birth, making a diagnosis in infancy is not clear-cut and may take multiple evaluations over several years.

QUESTIONS TO ASK YOUR DOCTOR

- Please describe the progress of Sotos syndrome from the time it first appears in a fetus.
- What specific signs and symptoms are typically associated with Sotos syndrome?
- What do parents need to do to manage a child's health as she or he matures with Sotos syndrome?
- In what respects will a child with Sotos syndrome be able or not be able to live a normal life?

There are many conditions and genetic syndromes that cause excessive growth, consequently, a baby and/or child who has accelerated growth needs to be thoroughly examined by a physician knowledgeable in overgrowth and genetic syndromes. The evaluation includes asking about health problems in the family as well as asking about the growth patterns of the parents and their final height. In some families, growth patterns are different and thus may account for the child's excessive growth. The child will also undergo a complete physical examination. Additional examination of facial appearance, with special attention paid to the shape of the head, width of the face at the level of the eyes, and the appearance of the chin and forehead is necessary as well. Measurement of the head circumference, arm length, leg length, and wing span should be taken. Laboratory testing such as chromosome analysis (karyotype) may be done along with testing for another genetic syndrome called fragile-X. A bone age will also be ordered. Bone age is determined by x-rays of the hand. If the child begins to lose developmental milestones or appears to stop developing, metabolic testing may be done to evaluate for a metabolic condition.

Treatment and management

There is no cure or method for preventing Sotos syndrome. However, the symptoms can be treated and managed. In the majority of cases, the symptoms developed by individuals with Sotos syndrome are treated and managed the same as in individuals in the general population. For example, physical and occupational therapy may help with muscle tone, speech therapy may improve speech, and behavioral assessments may assist with behavioral problems.

Managing the health of a child with Sotos syndrome includes regular measurements of the growth parameters (i.e., height, head circumference and weight); excessive

growth is not treated. Regular eye and dental examinations are also recommended. Medical screening for congenital heart defects and tumors is not routinely recommended, although it has been noted that symptoms should be evaluated sooner rather than later.

Prognosis

With appropriate treatment, management, and encouragement, children with Sotos syndrome can do well. Adults with Sotos syndrome are likely to be within the normal range for height and intellect. Sotos syndrome is not associated with a shortened lifespan.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Sotos Syndrome Support Association (SSSA), PO Box 4626, Wheaton, IL 60189, (888) 246-7772, info@sotossyndrome.org, <http://sotossyndrome.org>

Cindy L Hunter, CGC

SPARCA1 spectrin-associated autosomal recessive cerebellar ataxia type1

Definition

Spectrin-associated, autosomal-recessive cerebellar ataxia type1 (SPARCA1) is an inherited neurological disorder. It is characterized by delayed psychomotor development, severe early-onset ataxia (the inability to

KEY TERMS

Ataxia—The inability to control voluntary muscle movement.

Autosomal recessive—A pattern of genetic inheritance in which two abnormal genes are needed to express the trait or disorder.

Beta-III spectrin—A protein that forms the scaffolding (cytoskeleton) of cell membranes in combination with alpha spectrins.

Cerebellum—The part of the brain between the brain stem and the back of the cerebrum that is involved in muscle coordination and maintaining bodily equilibrium.

Lincoln ataxia (SCA5)—Spinocerebellar ataxia type 5; an adult-onset cerebellar ataxia caused by autosomal dominant mutations in the SPTBN2 gene.

Neuronal spectrinopathies—Neurological disorders such as SPARCA1 and SCA5 that are caused by mutations in genes encoding brain spectrins.

Spinocerebellar ataxia, autosomal recessive 14 (SCAR14)—Spectrin-associated autosomal recessive cerebellar ataxia type1 (SPARCA1).

SPTBN2—Spectrin, beta, nonerythrocytic 2; the gene that encodes beta-III spectrin.

coordinate voluntary movement), intellectual disability, abnormalities of eye movement, and atrophy (degeneration) of the cerebellum—the part of the brain that coordinates muscles and maintains equilibrium. SPARCA1 is also known as spinocerebellar ataxia, autosomal recessive 14 (SCAR14).

Description

Ataxia is a large family of disorders of varying degrees of severity, characterized by impaired balance, coordination, and speech. The many different subtypes of inherited ataxias are caused by mutations in a variety of different genes. SPARCA1 is a newly identified type of inherited severe ataxia. In addition to ataxia caused by progressive atrophy of the cerebellum, SPARCA1 is unusual in that it also causes mild-to-moderate global cognitive impairment beginning in childhood. It is related to spinocerebellar ataxia type 5 (SCA5) or "Lincoln ataxia," which was first identified in descendants of relatives of U.S. President Abraham Lincoln. SPARCA1 and SCA5 are both caused by mutations (changes) in a gene called *SPTBN2* that produces a protein in the cerebellum

called beta-III spectrin. However, unlike SPARCA1, Lincoln ataxia is a slowly progressing disorder of cerebellum function that usually does not develop until adulthood and does not involve intellectual impairment. SPARCA1 is inherited in an autosomal recessive pattern, meaning that an affected individual has inherited two copies of a mutated *SPTBN2* gene, one copy from each parent. In contrast, Lincoln ataxia is autosomal dominant, meaning that an affected individual has inherited only one altered copy of the *SPTBN2* gene, along with one normal copy of the gene. Autosomal dominant mutations causing SCA5 were first identified in the *SPTBN2* gene in 2006.

A genetic defect resulting in SPARCA1 was first identified in 2012 by whole-genome sequencing—determining the sequence of all of the DNA of affected individuals and their parents. The researchers also studied the condition in mice lacking beta-III spectrin and showed that the lack of this protein causes changes in the shape of nerve cells in brain areas important for coordinated movement and cognition. Thus, it appears that the complete absence of beta-III spectrin protein in autosomal recessive SPARCA1 causes childhood ataxia and intellectual impairment. These signs are not seen in SCA5, in which some beta-III spectrin is produced by the second normal *SPTBN2* gene. The researchers' data suggest that beta-III spectrin is involved in the development of the cortex of the brain as well as in cerebellar development and function. Furthermore, the early onset of SPARCA1 suggests that beta-III spectrin is important for prenatal cerebellar development.

Beta-III spectrin is only one of many spectrin proteins that are important for brain development and function. Spectrins are a diverse family of proteins that join together to form the scaffolding or cytoskeleton of cell membranes in many different types of cells. A growing number of conditions are being identified as resulting from abnormal spectrin functioning in nerve cells. These are referred to collectively as neuronal spectrinopathies and include SPARCA1, SCA5, and a form of West syndrome.

Genetic profile

More than 100 different genes have been associated with ataxia. Mutations in at least 20 different genes have been identified as causing autosomal recessive cerebellar ataxias, which are often apparent at birth and are accompanied by developmental delays. Nevertheless, about 40% of cases of autosomal recessive cerebellar ataxia are caused by mutations in genes that have not yet been identified.

QUESTIONS TO ASK YOUR DOCTOR

- What type of cerebellar ataxia does my child have?
- Is genetic testing available for cerebellar ataxia?
- What are the chances that we will have another child with the same disorder?
- What treatments are available for my child?
- What is my child's prognosis?

The *SPTBN2* gene (SPecTrin, Beta, Non-erythrocytic 2) that causes SPARCA1 (SCAR14) and SCA5 is located on the long arm (q) of chromosome 11 at 11q13. A single dominant mutation causes SCA5, and recessive mutations in both *SPTBN2* genes cause SPARCA1. The first known SPARCA1-associated mutation was identified in three affected members of a consanguineous (marriage between related individuals) Pakistani family living in the United Kingdom. The same mutation was present in both *SPTBN2* genes of the affected individuals. It was the first recessive mutation to be identified in any brain spectrin protein. The gene mutation introduced a stop codon that caused the beta-III spectrin protein to terminate prematurely. The parents of the affected family members each carried one mutated *SPTBN2* gene and one normal *SPTBN2* gene and had no symptoms of the disorder.

In 2014, researchers reported on an Egyptian family with SPARCA1-affected members who had two mutated *SPTBN2* genes with a five-base-pair deletion that also resulted in a truncated (shortened) beta-III spectrin protein.

Demographics

Ataxia and cerebellum atrophy affect about 1.5 million people worldwide. Autosomal recessive cerebellar ataxias affect about 5 people in 100,000. SPARCA1 is presumed to be very rare since, as of 2015, it had been identified in only two families. Likewise, SCA5 had been described in only three families.

Signs and symptoms

The signs and symptoms of SPARCA1 are the following:

- global developmental delay with severely delayed psychomotor development, including aided walking beginning between the ages of two and seven and a half years

- gait ataxia (uncoordinated walking)
- cognitive and speech delays in the learning-disabled range
- abnormal eye movements

Diagnosis

Diagnosis of SPARCA1 is based on developmental delays, early-onset cerebellar ataxia, brain imaging studies, and genetic analysis. Computed tomography (CT) scans of the brains of the youngest patients showed no abnormalities or only mild underdevelopment of the posterior corpus callosum that connects the two hemispheres of the cerebrum. However, by the age of six, magnetic resonance imaging (MRI) showed cerebellar atrophy that had progressed over time. The parents of affected children, each carrying one mutated *SPTBN2* gene, had normal neurologic exams with no evidence of ataxia.

Treatment and management

There is no specific treatment for inherited cerebellar ataxias. The children who have been identified with SPARCA1 walk with aids and receive special education.

Prognosis

There is no cure for SPARCA1 or other inherited cerebellar ataxias. People with SPARCA1 will require assistance throughout life. Life expectancy is unknown.

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ORGANIZATIONS

National Ataxia Foundation, 2600 Fernbrook Ln., Suite 119, Minneapolis, MN 55447, (763) 553-0020, (763) 553-0167, naf@ataxia.org, <https://www.ataxia.org>

National Institute of Neurological Disorders and Stroke (NINDS), PO Box 5801, Bethesda, MD 20824, (301) 406-5751 or (800) 352-9424, <http://www.ninds.nih.gov>

Margaret Alic, PhD

Spastic cerebral palsy

Definition

Spastic cerebral palsy (CP) is a disorder in which brain damage results in a movement disability.

Description

Cerebral palsy is a nonprogressive disorder of movement and/or posture caused by a brain abnormality. It is evident before the age of two. There are several types of CP, but spastic CP is the most common—about 60% of all cases. The term "spasticity" refers to increased muscle tone (stiffness), leading to uncontrolled, awkward movements.

Genetic profile

Only about 2% of cases of CP are believed to result from genetic causes. Most cases of CP are associated with risk factors such as low birth weight, premature birth, and lack of oxygen at birth. Multiple births (such as twins or triplets) also have an increased risk. A genetic cause is more likely if these risk factors are not present. If the paralysis and spasticity are symmetrical—that is, if both sides of the body are similarly affected—then the condition is more likely to be genetic in nature. Intellectual disability is usually, but not always, associated with genetic forms. Researchers have not yet found which gene is associated with the disease.

Demographics

CP has an overall incidence of 1 in 250 to 1,000 births. Most forms of CP that are genetic have an autosomal recessive pattern of inheritance. This means that in order for a child to have the disorder, they must inherit one altered copy of the causative gene from each parent. A person who has only one altered copy of the disease gene is called a carrier. Two carriers have a 25% chance of having a child with CP with each pregnancy. As studied in the British Pakistani population, a consanguineous marriage—marriage between relatives—appears to increase the prevalence of a genetic form of spastic CP.

KEY TERMS

Cerebral palsy—Movement disability resulting from nonprogressive brain damage.

Spasticity—Increased muscle tone, or stiffness, which leads to uncontrolled, awkward movements.

Signs and symptoms

CP may not be noticed immediately after birth. Children with CP are slow to meet developmental motor milestones, which are expected ages at which certain mobility skills are achieved. These milestones include reaching for toys, sitting, and walking. People with CP also have abnormal muscle tone (increased in spastic CP), abnormal or uncontrolled movements, and abnormal reflexes. The spasticity may not be present at birth but usually develops during the first two years of life. Many children with spastic CP have normal intelligence, but intellectual disability does occur, especially in inherited forms of the disease. Depending on the severity and extent of the paralysis, some affected individuals can walk (often late and with crutches or walkers), while others with more severe disability cannot walk at all. Seizures are not uncommon in individuals with CP.

Diagnosis

A diagnosis of spastic CP is based on delay in or lack of meeting developmental motor milestones, along with the presence of abnormal muscle tone, movements, and reflexes. Since the exact gene causing some cases of symmetric spastic CP has not yet been identified, molecular testing is not available at this time. Since CP-like symptoms can be found in other genetic conditions, chromosome testing and molecular testing for other suspected conditions may help determine the cause of the CP-like symptoms. Testing may also enable other family members to see if they carry the condition, and allow a fetus to be diagnosed prenatally. Prenatal diagnosis of known genetic conditions can be accomplished using procedures such as chorionic villi sampling, in which cells from the placenta are studied; and amniocentesis, in which skin cells from the fluid surrounding the fetus are studied.

Treatment and management

Treatment of spastic CP is focused on maximizing mobility through physical therapy, and/or providing necessary physical support using devices such as splints, walkers, and wheelchairs. Speech and occupational therapy are sometimes useful as well. Certain types of

QUESTIONS TO ASK YOUR DOCTOR

- What bodily changes are characteristic of a child with spastic cerebral palsy?
- What kind of home care will a child with spastic cerebral palsy require as he or she grows older?
- What physical, mental, and emotional problems is a child with spastic cerebral palsy likely to experience?
- What organizations provide advice and support for parents of a child with spastic cerebral palsy?

surgery of the bone, nerves, tendon, and brain tissue can correct abnormalities, improve mobility, and reduce spasticity. Orthodontic work on the teeth is often indicated in children with CP. Some level of special educational services is usually required.

Prognosis

Spastic CP is not a progressive condition, so living into old age is possible. However, complications such as reduced mobility, mental retardation, feeding difficulties, and respiratory infections can reduce the lifespan. More severe disabilities are associated with greater decreases in life expectancy, but at least half of people with CP live to at least age 35.

Resources

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ORGANIZATIONS

United Cerebral Palsy (UCP), 1825 K St., Suite 600,
Washington, DC 20006, (202) 776-0406 or (800)
872-5827, <http://ucp.org>

Toni I. Pollin, MS, CGC

Sphingomyelin lipidosis see **Niemann-Pick disease**

Sphingomyelinase deficiency see **Niemann-Pick disease**

Spina bifida

Definition

Spina bifida is a serious birth abnormality termed a neural tube defect, in which the spinal cord is malformed and lacks its usual protective skeletal and soft tissue coverings.

Description

Spina bifida is a lesion that may appear in the midline of the body anywhere from the neck to the buttocks. It is caused by the failure of the vertebrae to form properly in fetal development, leaving the spinal cord in some degree of vulnerability or exposure to the environment.

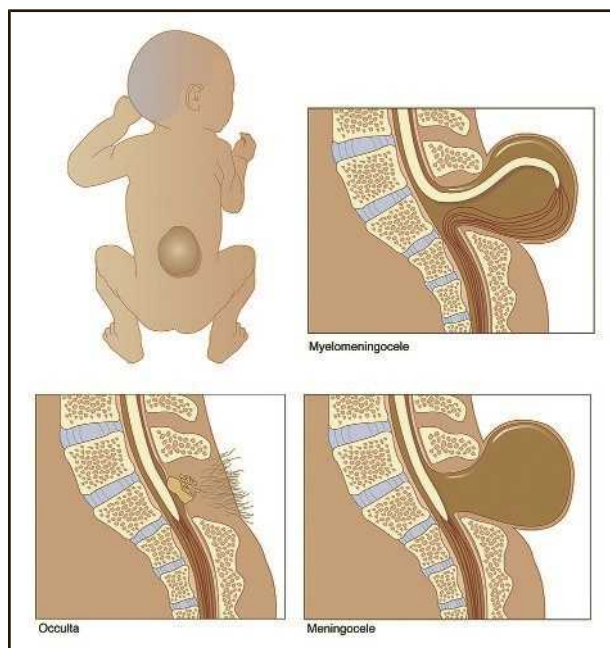


Illustration showing the three main types of spina bifida.
(Peter Gardiner/Science Source)

Spina bifida occurs in multiple forms of varying exposure of the spinal cord.

Spina bifida occulta

This form of spina bifida usually involves the deformation of a single vertebra in the cervical, lumbar, or sacral regions. The spinal cord and nerves are usually normal with no neurological symptoms. There is typically skin covering the vertebral abnormality, which is indicated visually by a dimple with a tuft of hair. Clinical symptoms are absent in the majority of cases.

Spina bifida cystica

Spina bifida cystica is a term used to describe several severe forms of spina bifida. The spinal cord protrudes outward through an open defect in the vertebrae, forming a cyst-like sac on the outside of the body that is filled with cerebrospinal fluid. When the sac includes the meninges, a protective three-layered membrane that covers the spinal cord, the condition is said to involve a meningocele. When the actual spinal cord or nerve roots are included in the sac, the condition is described as involving a meningocele. This is a more common form of spina bifida cystica. Neurological deficits occur because nervous tissue is integrated in the wall of the sac and disrupt their function. Both types of spina bifida cystica are most common in the lumbar and sacral regions of the spine.

Rachischisis and spina bifida with myeloschisis

The most severe type of spina bifida is caused by the failure of the neural folds to fuse. The entire spinal canal is open, exposing the spinal nerves completely and the spinal cord is only developed into a flattened mass of nervous tissue.

Spina bifida is usually readily apparent at birth because of the malformation of the back and clinical symptoms associated with most forms of the abnormality. There are varying degrees of neurological deficit present that depend on the position and degree of the abnormality. There is usually a loss of sensation to the skin with varying skeletal muscle paralysis in the region below the lesion. Paralysis of the urinary bladder or anal sphincters is also common in these forms of the disease.

Genetic profile

Spina bifida may occur as an isolated defect or associated with other malformations, such as partial absence of the brain. As an isolated abnormality, spina bifida is caused by a combination of genetic factors and environmental influences. The most important factor that causes

neural tube defects such as spina bifida is a maternal folic acid deficiency during early pregnancy. Folic acid levels are dependent on dietary intake; during pregnancy the requirement for folic acid is increased and is difficult to meet with an average contemporary diet. Mothers of children with neural tube defects may have reduced folate levels in their blood, along with a defect in the recycling pathway for digested folic acid. This defect can be caused by a genetic mutation in the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR). The mutation in the gene for MTHFR causes an unstable enzyme that cannot function properly in the metabolism of folic acid. The mutant allele for unstable MTHFR is very common in many populations. Between 5% and 15% of the population may have both alleles for a mutated form of MTHFR. Research has demonstrated that mothers of infants with neural tube defects are twice as likely to have all mutant alleles of the gene for MTHFR. A folic acid deficiency may be caused by other genetic defects or by dietary deprivation alone. A small percentage of neural tube defects such as spina bifida can be narrowed down to other specific causes, such as the early rupture of the amnion-forming fibrous amniotic bands that disrupt vertebral development. Exposure to some chemicals that produce abnormal fetal development (teratogens) may cause spina bifida. Other causes may include separate single gene mutations, chromosomal abnormalities, environmental insults such as maternal diabetes mellitus, or prenatal exposure to certain anticonvulsant drugs. The recurrence risk varies with each of these specific causes.

Demographics

Spina bifida occurs worldwide but there has been a steady decrease in occurrence rates over the past 50–70 years, most likely due to dietary supplementation with folic acid. Before folic acid fortification, some form of neural tube defect affected approximately 2,500–3,000 births in the United States annually. In 2001, there was a 24% decline in spina bifida in the United States from folic acid fortification of enriched grain products and other folic acid initiatives. The highest prevalence rates, about 1 in 200 pregnancies, have been reported from northern provinces in China. High prevalence rates of approximately 1 in 1,000 pregnancies have also been found in Central and South America. The lowest prevalence rates, fewer than 1 in 2,000 pregnancies, have been found in European countries. Regionally, the highest prevalence in the United States occurs in the Southeast, in approximately 1 in 500 pregnancies. A study performed by the Centers for Disease Control and Prevention (CDC) in North Carolina between 1995 and 1999 demonstrated a 32% decline in the incidence of spina bifida. The decline

KEY TERMS

Allele—One of two or more different variants of the same gene that encode specific and inheritable characteristics that occupy corresponding locations on a pair of chromosomes.

Amnion—The thin, protective sac that suspends the fetus in a protective amniotic fluid.

Anesthesia of the skin—A loss of feeling or sensation in the skin associated with spine-related injury or disorders.

Cerebrospinal fluid—Fluid that bathes and supports the brain and the spinal cord, protecting it from physical impact.

Chiari II anomaly—A structural abnormality of the lower portion of the brain (cerebellum and brain stem) associated with spina bifida; the lower structures of the brain are crowded and may be forced into the foramen magnum, the opening through which the brain and spinal cord are connected.

Hydrocephalus—The excess accumulation of cerebrospinal fluid around the brain that often causes enlargement of the head.

Neural folds and tube—Portions of the developing embryo from which the brain and spinal cord arise.

Vertebral divisions—The human vertebral regions are divided into cervical, thoracic, lumbar, and sacral from the neck to the tailbone.

in incidence was not uniform across the population but was dependent on geographic region, and correlated with maternal sociodemographic characteristics. Populations with higher income and education have undergone the greatest decline in spina bifida and, although the use of multivitamins has played a role in this population, much of the recent decline in neural tube defects in the United States has been a result of the mandatory government fortification program of enriched grain products.

Signs and symptoms

In most cases spina bifida is obvious at birth because of the malformation of the spinal column and associated neurological deficits. The spinal cord may be completely exposed, appearing as a mass on the back covered by the meningeal membranes or skin. Although spina bifida may occur anywhere from the base of the skull to the buttocks, about 75% of cases occur in the lumbar region. When the defect is covered by skin it may include a

dimple or depression, a port wine-colored birthmark, or a bulge with a tuft of hair.

Along with the malformations the neurological deficit is also obvious, often manifesting as a loss of sensation or feeling in the skin. This level of anesthesia of the skin depends on which dermatomes are affected. Dermatomes are patches of skin innervated by specific spinal nerves. The spinal nerves leave the spinal cord to innervate structures in descending order. The higher the lesion of spina bifida is located on the vertebral column, the more spinal nerves may be affected. Skeletal muscle may also be paralyzed in the same fashion, sometimes over the entire pelvic area and lower extremity. Saddle anesthesia is the term used to refer to the entire loss of sensation to the area of the body that touches the saddle during horseback riding. Saddle anesthesia is a symptom often seen when paralysis of urinary bladder and anal sphincters is present. A lack of response to touch, leg movement or resistance to passive-elicited movement, severe flaccidity, and lack of anal reflex (reflex of musculature in response to touch) in an infant are signs that neurological deficits in the lower region are present.

There are other complications that sometimes develop in association with spina bifida. Some infants develop hydrocephaly, an accumulation of excess fluid in the four cavities of the brain. At least one in every seven cases develops symptoms of Chiari II malformation, a condition in which the lower part of the brain is crowded and may be forced into the upper part of the spinal cavity. A lipomeningocele or lipomyelomeningocele may occur in the lumbar or sacral back area. In these conditions a tumor of fatty tissue becomes isolated among the nerves below the spinal cord, which may result in tethering of the spinal cord and complications similar to those with open spina bifida.

Diagnosis

A mother carrying a fetus with spina bifida will not experience any unusual signs or symptoms in early pregnancy. Initial signs and symptoms in the maternal amniotic fluid are often used to discover spina bifida prenatally. During amniocentesis obstetricians may screen for high levels of a protein called alphafetoprotein (AFP). High AFP is a general indicator that the fetus may have a defect. The AFP test is not indicative of spina bifida specifically, but alerts the obstetrician that a detailed ultrasonogram (use of ultrasound) may be necessary. Spina bifida may cause elevated levels of AFP because it is an open fetal defect that allows high levels of the AFP of the fetus to travel into maternal amniotic fluid and smaller amounts to enter maternal blood serum. A prenatal diagnosis of spina bifida may be made with ultrasonographic examination. Malformations may be

QUESTIONS TO ASK YOUR DOCTOR

- What is the probability that more than one child with spina bifida will be born into the same family?
- Is there a prenatal test for spinal bifida and, if so, how reliable is it?
- What types of medical problems is a person with spina bifida likely to encounter as he or she grows older?
- Are there Internet resources from which I can obtain additional information about spina bifida?

detected via ultrasonogram as early as 12–14 weeks of pregnancy. A postnatal diagnosis is usually obvious based on external lesions. In addition to the characteristic malformations, paralysis below the level of the lesion may be part of the diagnosis. In cases in which there are no external indicators the diagnosis may not become evident until neurological abnormalities develop weeks, months, or years following birth.

Treatment and management

Prevention of spina bifida and other neural tube defects is improved with the use of folic acid vitamin supplements for several months prior to and following conception. The CDC recommends an intake of 400 mcg of synthetic folic acid per day for all women of childbearing years to prevent neural tube defects.

Open fetal surgery has been performed for spina bifida during the several months of pregnancy. After direct closure of the spine malformation the fetus is returned to the womb. By preventing chronic intrauterine exposure to mechanical and chemical trauma, prenatal surgery improves neurological function and leads to fewer complications after birth. Fetal surgery is considered experimental and results have been mixed.

After birth, aggressive surgical and medical management have improved the survival and function of infants with spina bifida. Initial surgery on the spinal column defect may be performed in the first days of life, providing protection against injury and infection. Subsequent surgery is often necessary to protect against excessive curvature of the spine. When spina bifida occurs in conjunction with hydrocephaly, surgery is performed to implant a mechanical shunt to decrease the pressure and amount of cerebrospinal fluid in the cavities of the brain. Because of weakness or paralysis below the level of the

spinal defect, most children will require physical therapy, bracing, and other orthopedic assistance to enable them to walk. A variety of approaches including periodic bladder catheterization, surgical diversion of urine, and antibiotics are used to protect urinary function.

Although most individuals with spina bifida have normal intellectual function, learning disabilities or mental impairment may occur. This may result in part from hydrocephaly and/or infections of the nervous system. Children so affected may benefit from early educational intervention, physical therapy, and occupational therapy. Counseling to improve self-image and lessen barriers to socialization becomes important in late childhood and adolescence.

Prognosis

More than 80% of infants born with spina bifida survive with surgical and medical management. Although complications from paralysis, hydrocephaly, Chiari II malformation, and urinary tract deterioration threaten the well-being of survivors, the outlook for normal intellectual function is good.

Resources

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ORGANIZATIONS

- March of Dimes Birth Defects Foundation, 1275 Mamaroneck Ave., White Plains, NY 10605, (888) 663-4637, <http://www.marchofdimes.org>
- National Birth Defects Prevention Network, 1321 Upland Dr., Suite 1561, Houston, TX 77043, [nbdpn@nbdpn.org](http://nbdpn.org), <http://www.nbdpn.org>

Spina Bifida Association of America, PO Box 17427, Arlington, VA 22216, (202) 944-3285, (202) 944-3295, sbaa@sbaa.org, <http://www.sbaa.org>

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Spinal and bulbar muscular atrophy

Definition

Spinal and bulbar muscular atrophy (SBMA) is a disorder characterized by degradation of the anterior horn cells of the spinal cord resulting in slow progressive muscle weakness and atrophy. This disorder only affects males. Men diagnosed with SBMA often have breast enlargement (gynecomastia) and testicular atrophy, and may have infertility.

Description

Spinal and bulbar muscular atrophy is also known as Kennedy's disease. The disease was first characterized in 1968. SBMA is caused primarily from degradation of the anterior horn cells of the spinal cord, resulting in proximal weakness and atrophy of voluntary skeletal muscle. Anterior horn cells control the voluntary muscle contractions from large muscle groups such as the arms and legs. For example, if an individual wants to move his/her arm, electrical impulses are sent from the brain to the anterior horn cells to the muscles of the arm, which then stimulate the arm muscles to contract, allowing the arm to move. Degradation is a rapid loss of functional motor neurons. Loss of motor neurons results in progressive symmetrical atrophy of the voluntary muscles. Progressive symmetrical atrophy refers to the loss of function of muscle groups from both sides of the body. For example, both arms and both legs are equally affected by similar degrees of muscle loss and the inability to be controlled and used properly. Progressive loss indicates that muscle loss is not instantaneous; rather, muscle loss occurs consistently over a period of time. These muscle groups include those skeletal muscles that control large muscle groups such as the arms, legs, and torso. The weakness in the legs is generally greater than the weakness in the arms.

Proximal weakness is in contrast to distal weakness, and indicates that muscles such as the arms and the legs are affected rather than the muscles of the hands, feet, fingers, and toes. However, the motor neuron of the brain stem and sensory neurons of the dorsal root ganglia are also affected in SBMA. Motor neurons are the neurons that control large muscle groups (arms, legs, torso) of

which anterior horn cells are a subgroup. Sensory neurons are a distinct class of neurons that control an individual's senses. An example would be pain receptors that cause an involuntary reaction to a stimulus such as when a person accidentally grasps a boiling hot kettle and immediately releases the kettle. Dorsal root ganglia are analogous to a headquarters for neurons, through which essentially all neuronal stimuli are processed.

Genetic profile

SBMA is an X-linked recessive disease, meaning the abnormal gene is found on the X chromosome. Since males only inherit one X chromosome (the other is the Y chromosome) they will always express an X-linked disorder if the abnormal gene is on the X chromosome they receive. Females, on the other hand, inherit two X chromosomes. Even if one X chromosome contains the abnormal gene, the second X chromosome with a normal-functioning gene can usually compensate for the other. Males lack the second X chromosome that may be able to mask the effect of the abnormal gene.

The gene with the mutation that causes the symptoms of SBMA is known as the androgen receptor (*AR*) gene and it maps to the proximal long arm of the X chromosome.

The *AR* gene produces a protein that is a member of the steroid-thyroid hormone receptor family and is involved in transcription regulation. Transcription regulation is the molecular process that controls the "reading" of the genetic DNA information and turns it into RNA, which is the material that generates proteins.

Demographics

Because of the X-linked inheritance pattern of SBMA disease, only males are affected by this disorder. Females are carriers of the disease but do not exhibit symptoms. It is estimated that 1 in 50,000 males are affected with SBMA.

Signs and symptoms

SBMA is suspected clinically in a male with an early-adulthood onset of proximal muscle weakness of the limbs; fasciculations (small local contractions of the musculature that is visible through the skin) of the tongue, lips, or area around the mouth; absence of hyperactive reflexes and spasticity; and often evidence of enlarged breasts and/or small testes with few or no sperm.

Diagnosis

SBMA is primarily an adult-onset disease, with symptoms occurring between the third and fifth decades

KEY TERMS

Anterior horn cells—Subset of motor neurons within the spinal cord.

Atrophy—Wasting-away of normal tissue or an organ due to degeneration of the cells.

Degradation—Loss or diminishing.

Dorsal root ganglia—The subset of neuronal cells controlling impulses in and out of the brain.

Intragenic—Occurring within a single gene.

Motor neurons—Class of neurons that specifically control and stimulate voluntary muscles.

Motor units—Functional connection with a single motor neuron and muscle.

Sensory neurons—Class of neurons that specifically regulate and control external stimuli (e.g., sight, sound).

Transcription—The process by which genetic information on a strand of DNA is used to synthesize a strand of complementary RNA.

Voluntary muscle—A muscle under conscious control, such as arm and leg muscles.

of life. Once symptoms present, the disease is slowly progressive. In addition to neuronal cell loss, breast enlargement (gynecomastia), reduced fertility, and testicular atrophy have also been reported in affected males.

The diagnosis is made by a specific molecular genetic test that measures the number of "CAG trinucleotide repeats" in a particular part of the androgen receptor (*AR*) gene. The alteration of the *AR* gene that causes SBMA is an expansion of a CAG trinucleotide repeat in the first part of the gene. In unaffected individuals, between 11 and 33 copies of the CAG trinucleotide are present. In patients with SBMA, this number rises to over 38. The greater the number of expanded repeats, the earlier the age of onset.

Treatment and management

As the bulbar muscles of the face are affected, eating and swallowing can become difficult. Speech and swallowing therapy are useful for helping individuals with SBMA avoid choking due to weakened facial muscles. Due to the weakening of the respiratory muscles, breathing can also be labored. It is therefore essential for patients to undergo chest physiotherapy (CPT). CPT is a standard set of procedures designed to trigger and aid coughing in patients. Coughing is

QUESTIONS TO ASK YOUR DOCTOR

- At what age is SBMA normally diagnosed, and what are the symptoms that lead to that diagnosis?
- Please explain the bodily changes that occur as a result of SBMA.
- How will SBMA affect the projected lifespan of my son, who has just been diagnosed with the condition?
- What are the chances to have another son affected with SBMA, and what is the chance my daughter(s) is/are a carrier for SBMA?

important as it clears the patient's lungs and throat of moisture and prevents secondary problems, such as pneumonia.

As symptoms progress, patients may require a ventilator to aid breathing.

Individuals affected with SBMA can receive physical therapy to increase strength and maintain stability while walking. As the disease progresses, some individuals require braces and walkers to avoid falling.

Prognosis

The majority of patients with SBMA have a normal lifespan. About 10% of older, severely affected patients with SBMA may die from pneumonia or asphyxiation secondary to weakness of the bulbar muscles.

Resources

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ORGANIZATIONS

- Cure SMA, 925 Busse Rd., Elk Grove Village IL 60007, (800) 886-1762, info@curesma.org, <http://www.curesma.org>
- Fight SMA, 8016 Staples Mill Rd., Richmond, VA 23228-2713, (703) 299-1144, web@fightsma.org, <http://fightsma.org>
- Kennedy's Disease Association, PO Box 1105, Coarsegold, CA 93614, (559)-658-5950, info@kennedysdisease.org, <http://www.kennedysdisease.org>
- Muscular Dystrophy Association-USA (MDA), 222 S. Riverside Plaza, Suite 1500, Chicago, IL 60606, (800) 572-1717, mda@mdausa.org, <http://www.mda.org>

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Spinal muscular atrophy

Definition

Spinal muscular atrophy (SMA) is a disease characterized by degradation of the anterior horn cells of the spinal cord and has similar characteristics to spinal and bulbar muscular atrophy (SBMA). SBMA differs from SMA in its mode of inheritance, the disease-determining gene, the mutational events that trigger disease, and the cellular specificity of the disease pathology.

Description

The anterior horn cells control the voluntary muscle contractions from large muscle groups such as the arms and legs. For example, if an individual wants to move his/her arm, electrical impulses are sent from the brain down the anterior horn cells to the muscles of the arm, which then stimulates the arm muscles to contract, allowing the arm to move. Loss of motor neurons due to degradation results in progressive symmetrical atrophy of the voluntary muscles. Progressive symmetrical atrophy refers to the loss of function of muscle groups from both sides of the body. For example, both arms and both legs are equally affected to similar degrees of muscle loss and the inability to be controlled and used properly. Progressive loss indicates that muscle loss is not instantaneous; rather, muscle loss occurs consistently over a period of time. These muscle groups include skeletal muscles that control large muscle groups such as the

arms, legs, and torso. The weakness in the legs is generally greater than the weakness in the arms.

Spinal muscular atrophy (SMA) arises primarily from degradation of the anterior horn cells of the spinal cord and leads to proximal weakness and atrophy of voluntary skeletal muscle. Proximal weakness affects the limbs positioned closer to the body such as the arms and legs rather than more distant body parts such as the hands, feet, fingers, or toes.

Spinal muscular atrophy only affects the motor neurons of the spinal cord and voluntary muscles of the limb and trunk. Patients do not display sensory loss, heart problems, or intellectual disability. There are numerous secondary complications seen in SMA, including bending of the legs and arms and pneumonia. SMA development initially involves a substantial loss of motor units, followed by a stabilization of the surviving motor units. Motor units refer to an entire motor neuron and the connections within a muscle required for neuronal function.

Clinical subgroups

The childhood form of SMA is subdivided into three main clinical subgroups—type I, II, and III—and depends upon the age of onset and severity. A fourth subgroup, type O, was recently discovered in London.

TYPE I. Type I SMA, or Werdnig-Hoffmann disease, is the acute or severe form characterized by severe muscle atrophy. Guido-Werdig, an Austrian doctor, first identified the disease in 1891. He described two brothers displaying progressive muscle weakness from the age of 10 months, starting in the legs and progressing to the back and arms. The first brother died at the age of three with respiratory problems. The second brother survived to the age of six.

Symptoms emerge in the first three months of life, with the affected children never gaining the ability to sit, stand, or walk. Swallowing and feeding may be difficult and the child may show difficulties with his/her own secretions. There is general weakness in the intercostal and accessory respiratory muscles (the muscles situated between the ribs). The chest may appear concave or sunken in due to diaphragmatic breathing.

TYPE II. Type II SMA was first described in 1964. It is less severe than type I, with clinical symptoms emerging between three and 15 months of age. Most patients can sit but are unable to stand or walk unaided. Feeding and swallowing problems are uncommon in patients with type II SMA but as with patients diagnosed with type I SMA, the intercostal muscles are affected, with diaphragmatic breathing as a main characteristic of children with type II SMA. Most patients will survive beyond the age of four years and, depending upon how their respiratory system is affected, may live through adolescence.

KEY TERMS

Anterior horn cells—Subset of motor neurons within the spinal cord.

Atrophy—Wasting-away of normal tissue or an organ due to degeneration of the cells.

Dorsal root ganglia—The subset of neuronal cells controlling impulses in and out of the brain.

Intragenic—Occurring within a single gene.

Motor neurons—Class of neurons that specifically control and stimulate voluntary muscles.

Motor units—Functional connection with a single motor neuron and muscle.

Sensory neurons—Class of neurons that specifically regulate and control external stimuli (e.g., sight, sound).

Transcription—The process by which genetic information on a strand of DNA is used to synthesize a strand of complementary RNA.

Voluntary muscle—A muscle under conscious control, such as arm and leg muscles.

TYPE III. The chronic form of SMA, type III (Kugelberg-Welander disease) was first described in 1956. The clinical symptoms manifest after the age of four. It produces proximal muscle weakness, predominantly in the lower body. Affected individuals can walk unaided and have a normal lifespan depending upon the extent of respiratory muscle loss.

TYPE O. Clinicians in London have recently identified a fourth form of the childhood disease. The type O form appears to have a fetal onset in that affected individuals display reduced movement within the uterus and are born with severe muscular atrophy with massive motor neuronal cell death. Therefore, these patients have very few functional motor neurons and motor units.

Genetic profile

All forms of childhood SMA are autosomal recessive, which requires both parents to be carriers of the disease to pass it to their offspring. If both parents are carriers, there is a 25% chance of their child being affected. All three forms are caused by a decrease in the production of a protein, termed “survival of motor neuron” (SMN). Two almost identical genes that are located on chromosome 5 encode the SMN protein: *SMN-1* and *SMN-2* (previously referred to as telomeric and centromeric SMN, respectively). Remarkably, only mutations or deletions of *SMN-1* result in disease development.

In most unaffected individuals there are two *SMN-1* and two *SMN-2* genes. A subset of SMA-causing mutations is intragenic to single amino acid substitutions within the *SMN-1* gene. Intragenic mutations are those that occur within an otherwise intact *SMN* gene, but that there is a small and very subtle mutation that is only found within the *SMN* gene. This is in contrast to large genomic deletions that can affect the *SMN* gene and its neighboring genes. The intragenic or small mutations thereby confirm *SMN-1* as the SMA-determining gene.

Demographics

Approximately 1 in 10,000 live births is affected with SMA, which is slightly lower than expected since the carrier frequency is between 1 in 40 and 1 in 50. Since this is a recessive disease, meaning two copies of the abnormal gene must be present for the disease to occur, carriers are unaffected because only one copy of the abnormal gene is not sufficient to cause the disease.

The genomic *SMN* region is remarkably unstable and *de novo* mutations (mutations that are new and not inherited from the parents) are quite frequent, accounting for nearly 2% of all SMA cases. In 90% of patients death occurs before the age of two due to respiratory failure. In North America and Europe, type I SMA accounts for 1 in every 25,000 infant mortalities. SMA is the leading genetic cause of infantile death and is the second most common autosomal recessive disorder behind cystic fibrosis. Carrier frequencies and disease frequencies are similar throughout the world, although slight variations can exist. Asian populations have a slightly reduced carrier frequency, although it is not known why this discrepancy has occurred.

Signs and symptoms

Research shows that in SMA, the reduced *SMN* protein levels result in motor neuronal cell degradation. How and why this occurs is still not known.

Diagnosis

One of the main diagnostic tools is electromyography (EMG). Contraction of voluntary muscle is controlled by electrical impulses originating from the brain. These impulses travel down the motor neurons of the spinal cord to the connecting muscles where it triggers the contraction. The EMG records this electrical impulse and determines whether the electric current is the same as in normal individuals. Metal needles are inserted into the arms and thigh and the electrical impulse is recorded.

In addition, the speed at which the electric impulse passes down the motor neuron can also be used as a diagnostic test. In SMA patients both the nerve conduction velocity (NCV) and the EMG readings are reduced.

QUESTIONS TO ASK YOUR DOCTOR

- How do the four types of spinal muscular atrophy differ from each other?
- What is the genetic basis for this disease? Is it the same for all four forms of the condition?
- What are the most common signs and symptoms of spinal muscular atrophy?
- What are the most serious long-term medical problems associated with this genetic disorder?

The third test is an invasive procedure called a muscle biopsy. This involves a surgeon removing a small section of muscle and testing it for signs of degradation.

Treatment and management

To date there is no treatment for childhood SMA, and treatment focuses on providing comfort from the symptoms associated with the disease.

Prognosis

In type I SMA, eating and swallowing can become difficult as the muscles of the face are affected. Due to the degradation of the respiratory muscles breathing can also be labored. It is therefore essential for patients to undergo chest physiotherapy (CPT). CPT is a standard set of procedures designed to trigger and aid coughing in patients. Coughing is important as it clears the patient's lungs and throat of moisture and prevents secondary problems such as pneumonia.

As symptoms progress patients may require a ventilator to aid breathing. There are two main forms of ventilation systems. Negative pressure ventilation can be achieved by placing the patient in a Port-A-Lung. This machine ensures that the air pressure around the patient is lower than the air pressure within the patient's lungs, enabling easier breathing. The pressure can be raised or lowered if the patient's ventilation rate increases or decreases.

The second method is called biphasic positive airway pressure (Bi-Pap). This procedure involves the insertion of a small tube down the nose and into the patient's lungs, through which oxygen is pumped into the lungs and carbon dioxide is removed. This system allows maximum inspiration and expiration levels to be reached.

Of all the forms of childhood SMA, type II is the most diverse. It is therefore hard to tell when muscle weakness will occur and how severe the disease will be. With the aid

of leg braces and walking devices some children may gain the ability to stand. Unlike type I SMA, not all children with type II are affected by respiratory weakness. The main cause of death in patients with type II is respiratory failure resulting from a respiratory infection. It is therefore important to ensure that mucus does not build up in a patient's respiratory tract as this could aid viral and bacterial infections.

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ORGANIZATIONS

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Spindle transfer technique

Definitions

The spindle transfer technique, also known as maternal spindle transfer or MST, is one technique employed in mitochondrial replacement therapy (MRT), which is the only approach known to prevent a mitochondrial disease in human offspring as of 2021. Given the lack of treatments for mitochondrial diseases and the limitations of prenatal diagnosis, researchers have focused on preventing the transmission of mitochondrial diseases through germline gene replacement therapy. MST is used during in vitro fertilization (IVF) to replace mitochondria with harmful mutations within a female oocyte (a cell that develops into an ovum by meiosis). The healthy

replacement mitochondria are obtained from a donated oocyte. Because children born as a result of MST and IVF have genetic material derived from two women and one man, they have been referred to in the popular press as three-parent babies.

The term *spindle* in the context of spindle transfer refers to a microscopic network of microtubules (sometimes called spindle fibers) that forms during cell division to pull chromosomes to the poles of the cell during the phase of cell division called metaphase.

Description

Mitochondrial diseases

To understand the significance of spindle transfer and other forms of mitochondrial replacement therapy (MRT), some background information is helpful. Mitochondrial diseases are a group of metabolic disorders in which defective mitochondria within the affected person's cells fail to produce enough energy to meet the body's needs. Mitochondria are microscopic organelles found within all cells of the human body except red blood cells. Sometimes called the powerhouses of the cell, mitochondria convert energy derived from food into adenosine triphosphate (ATP), an organic molecule necessary for most cell functions. But because mitochondria perform a wide range of functions within different body tissues and organs, the symptoms of mitochondrial diseases vary widely, ranging from muscular weakness, loss of balance, nausea, vomiting, developmental delays, and dementia, to pain, kidney or liver failure, vision loss, and difficulty breathing. The website of the United Mitochondrial Disease Foundation (UMDF) contains detailed descriptions of 43 different mitochondrial diseases, but researchers estimate that there are at least several hundred disorders in this category.

Most mitochondrial diseases are genetic disorders. They may be caused either by mutations in the nuclear DNA in the cell or by mutations in the mitochondrial DNA (abbreviated as mtDNA). Most mitochondrial function is encoded by the DNA in the cell nucleus, which in humans is inherited from both parents. In contrast, mtDNA is inherited only from the mother; it contains only 37 genes and encodes 13 proteins. Another difference is that while there are only two copies of DNA in a human cell nucleus, each mitochondrion contains between 2 and 10 copies of mtDNA.

As there are about 500 mitochondria in an average human cell (although liver and muscle cells may contain thousands), the difference in the number of DNA copies means that mutations occur at a much higher rate in mtDNA than in nuclear DNA. When mitochondria multiply during the normal process of cell division, they can accumulate random mutations, a condition called

KEY TERMS

Adenosine triphosphate (ATP)—An organic molecule found in all living organisms, involved in energy production for metabolic processes and RNA synthesis.

Cytoplasm—All of the material within a cell enclosed by the cell membrane, excluding the nucleus. The cytoplasm includes cytosol, organelles (including mitochondria), and various inclusions.

Diploid—Referring to a cell or nucleus that contains two copies of genetic material, or a complete set of chromosomes.

Gamete—A sex cell (sperm or ovum) containing the haploid number of chromosomes, and capable of fusing with a gamete of the opposite sex to form a zygote.

Genome—The total amount of genetic information within an organism's chromosomes, including its genes and DNA sequences.

Germline—The population of a complex organism's cells that pass on genetic information to offspring. Germline cells include eggs, sperm, and fertilized eggs.

Haploid—Referring to cells that have only one chromosome of each type and therefore have only one complete set of genes.

Heteroplasmy—The presence of two or more sources of mitochondrial DNA within a cell, person, or mitochondrion. It is an important factor in determining the severity of a mitochondrial disease.

In vitro fertilization (IVF)—A form of assisted reproduction technology in which a human ovum (egg) is combined with sperm outside the body in a laboratory container ("in vitro" means "in a glass").

Leigh syndrome—A rare genetic disease associated with mutations in either mitochondrial DNA or nuclear DNA, and characterized by degeneration of the central nervous system. It is named for Archibald Denis Leigh, a British psychiatrist who first described the syndrome in 1951.

Meiosis (pronounced my-OH-sis)—The process of cell division during the production of ova and sperm, in which the material in the chromosomes undergoes recombination (first-stage meiosis), and the chromosomes are reduced to a single set of

23 instead of the normal number of 23 pairs (second-stage meiosis)

Metaphase—A stage in the cycle of cell division in which the cell's genetic material condenses into chromosomes, which become visible and line up in the center of the dividing cell.

Mitochondria (singular, mitochondrion)—Organelles in the cytoplasm of cells that contain genetic material and enzymes responsible for converting food to usable energy.

Mitochondrial replacement therapy (MRT)—A technique to prevent or treat certain genetic diseases by replacing the mitochondria in one or more cells. It is also called mitochondrial donation.

Oocyte (pronounced OH-eh-site)—A diploid cell in females from which an egg or ovum develops by meiosis.

Organelle—A specialized structure found within a cell that performs a specific function or carries out a specific life process. Mitochondria are organelles.

Polar body—Either of two small cells produced during the two meiotic divisions in the production of an oocyte. Polar bodies contain only small amounts of cytoplasm and eventually disintegrate.

Pronuclear transfer—A mitochondrial replacement technique in which the mother's egg is first fertilized by the father's sperm; then the two pronuclei are inserted into a donor egg that has been fertilized and has had its own nucleus removed.

Pronucleus (plural, pronuclei)—The nucleus of a sperm or egg cell during the process of fertilization.

Spindle apparatus—A network of microtubules (also known as spindle fibers) that forms during cell division to pull chromosomes during metaphase to the poles of the cell. The microtubules are formed from a protein called tubulin.

Three-parent baby—A term used in the mass media to describe a baby produced from the genetic material of one man and two women through the use of mitochondrial replacement technologies and three-person in vitro fertilization (IVF). It is not a scientific term.

Zygote—A fertilized egg cell that results from the union of two gametes, an egg and a sperm.

heteroplasmy. In some people, only a few mitochondria are affected by these mutations. In others, however, the number of mutant mitochondria increases over time until the mutant organelles dominate the pool of mtDNA. When this threshold is reached, typically in adolescence or early adult life, the person will begin to show symptoms of a mitochondrial disease. About 0.5% of the population carries mtDNA mutations, and about 1 person in every 5,000 (0.02%) is at risk of developing a mitochondrial disease.

In vitro fertilization

Spindle transfer or MST is a recent specialized form of in vitro fertilization, or IVF, which has helped couples with fertility difficulties have children since 1978. About 5 million children around the world have been born through IVF as of 2021. The basic IVF technique involves the administration of hormone therapy to the intended mother to stimulate the release of multiple eggs into the uterus. The eggs are retrieved, selected for health and maturity, and either mixed with sperm or fertilized by the injection of a single sperm into an egg.

The resultant embryos are allowed to mature for a short period of time and then subjected to genetic testing to screen for genetic disorders, abnormal chromosomes, or (as of 2014) defective mitochondrial DNA. The embryos that pass screening are returned to the mother's uterus, where it is hoped that at least one will implant and produce a successful pregnancy.

Spindle transfer technique

If the mother's eggs indicate the presence of mutant mtDNA, an oocyte is removed from the mother. When it reaches the metaphase stage of cell division, the spindle-chromosome complex is removed from the intended mother's oocyte, which is then discarded. The spindle complex is then transferred to a donated oocyte that has had its nuclear DNA removed. The result is a mature egg that contains a selection of the mother's haploid DNA along with healthy mitochondria from the donor. The egg is then fertilized with the father's sperm.

After fertilization, the embryo is allowed to grow until it forms a blastocyst, which is an early pre-implantation stage of the embryo consisting of a hollow sphere of 16 to 40 cells. The blastocyst can then be investigated with preimplantation genetic testing for the presence of mtDNA mutations. If no mutations are found, the blastocyst can be implanted in the intended mother's uterus.

The spindle transfer technique has been performed only rarely since its first use in 2014, as the number of births among women at risk of transmitting diseases

caused by defective mtDNA is estimated to be quite small—about 150 per year in the United Kingdom and 800 per year in the United States.

Legal and regulatory status of spindle transfer

As of 2021, spindle transfer or MST has been approved in the United Kingdom, but is only permitted within clinics approved by the country's Human Fertilization and Embryology Authority (HFEA), and only for patients approved by the HFEA. These approved patients must sign an informed consent form stating that they understand that the risks and benefits of the procedure are not yet well understood. Another country that permits clinical trials of the spindle transfer technique is Greece, where a baby boy was born in April 2019 following use of the technique.

The spindle transfer technique has not been approved by the U.S. Food and Drug Authority (FDA) for use in the United States as of 2021. The agency states that its "jurisdiction includes human cells used in therapy involving the transfer of genetic material by means other than the union of gamete nuclei." In 2014, the FDA convened a meeting of an advisory committee "to discuss oocyte modification in assisted reproduction for the prevention of mitochondrial disease or treatment of infertility."

The meeting was followed in 2015 by a request to the Institute of Medicine (IOM; now called the National Academy of Medicine or NAM) to produce a report on the social and ethical issues involved in mitochondrial replacement therapy. The IOM's report concluded that the spindle transfer technique and other forms of MRT are ethically permissible, provided two conditions are met: 1) treatment should be limited to women at risk of transmitting a severe mitochondrial disease, and 2) research should be limited, at least initially, to male embryos, because female embryos produced by MRT would result in heritable genetic modifications. Paternal mtDNA is not transmitted to offspring, and thus changes made to mtDNA in the male germline are not heritable. The FDA posted its most recent statement on MRT on March 16, 2018.

Because of the FDA's refusal to allow the use of the spindle transfer technique within the United States, the sole American child born to date as a result of MST was delivered in a Mexican hospital in 2016. The baby boy's mother has Leigh syndrome, a rare neurological disorder caused by a mutation in her mtDNA. The physician, John Zhang, runs the New Hope Fertility Center in New York City. Other American women interested in the spindle transfer technique to prevent mitochondrial disease in their offspring must travel to foreign clinics as of 2021. Dr. Zhang has offered the technique in such clinics at a

QUESTIONS TO ASK YOUR DOCTOR

- What is your opinion of the spindle transfer technique?
- Do you think there are limits to the types of assisted reproductive technology that should be allowed?
- What do you consider the most significant risks of mitochondrial replacement therapy?
- Have you ever treated a patient at high risk of bearing a child with a mitochondrial disease? If so, what advice did you offer?

price of \$80,000 to \$100,000 per patient, which prices spindle transfer beyond the reach of most patients.

Limitations

The most important limitation of the spindle transfer technique is that its long-term risks and benefits are unknown as of 2021 because so few children have been born as a result of its use. In the case of the child born in Mexico, the parents of the child have refused to allow ongoing testing of the child's mtDNA, which means that the success of the first human spindle transfer cannot be fully evaluated.

Alternatives

There are several alternatives to spindle transfer to prevent the presence of mutant mtDNA in an embryo. The oldest, in which the doctor or researcher took cytoplasm that included proteins, mRNA, mitochondria, and other organelles from the donor's egg and injected it into the intended mother's egg, is no longer used as of 2021 because several children born as a result of the process were found to have developmental disorders.

The other MRT techniques that have been used are pronuclear transfer (PNT) and polar body transfer (PBT). In pronuclear transfer, the oocyte from the intended mother and the oocyte from the donor are both fertilized with sperm from the same person. The male and female pronuclei (the nucleus of an ovum or sperm before these have united to form the definitive nucleus of an impregnated ovum) are removed from each fertilized egg prior to their fusing, and the pronuclei from the recipient's fertilized egg are inserted into the fertilized egg from the donor.

In polar body transfer, a polar body, which is a small cell with very little cytoplasm created when an oocyte

divides, is taken from the intended mother and used in its entirety instead of using material extracted from the normal egg. The advantage of PBT is that there is a greatly reduced chance of transmitting mitochondria from the intended mother, because polar bodies contain very few mitochondria.

Research

There are no clinical trials of the spindle transfer technique registered with the NIH as of mid-2021—or of any other form of mitochondrial replacement therapy.

Resources

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ORGANIZATIONS

- American College of Medical Genetics and Genomics (ACMG), 7101 Wisconsin Avenue, Suite 1101, Bethesda, MD 20814, (301) 718-9603, (301) 718-9604, acmg@acmg.net, <https://www.acmg.net/>
- MitoAction, P.O. Box 310, Novi, MI 48376, (888) 648-6228, info@mitoaction.org, <https://www.mitoaction.org/>
- National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, <https://www.genome.gov/about-nhgri/Contact>, <https://www.genome.gov/>
- National Organization for Rare Disorders (NORD), 55 Kenosia Avenue, Danbury, CT 06810, (203) 744-0100, (203) 263-9938, <https://rarediseases.org/contact-us/>, <https://rarediseases.org/>
- National Society of Genetic Counselors (NSGC), 330 North Wabash Avenue, Suite 2000, Chicago, IL 60611, (312) 321-6834, nsgc@nsgc.org, <https://www.nsgc.org>
- United Mitochondrial Disease Foundation (UMDF), 8085 Saltzburg Road, Suite 201, Pittsburgh, PA 15239, (888) 317-UMDF (8633), info@umdf.org, <https://www.umdf.org/>
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) 463-6332, <https://www.fda.gov/>

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Spinocerebellar ataxia

Definition

The spinocerebellar ataxias (SCAs) are a group of inherited conditions that affect the brain and spinal cord and cause progressive difficulty with coordination. Some types of SCA also involve impairment of speech and eye movement.

Description

The SCAs are named for the parts of the nervous system that are affected in this type of condition. *Spino* refers to the spinal cord, and *cerebellar* refers to the cerebellum, the area of the brain that controls coordination. People with SCA often demonstrate smaller and atrophied cerebellums. Symptoms of SCA usually begin in the 30s or 40s but onset from childhood through the 70s has been reported.

At least 60 different types of SCA have been described and are given a designated number as a new case is documented. Each SCA type is caused by mutations in a different gene. Spinocerebellar ataxia has also been called olivopontocerebellar atrophy, Marie’s ataxia, and cerebellar degeneration. SCA3 is sometimes called Machado-Joseph disease, named after two of the first families described with this condition. All affected people in a family have the same type of SCA mutation.

Genetic profile

Although each of the SCAs is caused by mutations in different genes, the types of mutations are the same in all of the genes that have been found. In humans, all genes come in pairs; one copy of a pair comes from a person’s mother and the other one comes from the father. Genes are made up of deoxyribonucleic acid (DNA), composed of the chemical bases cytosine, thymine, guanine, and adenosine, which are represented by the letters C, T, G, and A. This is the DNA alphabet. The bases are usually put together in three-letter combinations called codons. The arrangement of the codons is what give the gene its meaning.

In each of the genes that cause SCA, there is a section of the gene where a three-base DNA codon is repeated a certain number of times. In most of the types of SCA the codon that is repeated is CAG. In people who have SCA this DNA segment is repeated too many times, making this section of the gene too big. This is called a trinucleotide repeat expansion. Other types of SCA are caused by other codon repeats; for example, in SCA8, the DNA codon that is repeated is CTG. In SCA10, the repeated DNA is five DNA bases long and

is ATTCT. This is called a pentanucleotide expansion. The actual number of DNA repeats that is normal or that causes SCA is different in each type of SCA.

In each type of SCA there is a certain range or number of repeats that still fall within the normal range. People who have repeat numbers in the normal range will not develop SCA and cannot pass it to their children. There are also a certain number of repeats that cause SCA that fall within the affected range of nucleotide repeats. People who have repeat numbers in the affected range will go on to develop SCA sometime in their lifetime if they live long enough and potentially pass SCA onto their children. Between the normal and affected ranges there is a gray range. People who have repeat numbers in the gray range may or may not develop SCA in their lifetime and why some people with numbers in the gray range develop SCA and others do not is not known. People with repeat numbers in the gray range can also pass SCA onto their children.

In general the more repeats in the affected range that someone has, the earlier the age of onset of symptoms and the more severe the symptoms will be. However, this is a generalized rule and it is not possible to look at a person's repeat number and predict at what age they will begin to have symptoms or how their condition will progress.

Sometimes when a person with trinucleotide repeat expansion in SCA genes has children, the DNA expansion grows larger during the passing on of genes. This is called anticipation and can result in an even earlier age of onset in children than in their affected parent. Anticipation does not occur in all types of SCA, but significant anticipation can occur in other types; for example, it is not unusual for a child with SCA7 to be affected before their parent or even grandparent begins to show symptoms. In most types of SCA anticipation happens more often when SCA is inherited from the father. However, in SCA8 the opposite is true; anticipation happens more often when a mother passes SCA8 to her children. Occasionally repeat sizes stay the same or even get smaller when they are passed to a person's children.

The SCAs are passed on by autosomal dominant inheritance. This means that males and females are equally likely to be affected by the disorder. It also means that only one gene in the pair needs to have the mutation in order for a person to become affected. Since a person only passes one copy of each gene on to their children, there is a 50% chance that a person who has SCA will pass it on to each of his/her children. A person who has repeat numbers in the gray range also has a 50% chance of passing the gene onto each of his/her children. However, whether or not his/her children will develop SCA

depends on the number of their repeats. A person who has repeat numbers in the normal range cannot pass SCA onto his/her children.

Usually a person with SCA has a long family history of the condition. Sometimes a person with SCA appears to be the only one affected in the family and this can be due to a couple of reasons. First, it is possible that one of the parents is or was affected but died before beginning to show symptoms. Second, the parent may have a mutation in the gray range and was not affected, but the mutation expanded into the affected range when it was passed on to the child. Third, the family members may also have SCA but have been misdiagnosed with another condition or are having symptoms, but have no definitive diagnosis. Lastly, a person can have a new mutation for SCA. New mutations are changes in the gene that happen for the first time in an affected person. Although a person with a new mutation may not have other affected family members, they still have a 50% chance of passing it on to his/her children.

Demographics

SCA has been found in people from all over the world. Some of the types of SCA are more common in certain areas and ethnic groups; the most commonly documented autosomal dominant SCA types are SCA 1, 2, 3, 6, 7, and 8. SCA1 accounts for at least 25% of SCA cases in South Africa and Italy. SCA2 accounts for 25% of SCA cases in Singapore, India, and Italy. SCA3 appears to be the most common type and was first described in families from Portugal and accounts for almost 100% of SCA cases in Brazil. SCA3 also accounts for the majority of SCA cases in Portugal, the Netherlands, Germany, China, Singapore, and a significant proportion in Japan. SCA6 accounts for a significant proportion of SCA cases in the Netherlands, Germany, and Japan. In the United States, SCA2, SCA3, and SCA6 account for the majority of documented cases; these three types also account for 51% of worldwide cases. SCA1, SCA7, and SCA8 each account for less than 10% of SCA cases worldwide.

SCA types 4, 5, and 10 through 26 are rare and have each only been described in a few families. The first family described with SCA5 may have been distantly related to President Abraham Lincoln and was first called Lincoln ataxia. SCA10 has only been described in Mexican families, SCA13 and 25 have each only been described in single French families, SCA14 and 16 have each only been described in single families from Japan, and SCA19 and 23 have each only been described in single Dutch families.

KEY TERMS

Anticipation—Increased severity and onset of disease in successive generations.

Ataxia—A deficiency of muscular coordination, especially affecting voluntary movements such as grasping or walking.

Calcification—The accumulation of calcium deposits.

Trinucleotide repeat expansion—A sequence of three nucleotides that is repeated too many times in a gene sequence.

Signs and symptoms

Although different genes cause each of the SCAs, they all have similar symptoms. All people with SCA have ataxia or a lack of muscle coordination. Walking is affected and eventually the coordination of the arms and hands, speech, and swallowing are also affected. One of the first symptoms of SCA is often difficulties with walking and balance. The muscles that control speech and swallowing are affected by the onset of SCA; this results in dysarthria, or slurred speech, and difficulties with eating. Choking while eating can become a significant problem and can lead to a decrease in the number of calories a person can take in.

As the condition manifests, walking becomes more difficult and it is necessary to use a cane, walker, and often a wheelchair. Because of the uncoordinated walking that develops it is common for people with SCA to be mistaken for being intoxicated. Carrying around a note from their doctor explaining their medical condition can often be helpful in these cases.

Some of the SCA types can also have other symptoms, although not all of these are seen in every person with that particular type. SCA2 may have slower eye movements that do not usually interfere with a person's sight. People with SCA1 and 3 may develop problems with the peripheral nerves, which carry information to and from the spinal cord. This can lead to decreased sensation and weakness in the hands and feet. In SCA3, people may also have twitching in the face and tongue and bulging eyes. SCA4 may cause a loss of sensation, but affected individuals often have a normal lifespan. SCA5 often has an adult onset and is slowly progressive, not affecting the lifespan. SCA6 often has a later onset, progresses very slowly, and does not shorten the lifespan. SCA7 involves progressive vision loss that eventually leads to blindness. SCA8 may cause sensory loss but

people have a normal lifespan. SCA10 may cause affected individuals to develop seizures. SCA11 is a relatively mild type and does not affect the lifespan for the affected person. Cases of SCA12 often develop a tremor as the first noticeable symptom and the individuals may eventually develop dementia. SCA13 may cause individuals to be shorter than average and have mild mental retardation. SCA14 may have an early onset, between 12 and 42 years of age, with an average of 28 years of age. SCA15 and 22 may be slow to progress, with SCA22 sometimes being early onset. SCA16 may involve tremors, SCA17 may involve mental deterioration, and SCA19 may involve both. SCA20 may result in calcification of some brain areas that shows up on brain imaging tests. SCA21 can be early onset, but involve only mild cognitive impairment. SCA23 is late onset and may involve sensory loss. SCA25 may also cause sensory loss. SCA26 may involve irregular eye movements.

Diagnosis

Genetic forms of ataxia must be distinguished from nongenetic causes of ataxia that may have their own, individual treatment. Nongenetic causes of ataxia are not types of SCA and can include alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, and some cancers. Family history, physical examination, and brain imaging diagnose the genetic forms of ataxia, such as SCA.

An initial workup of people who are having symptoms of ataxia will include questions about a person's medical history and a physical examination. Magnetic resonance imaging (MRI) of the brain in people with SCA will usually show degeneration or atrophy of the cerebellum and may be helpful in suggesting a diagnosis of SCA. A thorough family history should be taken to determine if others in the family have similar symptoms and the inheritance pattern in the family.

Since there is so much overlap between symptoms in the different types of SCA it is not usually possible to tell the different types apart based on clinical symptoms. The only way to definitively diagnose SCA and determine a specific subtype is by genetic testing. DNA in the blood cells is examined, and the number of CAG repeats in each of the SCA genes is counted. Clinical testing is available to detect the mutations that cause SCA types with known gene mutations. These tests may be offered as two sequential groups based on population frequency. Testing is often first performed for the more common ataxias, SCA1 through SCA7. Testing for the less common hereditary ataxias are often individualized as appropriate. Factors that may indicate the need for testing for less common SCA types can include ethnic background (SCA10 in the Mexican population), or specific symptoms, such as the presence of a tremor (SCA12). In these

cases, testing can be performed for a single disease. If the outcome is negative for the SCA type tested for, it does not mean that a person does not have SCA, it could mean that he/she has a type of SCA for which genetic testing is not yet available.

It is possible to test someone who is at risk for developing SCA before they are showing symptoms to see whether he/she inherited an expanded trinucleotide repeat. This is called predictive testing. Predictive testing cannot determine the age of onset that someone will begin to have symptoms or the course of the disease. The decision to undergo this testing is a very personal decision and some people choose to have testing so that they can make decisions about having children, about their future education, career, or finances. Protocols for predictive testing have been developed and only certain centers perform this testing. Most centers require that the diagnosis of SCA be confirmed by genetic testing in another family member.

A team of specialists will see a person who is interested in testing over the course of a few visits. Often they will meet a neurologist who will perform a neurological examination to see if they may be showing early signs of the condition. If a person is having symptoms, testing may be performed to confirm the diagnosis, and the person will also meet with a genetic counselor to talk about SCA, how it is inherited, and what testing can and cannot determine. He/she will also explore reasons for testing and what impact the results may have on his/her life, family, job, and insurance. Most centers also require a person going through predictive testing to meet a few times with a psychologist. The purpose of these visits is to make sure that the person has thought through the decision to be tested and is prepared to deal with whatever the results may be.

If a child is having symptoms, it is appropriate to perform testing to confirm the cause of his/her symptoms. However, testing will not be performed on children who are at risk for developing SCA, but are not having symptoms. Children can make their own choice whether to know this information when they are old enough to make a mature decision. Testing a child who does not have symptoms could lead to possible problems with future relationships, education, career, and insurance.

Testing a pregnant woman to determine whether an unborn child is affected is possible if genetic testing in a family has identified a certain type of SCA. This can be done between 10 and 12 weeks gestation by a procedure called chorionic villus sampling (CVS) that involves removing a tiny piece of the placenta and examining the cells. It can also be done by amniocentesis after 16 weeks gestation by removing a small amount of the amniotic fluid surrounding the fetus and analyzing the cells in the fluid. Each of these procedures has a small risk of

QUESTIONS TO ASK YOUR DOCTOR

- A distant relative was once diagnosed with spinocerebellar ataxia. Is there any way of knowing if I am at risk for this condition?
- What are the most common symptoms associated with this disorder?
- At what age does spinocerebellar ataxia first manifest?
- What is the prognosis for spinocerebellar ataxia once it has been diagnosed?

miscarriage associated with it. Continuing a pregnancy that is affected is like performing predictive testing on a child. Therefore, couples interested in these options should have genetic counseling to carefully explore all of the benefits and limitations of these procedures.

There is also another procedure, called preimplantation diagnosis, that allows a couple to have a child that is unaffected with the genetic condition in their family through the application of in vitro fertilization.

Treatment and management

Although there is a lot of ongoing research to learn more about SCA and develop treatments, no cure currently exists for the SCAs. Although vitamin supplements are not a cure or treatment for SCA, they may be recommended if a person is taking in fewer calories because of feeding difficulties. Different types of therapy might be useful to help people maintain as independent a lifestyle as possible. An occupational therapist may be able to suggest adaptive devices to make the activities of daily living easier. Canes, walkers, and wheelchairs are often useful. A speech therapist may recommend devices that may make communication easier as speech progressively becomes affected. As swallowing becomes more difficult, a special swallow evaluation may lead to better strategies for eating and to help lessen the risk of choking.

Genetic counseling helps people and their families make decisions about their medical care, genetic testing, and having children. It can also help people to deal with the medical and emotional issues that arise when there is a genetic condition diagnosed in the family.

Prognosis

Most people with the SCAs do have progression of their symptoms that leads to full-time use of a wheelchair. The duration of the disease after the onset of symptoms is

about 10–30 years but can vary depending in part on the number of trinucleotide repeats and age of onset. In general, people with a larger number of repeats have an earlier age of onset and more severe symptoms. Choking can be a major hazard because if food gets into the lungs, life-threatening pneumonia can result. As the condition progresses, it can become difficult for people to cough and clear secretions. Most people die from respiratory failure or pulmonary complications.

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ORGANIZATIONS

National Ataxia Foundation (NAF), 2600 Fernbrook Lane, Suite 119, Minneapolis, MN 55447, (763) 553-0020, <http://www.ataxia.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Spinocerebellar ataxia 3

Definition

Spinocerebellar ataxia Type 3 (SCA3) is a rare hereditary disorder affecting the central nervous system, especially the areas responsible for movement coordination of limbs, facial muscles, and eyes. The disease involves the slow and progressive degeneration of areas

of the brain, including the cerebellar, extrapyramidal, pyramidal, and motor areas. Although SCA3 leads to paralysis of different levels of severity, intellectual functions usually remain normal. Other names for SCA3 are Portuguese-Azorean disease, Machado-Joseph disease, and Azorean disease.

Description

Many of the reported cases have been found in the direct descendants of William Machado, an Azorean native who immigrated to the New England region of the United States, and Atone Joseph, a Portuguese sailor from the island of Flores who came to California in 1845. SCA3 was first described and documented as Machado-Joseph disease in 1972 among the descendants of Portuguese-Azorean immigrants to the United States, including the family of William Machado. In 1976, investigators went to the Azores Archipelago to study an existing neurodegenerative disease in the islands of Flores and São Miguel. In a group of 15 families, they found 40 people with neurological disorders with a variety of symptoms among the affected individuals, suggesting that SCA3 can vary in the degree of neurological degeneration and movement impairment among the affected individuals.

Another research team in 1976 reported an inherited neurological disorder of the motor system in Portuguese families, which they named Joseph disease. During the same year, the two groups of scientists both published independent evidence suggesting that the same disease was the primary cause for the symptoms observed. When additional reports from other countries and ethnic groups were associated with the same inherited disorder, it was thought that Portuguese-Azorean sailors had been the probable disseminators of SCA3 during the sixteenth-century period of Portuguese colonial explorations and commerce.

Genetic profile

SCA3 is inherited as an autosomal dominant trait. This means that only one parent has to pass on the gene mutation in order for the child to be affected with the disease.

Each gene in the human body is made up of units called nucleotides, abbreviated C (cytosine), A (adenine), T (thymine), and G (guanine). A sequence of three nucleotides is called a codon. SCA3 is caused by a genetic mutation that results in the overduplication of a repeated CAG codon in the gene sequence. This form of mutation is called a trinucleotide repeat expansion. The location of the mutant gene in SCA3 is *14q32*, on the long arm of chromosome 14. This gene normally encodes

the formation of a cellular protein called ataxin-3 (ATXN3). In the general population, there are between 13 and 36 repeats of the CAG codon, but in those individuals with SCA3 there may be between 61 and 84 repeats. The increased number of repetitions causes the gene to encode an abnormal ATXN3 protein product that is believed to cause cell death in the brain and spinal cord.

In successive generations the number of the repetitions may increase and cause the disease to develop at earlier ages and with more severity, a phenomenon known as genetic anticipation. In addition, there appears to be a strong relationship between the number of repetitions and the age of onset of SCA3: the more repetitions, the sooner the disease presents and the more serious the symptoms are. Also, if the individual is homozygous for the mutated gene, meaning he or she inherits the gene from both parents, SCA3 is more severe, and onset can be as early as 16 years old.

Demographics

Due to its origins, SCA3 is primarily found in people of Portuguese ancestry, particularly people from the Azores islands. In the Azores islands, the incidence of SCA3 is approximately 1 in every 4,000 people, while among those of Azorean descent it is 1 in every 6,000. SCA3 has also been identified in other ethnic groups including Japanese, Brazilians, Chinese, Indians, Israelis, and Australian aborigines.

Signs and symptoms

The symptoms of SCA3 result from the loss of brain cells, leading to the impairment of neurological connections in the brain and spinal cord. This degradation of the central nervous system is caused by gene mutation, which produces an abnormal form of a protein. The first symptoms usually appear in early adolescence. Dystonia (gait ataxia) is usually the initial symptoms in children. Gait ataxia is characterized by unstable walking and standing, and can slowly progress with the appearance of some of the other symptoms, such as hand dysmetria, involuntary eye movements, loss of hand and superior limb coordination, and facial dystonia. Another characteristic of SCA3 is clinical anticipation, which means that the disease presents earlier and with more severity in subsequent generations. Among families, some members may show a predominance of muscle tone disorders, loss of coordination, have bulging eyes, or some may be free of symptoms during their entire life. In the late stages of SCA3, some people may experience delirium or dementia.

Depending on the affected brain area, SCA3 is classified as type I, extrapyramidal insufficiency; type II, cerebellar, pyramidal, and extrapyramidal insufficiency; and

KEY TERMS

Ataxia—A deficiency in muscular coordination, especially voluntary movements, such as grasping or walking.

Autosomal chromosomes—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomal chromosomes and one pair of sex chromosomes.

Cerebellum—The part of the brain that is responsible for the control of walking, balance, and coordination.

Codon—A sequence of three nucleotides that code for specific amino acids.

Dysarthria—Slurred speech.

Dystonia—Painful involuntary muscle cramps or spasms.

Extrapyramidal—Refers to brain structures located outside the pyramidal tracts of the central nervous system.

Genetic anticipation—The tendency for an inherited disease to become more severe in successive generations.

Genotype—The genetic makeup of an organism.

Homozygous—Having two identical copies (alleles) of a gene.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease. Some mutations can be transmitted to offspring.

Nucleotide—The single building block of DNA and RNA.

Penetrance—The degree to which individuals possessing particular genetic mutations express the trait that this mutation causes. One hundred percent penetrance is expected for truly dominant traits.

Phenotype—The physical expression of an individual's genotype.

Spasticity—Increased muscle tone or stiffness that leads to uncontrolled, awkward movements.

Trinucleotide repeat expansion—The addition of extra nucleotides during DNA replication of highly repetitive genetic sequences. This can lead to mutations in genes coded in the affected region of the genome.

type III, cerebellar insufficiency. Extrapyramidal tracts are networks of uncrossed motor nerve fibers that function as relays between the motor areas and corresponding areas of the brain. The pyramidal tract consists of groups

of crossed nerves located in the white matter of the spinal cord that conduct motor impulses that originate in the opposite area of the brain to the arms and legs. Pyramidal tract nerves regulate both voluntary and reflex muscle movements. In type I, onset is usually before age 25, and affected individuals experience extreme muscle stiffness and rigidity. In type II, onset is typically in the mid-30s, and progressive loss of muscle coordination (ataxia) occurs, resulting in the inability to walk. In type III, the average age of onset is 40 or later, and the main symptoms include weakness and loss of sensation in the legs. While in all types of SCA3 movement and coordination is affected, mental ability is rarely impaired by progression of the disease.

Diagnosis

Diagnosis depends mainly on the clinical history of the family. Because the mutation that causes SCA3 is known, genetic screening to reveal the presence of the increased number of CAG trinucleotide repeats can be useful in cases of persons at risk or when the family history is not known or a person has symptoms that raise suspicion of SCA3. Additionally, imaging studies of the brain using computerized tomography (CT) and magnetic resonance imaging (MRI) may be used to investigate changes in brain physiology and function. Initial diagnosis may be difficult, as people present symptoms easily mistaken for other neurological disorders such as Parkinson and Huntington diseases, or multiple sclerosis.

Treatment and management

Although there is no cure for SCA3, some symptoms can be treated. The medication Levodopa or L-dopa can lessen muscle rigidity and tremors and is often given in conjunction with the drug Carbidopa. However, as the disease progresses and the number of neurons decreases, this treatment becomes less effective. Antispasmodic drugs such as baclofen are also prescribed to reduce spasticity. Dysarthria, or difficulty speaking, and dysphagia, difficulty swallowing, can be treated with proper medication and speech therapy. Physical therapy can help patients with an unsteady gait, but walkers or wheelchairs may be needed as the disease progresses. Other symptoms, such as muscle cramps, urinary disorders, and sleep problems, can also require palliative treatment.

Genetic counseling is recommended for people with a family history of the disease since SCA3 is a dominant inherited disorder.

Prognosis

SCA3 presents a 94.5% penetrance, which means that 94.5% of the people who have the mutation will

QUESTIONS TO ASK YOUR DOCTOR

- My SCA3 has been diagnosed as type II. What does that mean and how does it differ from other types of SCA3?
- Do scientists know the cause of various types of SCA3?
- What treatments are available for my type of SCA3?
- How likely is it that my children will inherit my medical condition?

develop the symptoms during their lives, and less than 5% will remain free of symptoms. Because the intensity and range of symptoms are highly variable among affected individuals, it is difficult to determine the prognosis for a given individual. Because SCA3 can progress slowly, most patients survive until middle age or older.

Resources

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ORGANIZATIONS

Dystonia Medical Research Foundation, 1 E. Wacker Dr., Suite 2810, Chicago, IL 60601-1905, (312) 755-0198 or (800) 377-3978, (312) 803-0138, dystonia@dystonia-foundation.org, <http://www.dystonia-foundation.org>

National Ataxia Foundation (NAF), 2600 Fernbrook Lane, Suite 119, Minneapolis, MN 55447, (763) 553-0020, <http://www.ataxia.org>

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Spinocerebellar atrophy I see **Spinocerebellar ataxia**

Spondyloepiphyseal dysplasia

Definition

Spondyloepiphyseal dysplasia is a group of rare hereditary disorders characterized by growth deficiency, spinal malformations, and, in some cases, ocular abnormalities.

Description

Spondyloepiphyseal dysplasia is one of the most common causes of short stature. There are multiple rare and inherited forms of spondyloepiphyseal dysplasia including congenital spondyloepiphyseal dysplasia, X-linked spondyloepiphyseal dysplasia tarda, progressive pseudorheumatoid dysplasia, CHST3-related skeletal dysplasia, pseudoachondroplasia, and hypochondrogenesis. Congenital spondyloepiphyseal dysplasia is primarily characterized by prenatal growth deficiency and spinal malformations. Growth deficiency results in short stature (dwarfism). Abnormalities of the eyes may be present, including nearsightedness (myopia) and retina (the nerve-rich membrane lining the eye) detachment in approximately half of individuals with the disorder. Congenital spondyloepiphyseal dysplasia is inherited as an autosomal dominant genetic trait.

Congenital spondyloepiphyseal dysplasia is also known as SED, congenital type; SED congenita; and SEDC. Spondyloepiphyseal dysplasia tarda primarily affects males. It is characterized by dwarfism and hunched appearance of the spine. The disorder doesn't become evident until five to 10 years of age. Spondyloepiphyseal dysplasia tarda is an X-linked recessive inherited disorder.

Spondyloepiphyseal dysplasia tarda is also known as SEDT; spondyloepiphyseal dysplasia, late; and SED tarda, X-linked.

Other forms of dysplasia are due to mutations in the development, production, and/or proliferation of cartilage, leading to a multitude of abnormalities not just in

the bones and joints but also in the facial features and abdomen due to the wide range of locations and functions of cartilage throughout the body.

Genetic profile

Congenital spondyloepiphyseal dysplasia is thought to probably always result from abnormalities in the *COL2A1* gene, which codes for type II collagen. Collagen is a protein that is a component of bone, cartilage, and connective tissue. A variety of abnormalities (such as deletions and duplications) involving the *COL2A1* gene may lead to the development of the disorder.

It is one of a group of skeletal dysplasias (dwarfing conditions) caused by changes in type II collagen. These include hypochondrogenesis; spondyloepimetaphyseal dysplasia type, Strudwick (SEMD); and Kniest dysplasia. Type 2 collagen is the major collagen of a component of the spine called the nucleus pulposus, of cartilage, and of vitreous (a component of the eye). All of these conditions have common clinical and radiographic findings including spinal changes resulting in dwarfism, myopia, and retinal degeneration.

Congenital spondyloepiphyseal dysplasia is inherited as an autosomal dominant genetic trait. In autosomal dominant inheritance, a single abnormal gene on one of the autosomal chromosomes (one of the first 22 "nonsex" chromosomes) from either parent can cause the disease. One of the parents will have the disease (since it is dominant) and is the carrier. Only one parent needs to be a carrier in order for the child to inherit the disease. A child who has one parent with the disease has a 50% chance of also having the disease.

Autosomal recessive inheritance of congenital spondyloepiphyseal dysplasia has been considered in cases when a child with the disorder is born to parents who are not affected by the disorder. It is considered more likely that in these cases the disorder resulted from germ-line mosaicism in the collagen type II gene of the parent. Germ-line mosaicism occurs when the causal mutation, instead of involving a single germ cell, is carried only by a certain proportion of the germ cells of a given parent. Thus, the parent carries the mutation in his or her germ cells and therefore runs the risk of generating more than one affected child, but does not actually express the disease.

Spondyloepiphyseal dysplasia tarda is caused by mutations in the *TRAPPC2* (also called *SEDL*) gene, which is located on the X chromosome at locus xp22.2-p22.1. This gene provides instructions for producing the protein sedlin, believed to be part of a large molecule called the trafficking protein particle (TRAPP) complex,

known to play a role in the transport of proteins between various cell compartments.

Spondyloepiphyseal dysplasia tarda is inherited as an X-linked disorder. The following concepts are important to understanding the inheritance of an X-linked disorder. All humans have two chromosomes that determine their gender: females have XX, males have XY. X-linked recessive, also called sex-linked, inheritance affects the genes located on the X chromosome. It occurs when an unaffected mother carries a disease-causing gene on at least one of her X chromosomes. Because females have two X chromosomes, they are usually unaffected carriers. The X chromosome that does not have the disease-causing gene compensates for the X chromosome that does. For a woman to show symptoms of the disorder, both X chromosomes would have the disease-causing gene. That is why women are less likely to show such symptoms than males.

If a mother has a female child, the child has a 50% chance of inheriting the disease gene and being a carrier who can pass the disease gene on to her sons. On the other hand, if a mother has a male child, he has a 50% chance of inheriting the disease-causing gene because he has only one X chromosome. If a male inherits an X-linked recessive disorder, he is affected. All of his daughters will be carriers, but none of his sons.

Progressive pseudorheumatoid dysplasia is an autosomal recessive genetic disorder characterized by a mutation in the *WISP3* gene located on the long arm of chromosome 10 that codes for proteins responsible for bone growth and the maintenance of cartilage.

As its name suggests, CHST-related skeletal dysplasia is due to a mutation in the *CHST3* gene. This gene, located on the long arm of chromosome 10, codes for the C6ST-1 enzyme, which is responsible for the development of cartilage. This type of dysplasia is inherited in an autosomal recessive pattern.

Pseudoachondroplasia is an autosomal dominantly inherited dysplasia associated with a mutation of the *COMP* gene, located on the short arm of chromosome 19, which codes for the protein responsible for the normal development of cartilage and the ossification process that cartilage goes through during skeletal immaturity.

Hypochondrogenesis is an autosomal dominantly inherited disorder characterized by a mutation in the *COL2A1* gene located on the long arm of chromosome 12 that is very important in making type 2 collagen. Type 2 collagen is not only important for normal bone growth but also for the cushioning between bones; cartilage of the nose, eyes, and ears; and the cushioning between organs.

Demographics

Spondyloepiphyseal dysplasia is rare, and its incidence is unknown. As of 2015, some 175 cases of congenital spondyloepiphyseal dysplasia had been reported, and roughly 30 individuals with CHST3 type had been reported. Spondyloepiphyseal dysplasia tarda has an incidence estimated at 1 in 150,000 to 200,000 people worldwide, and progressive pseudorheumatoid dysplasia has an incidence of approximately 1 in 1 million in the United Kingdom, with a possible higher incidence in the Middle East. This incidence may be skewed due to the possible misdiagnosis since the signs and symptoms of this dysplasia are very similar to those of juvenile rheumatoid arthritis. The estimated incidence of pseudoachondroplasia is 1 in 30,000. Hypochondrogenesis and another related disorder known as achondrogenesis type 2 have an incidence of 1 in 40,000–60,000 newborns combined.

Congenital spondyloepiphyseal dysplasia affects both males and females. Spondyloepiphyseal dysplasia tarda affects mostly males.

Signs and symptoms

The signs and symptoms of dysplasia generally include abnormal growth and development of bones, joint and cartilage; altered gait; spinal malformations; decreased muscle tone; calcium deposits; clubfeet; flattening of bones; pain in joints; and dislocations. These signs and symptoms range depending on the type of dysplasia inherited. Congenital spondyloepiphyseal dysplasia is characterized by these main features:

- Prenatal growth deficiency occurs prior to birth, and growth deficiencies continue after birth and throughout childhood, resulting in short stature (dwarfism). Adult height ranges from approximately 36–67 in. (91–170 cm).
- Spinal malformations include a disproportionately short neck and trunk and a hip deformity wherein the thigh bone is angled toward the center of the body (coxa vara). Abnormal front-to-back and side-to-side curvature of the spine (kyphoscoliosis) may occur, as may an abnormal inward curvature of the spine (lumbar lordosis). Spinal malformations are partially responsible for short stature.
- Hypotonia (diminished muscle tone), muscle weakness, and/or stiffness is exhibited in most cases.
- Progressive nearsightedness (myopia) and/or retinal detachment may develop. Retinal detachment, which can result in blindness, occurs in approximately 50% of cases.
- An abnormally flat face, underdevelopment of the cheekbone (malar hypoplasia), and/or cleft palate may

present in some individuals with congenital spondyloepiphyseal dysplasia.

- Additional associated abnormalities may include underdevelopment of the abdominal muscles; a rounded, bulging chest (barrel chest) with a prominent sternum (pectus carinatum); diminished joint movements in the lower extremities; the heel of the foot may be turned inward toward the body while the rest of the foot is bent downward and inward (clubfoot); and, rarely, hearing impairment due to abnormalities of the inner ear.

The hypotonia, muscle weakness, and spinal malformations may result in a delay in affected children learning to walk. In some cases, affected children may exhibit an unusual “waddling” gait.

Symptoms of spondyloepiphyseal dysplasia tarda are not usually apparent until five to 10 years of age. At that point, a number of symptoms begin to appear:

- abnormal growth causes mild dwarfism
- spinal growth appears to stop and the trunk is short
- the shoulder may assume a hunched appearance
- the neck appears to become shorter
- the chest broadens (barrel chest)
- additional associated abnormalities may include unusual facial features such as a flat appearance to the face; progressive degenerative arthritis may affect hips and other joints of the body

Spine and hip changes become evident between 10 and 14 years of age. In adolescence, various skeletal abnormalities may cause pain in the back, hips, shoulders, knees, and ankles; a large chest cage; and relatively normal limb length. In adulthood, height usually ranges from 52 to 62 inches; hands, head, and feet appear to be of normal size.

Progressive pseudorheumatoid dysplasia is a progressive form of dysplasia, meaning the symptoms worsen over time and is characterized by the degradation of bone over time. This type of dysplasia usually presents itself clinically between the ages of three and eight with pain in joints and altered gait, which may develop into other spinal abnormalities including but not limited to platyspondyly, increased curvatures of the spine, short stature, and abnormal calcium deposits within or around joints.

CHST3-related skeletal dysplasia is another form of progressive bone and joint dysplasia, characterized by dwarfism and joint dislocations present at birth with or without cardiac complications and abnormalities.

Pseudoachondroplasia is a congenital dysplasia similar to achondroplasia without characteristic facial features. Typical bone abnormalities associated with this

KEY TERMS

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Coxa vara—A deformed hip joint in which the neck of the femur is bent downward.

Dysplasia—The abnormal growth or development of a tissue or organ.

Epiphyseal—The region of the bone responsible for growth of the bone.

Hypotonia—Reduced or diminished muscle tone.

Kyphoscoliosis—Abnormal front-to-back and side-to-side curvature of the spine.

Lumbar lordosis—Abnormal inward curvature of the spine.

Malar hypoplasia—Small or underdeveloped cheekbones.

Myopia—Nearsightedness. Difficulty seeing objects that are far away.

Ochronosis—A condition marked by pigment deposits in cartilage, ligaments, and tendons.

Ossification—The process of the formation of bone from its precursor, a cartilage matrix.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

type of dysplasia include but are not limited to short stature shown by the age of two, joint pain, hypermobility, varus/valgus deformity of the arms and/or legs, and an alteration in the spinal curvatures.

Hypochondrogenesis is a severe form of dysplasia characterized by short stature, short extremities, and ossification of the joints of the spine and pelvis. This form of dysplasia also affects the development of other cartilage related tissues such as in the facial and abdominal structures. Due to widespread malformation, the prognosis of hypochondrogenesis is very poor, with infants dying soon after birth from respiratory complications.

Diagnosis

X-rays may be used to diagnose spondyloepiphyseal dysplasia when it is suspected, utilizing the cardinal signs of each type of dysplasia. Genetic sequencing may also be utilized to distinguish between the different types of

dysplasias as well as from other bone and joint disorders with similar clinical presentations.

Individuals with congenital spondyloepiphyseal dysplasia have characteristic x-rays that show delayed ossification of the axial skeleton with ovoid vertebral bodies. With time, the vertebral bodies appear flattened. There is delayed ossification of the femoral heads, pubic bones, and heel. The coxa vara deformity of the hip joint is common.

It should be noted that x-rays of individuals with spondyloepimetaphyseal dysplasia type Strudwick are virtually identical to congenital spondyloepiphyseal dysplasia. In early childhood, irregularity in the region beneath the ends of bones (metaphyseal) and thickening of the bones (sclerosis) are noted in spondyloepimetaphyseal dysplasia type Strudwick. Also, there is platyspondyly (flattened vertebral bodies) and odontoid hypoplasia.

Radiologic diagnosis of spondyloepiphyseal tarda cannot be established before four to six years of age. Symptoms usually begin to present between five and ten years of age. Symptomatic changes in the spine and hips usually present between 10 and 14 years of age.

In adults, vertebral changes, especially in the lumbar region, may be diagnostic. Ochronosis (pigment deposits in cartilage, ligaments, and tendons) is suggested by apparent intervertebral disc calcification, and the vertebral bodies are malformed and flattened with most of the dense area part of the vertebral plate.

Treatment and management

Individuals with spondyloepiphyseal dysplasia should be under routine health supervision by a physician who is familiar with the disorder, its complications, and its treatment as related to the specific form of dysplasia present.

Congenital spondyloepiphyseal dysplasia

Treatment is mostly symptomatic, and may include the following:

- Orthopedic care throughout life. Early surgical interventions may be needed to correct clubfoot and/or cleft palate. Hip, spinal, and knee complications may occur, and hip replacement is sometimes warranted in adults. Additionally, arthritis may develop due to poorly developed type II collagen. Spinal fusion may be indicated if evaluation of the cervical vertebrae C1 and C2 detects odontoid hypoplasia. (If the odontoid is hypoplastic or small, it may predispose to instability and spinal cord compression in congenital spondyloepiphyseal dysplasia).

QUESTIONS TO ASK YOUR DOCTOR

- What type of dysplasia does my child have and what is the prognosis?
- Other than reduced growth, what physical or mental abnormalities are associated with spondyloepiphyseal dysplasia?
- How does this condition affect a person's lifespan and activities of daily living?
- What type of medical surveillance is needed for a person with spondyloepiphyseal dysplasia during his or her lifetime?
- What are the risks and benefits of having surgery for lengthening arm and leg bones?
- What other treatment and management options are available for my child?

- Ophthalmologic examinations are important for the prevention of retinal detachment and treatment of myopia and early retinal tears if they occur.
- Hearing should be checked and ear infections should be closely monitored. Tubes may need to be placed in the ear.
- Due to neck instability, persons with SEDC should exercise caution to avoid activities/sports that could result in trauma to the neck or head.

Individuals with congenital spondyloepiphyseal dysplasia should be closely monitored during anesthesia and for complications during a respiratory infection. In particular, during anesthesia, special attention is required to avoid spinal injury resulting from lax ligaments causing instability in the neck. This condition may also result in spinal injury in contact sports and car accidents. Chest constriction may also cause decreased lung capacity.

Spondyloepiphyseal dysplasia tarda

Treatment is mostly symptomatic, and may include the following:

- Physical therapy to relieve joint stiffness and pain.
- Orthopedic care may be needed at different times throughout life. Bone changes of the femoral head often lead to secondary osteoarthritis during adulthood and some patients require total replacement of the hip before the age of 40 years.

Some individuals with short stature resulting from spondyloepiphyseal dysplasia may consider limb-lengthening surgery. This is a controversial surgery that

lengthens leg and arm bones by cutting the bones, constructing metal frames around them, and inserting pins into them to move the cut ends apart. New bone tissue fills in the gap. While the surgery can be effective in lengthening limbs, various complications may occur.

Genetic counseling

Genetic counseling may be of benefit for patients and their families.

In congenital spondyloepiphyseal dysplasia, only one parent needs to be a carrier in order for the child to inherit the disorder. A child has a 50% chance of having the disorder if one parent has the disorder and a 75% chance of having the disease if both parents have congenital spondyloepiphyseal dysplasia.

In spondyloepiphyseal dysplasia tarda, if a mother has a male child, he has a 50% chance of inheriting the disease-causing gene. A male who inherits an X-linked recessive disorder is affected, and all of his daughters will be carriers, but none of his sons.

Prenatal testing

Prenatal testing may be available to couples at risk for bearing a child with spondyloepiphyseal dysplasia. Testing for the genes responsible for congenital spondyloepiphyseal dysplasia and spondyloepiphyseal dysplasia tarda is possible. Congenital spondyloepiphyseal dysplasia testing may be difficult, however, since although the gene has been located, there is variability in the mutations in the gene among persons with the disorder.

Either chorionic villus sampling (CVS) or amniocentesis may be performed for prenatal testing. CVS is a procedure to obtain chorionic villi tissue for testing. Examination of fetal tissue can reveal information about the defects that lead to spondyloepiphyseal dysplasia. CVS can be performed at 10–12 weeks gestation.

Amniocentesis is a procedure that involves inserting a thin needle into the uterus, into the amniotic sac, and withdrawing a small amount of amniotic fluid. DNA can be extracted from the fetal cells contained in the amniotic fluid and tested. Amniocentesis is performed at 16–18 weeks gestation.

Prognosis

Prognosis is variable dependent upon severity of the disorder. Generally, congenital spondyloepiphyseal dysplasia is more symptomatic than spondyloepiphyseal dysplasia tarda. Neither form of the disorder generally leads to shortened lifespan. Cognitive function is generally normal. The prognosis of hypochondrogenesis is very poor, with infants dying soon after birth from respiratory

complications. Those patients who do live with this type of hypochondrogenesis are then reclassified as having congenital spondyloepiphyseal dysplasia.

Resources

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- Human Growth Foundation, 997 Glen Cove Ave., Suite 5, Glen Head, NY 11545, (516) 671-4041 or (800) 451-6434, hgf1@hgfound.org, <http://www.hgfound.org>
- Little People of America, 250 El Camino Real, Suite 211, Tustin, CA 92780, (714) 368-3689 or (888) LPA-2001, (714) 368-3367, info@lpaonline.org, <http://www.lpaonline.org>
- National Organization for Rare Disorders (NORD), Nat. 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Spondyloepiphyseal dysplasia congenita

Definition

Spondyloepiphyseal dysplasia congenita (SEDC) is a form of dwarfism (achondroplasia) that is caused by a gene mutation interfering with prenatal bone development. People with SEDC have a short physique, misshaped bones, and a flattened face. The name for this

condition was derived from the Greek words “spondylos” (referring to the spine) and “epiphyseal” (referring to the formative areas of the bones). The Greek word “dysplasia” refers to abnormal tissue formation.

Description

This disorder is caused by a mutation on the gene responsible for producing collagen II. Collagen II is an organic gel that influences the transformation of cartilage into bone. It is also essential in developing the lubricants of the joints and the eyes. People with SEDC are affected mostly in the development and structure of their bones. Almost half suffer from myopia, or nearsightedness. There is no effect on intellectual function.

SEDC is distinguished from other forms of achondroplasia by its onset at birth and by the mutation causing it. Spondyloepiphyseal dysplasia tarda is not observable until later in life. The most notable feature of SEDC is the short stature of those affected. Other observable features are a skeletal framework that is not properly aligned and that has an abnormal shape, the chest is barrel shaped, and the trunk and the neck are unusually short.

Genetic profile

The skeletal disorder SEDC is caused by a mutation in the *COL2A1* gene on chromosome 12. This gene is responsible for producing collagen II, which is essential in the development of the lubricants for the bones and eyes. It is also involved in the prenatal development of bone from cartilage. Any mutation in the *COL2A1* gene interferes with proper development of bones and, more generally, the skeletal system. Because the mutation produces an autosomal dominant trait, only one gene with the mutation is necessary for the condition to occur. Most observed cases are from sporadic mutations, which means that the parents had normal genes that for some reason mutated. However, a person with the mutation could pass it on to offspring who would then have a 50% chance of developing the condition, given that both parents do not have the disorder.

The siblings of affected individuals have no chance of passing the trait on to their children. If both parents have the mutated genes, there is a 50% chance that either one will pass on the gene to the child who will then develop SEDC. There is a 25% chance that neither parent will pass on the gene; the child will grow normally. However, there is a 25% chance that both will pass on the gene; in this case, the child is not likely to survive the first few years of life.

Demographics

This condition is most often caused by a sporadic mutation; therefore, it is very rare. It is estimated that it is observed in only 1 out of 100,000 births. Although the exact number is not known, scientific literature has reports of more than 175 cases. The gene responsible for this disorder has been determined to be autosomal dominant. This means that it is not sex related; men and women are equally affected. Because most cases are due to a sporadic mutation, there are no racial trends in its occurrence, as is true for most cases of achondroplasia.

Signs and symptoms

Some of the expected characteristics of people with SEDC include the following:

- shortened limbs
- average-sized hands and feet
- abnormal spine curvature
- vertebral instability in the neck
- flattened vertebrae
- bow legs
- early onset of arthritis
- flattened face

Other characteristics may include the following:

- clubfoot in one or both feet
- moderate hearing loss
- lack of muscle tone
- cleft palate

Some of the common deformities that continue to cause problems throughout a person's life include hip and knee irregularities that may cause pain in the joints and contribute to abnormal walking patterns. Many people with SEDC suffer from spinal deformities that contribute to breathing and standing problems. Most have a curvature of the spine to some degree. Spinal deformities contribute to a rigid posture and uncontrollable spasms throughout the skeletal system. Spinal cord compression can result from these deformities, creating even more complications.

Diagnosis

There are signs of this form of achondroplasia that are observable from birth. However, ascertaining that this condition is actually SEDC with its accompanying complications is only possible through a blood test. Unlike other congenital forms of achondroplasia, babies with SEDC show signs of the disorder; they tend to have a flattened spine and a flattened face because of poorly developed facial muscle. The short stature, along with the

disproportionate ratio of head to body and trunk to body, indicates that the baby has some form of achondroplasia; the face and spine indicate that it is very likely SEDC.

Because these characteristics are observed at birth, the question arises, “Why are they not observable through the prenatal ultrasound?” Most ultrasound images of the developing fetus are not powerful enough to detect the subtle features that would suggest achondroplasia, or more specifically SEDC.

As the child with SEDC grows, development must be constantly assessed. Normal scale of development, particularly motor development, may indicate delays. However, there should be normal development expected for cognitive and language development. All areas of motor and skeletal development should be constantly assessed, including signs for spinal cord compression, motor weakness, problems with walking, and a lack of physical endurance. The prevalent curvature of the spine is expected to increase with age and should be continuously assessed as it tends to lead to problems with flexibility in the hips. Any deformation observed at birth or with later development has a strong likelihood of contributing to later deterioration of any part of the skeletal system. Particular attention should be given to problems of the hips.

Treatment and management

Because most cases are unpredictable due to a spontaneous mutation, it is not easy to detect SEDC before birth. The differences suggesting SEDC are too subtle in the developing fetus to detect in the womb by ultrasound. However, recent research conducted at the Clinical School of Medical College, Nanjing University in China has demonstrated that detection through analysis of amniotic fluid is possible. Detecting the mutation for SEDC is not usually a goal of typical amniocentesis because the condition is so rare. Prenatal counseling is recommended for a couple when one or both are carriers of the mutated gene. It is also recommended when the father is over 56 years of age, because more mutations take place in the sperm of older men.

Although there are some forms of achondroplasia that respond well to growth therapies, the treatment for SEDC and most forms of achondroplasia is not focused on increasing physical stature. Because SEDC is not a result of growth hormone deficiency, growth therapies would not be appropriate. The various treatments for SEDC are concerned with easing associated disabilities and delaying any perceived deterioration.

Traditional treatment

The usual treatment for children with any form of achondroplasia is continuous evaluations by a team of specialists. This is especially true for the child with SEDC

QUESTIONS TO ASK YOUR DOCTOR

- What corrective surgery should I expect?
- How do other people with SEDC cope with daily living skills?
- Is genetic counseling important for my situation?
- What are the chances that a child of mine will be born with SEDC?
- How often should I be physically evaluated per year?
- What do I do when conditions get worse?

who has to face the strong possibility of deterioration in sight, hearing, breathing, and motor function. Orthopedic surgery is a certainty; however, physical therapy and adaptive devices may reduce the number of operations necessary. Some of the more common adaptive devices include leg braces, forearm crutches, and orthopedic footwear.

Some of the purposes of orthopedic surgery include procedures to help steer growing bones into the appropriate direction. Another procedure designed for straightening out a crooked bone involves breaking the bone and then resetting it as straight. Metal plates are inserted to hold it in the corrected position. Surgery to correct the curved spine is common, as well as surgery to offset spinal compression.

In recent years there have been experiments to lengthen the limbs of people with achondroplasia. This procedure is controversial because it means having the child undergo surgery and does not resolve the underlying problems of SEDC and undergoing the procedure implies that there is something wrong with short height. In this surgical procedure, a bone is broken and the two parts of the bone are attached to a metal rod. The bone is expected to grow around the rod and the limb is expected to stretch to accommodate the new length. However, the deficiency of collagen II still exists for the person undergoing this surgery. The bone cannot grow at a normal or predictable rate. The deterioration and lack of lubrication in the joints will still continue.

Prognosis

The first point in considering the prognosis for a person born with SEDC is that there is no cure. A baby born with SEDC will still have the condition into adulthood. For the most part, life expectancy is no different for someone born with SEDC than for the general population. There are two exceptions. The first exception is that

the child who inherits the mutated gene from both parents is not likely to live past the third birthday. However, since most cases are due to sporadic mutations, this situation is very rare. The other exception is that neck injuries pose a greater threat for the person with SEDC. Thus, children with the disorder must be extremely careful in situations that could cause neck injuries.

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Human Growth Foundation (HGF), 997 Glencove Ave., Suite 5, Glenhead, NY 11545, (800) 451-6434, (517) 671-4055, hgf1@hgfound.org, <http://www.hgfound.org>

Little People of America (LPA), 250 El Camino Real, Suite 211, Tustin, CA 92780, (888) 572-2001 or (714) 368-3689, (714) 368-3367, info@lpaonline.org, <http://www.lpaonline.org>

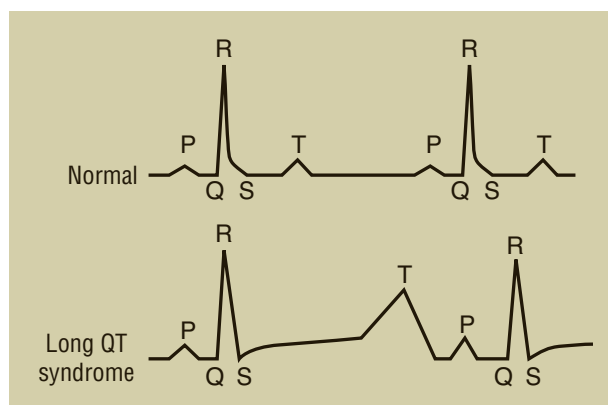
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Ray F. Brogan, PhD

SRY (sex-determining region Y)

Definition

The sex-determining region Y (*SRY*) gene is located on the Y chromosome. *SRY* is the main genetic switch



Flow chart of male and female sex differentiation from conception through development. (Gale)

for the sexual development of the human male. If the *SRY* gene is present in a developing embryo, typically it will become male.

Description

The development of sex in a human depends on the presence or absence of a Y chromosome. Chromosomes are the structures in our cells that contain genes. Genes instruct the body on how to grow and develop by making proteins. For example, genes (and the proteins they make) are responsible for what color hair or eyes people may have, how tall they will be, and what color skin they will have. Genes also direct the development of organs, such as the heart and brain. Genes are constructed out of DNA, deoxyribonucleic acid. DNA is found in the shape of a double helix, like a twisted ladder. The DNA contains the "letters" of the genetic code that make up the "words" or genes that govern the development of the body. The genes are found in the "books" or chromosomes in the cells.

Normally, there are 46 chromosomes, or 23 pairs, in each cell. The first 22 pairs are the same in men and women and are called the autosomes. The last pair, the sex chromosomes, consists of two X chromosomes in females (XX) and an X and a Y chromosome in males (XY). These 23 pairs of chromosomes contain approximately 35,000 genes.

Human males differ from human females in the fact that they have a Y chromosome, and females do not. Scientists thought there must be a gene on the Y chromosome that is responsible for determining maleness. The gene for determining maleness was called *TDF* for testis-determining factor. In 1990, the *SRY* gene was found and scientists believed it was the *TDF* gene they had been looking for. The evidence scientists had to show *SRY* was indeed *TDF* included the fact that it was

KEY TERMS

Cartilage—Supportive connective tissue that cushions bone at the joints or that connects muscle to bone.

Embryo—The earliest stage of development of a human infant, usually used to refer to the first eight weeks of pregnancy. The term “fetus” is used from roughly the third month of pregnancy until delivery.

Epididymis—Coiled tubules that are the site of sperm storage and maturation for motility and fertility. The epididymis connects the testis to the vas deferens.

Gonad—The sex gland in males (testes) and females (ovaries).

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Nucleus—The central part of a cell that contains most of its genetic material, including chromosomes and DNA.

Ovary—The female reproductive organ that produces the reproductive cell (ovum) and female hormones.

Seminal vesicles—The pouches above the prostate that store semen.

Testes—The male reproductive organs that produce male reproductive cells (sperm) and male hormones.

Vas deferens—The long, muscular tube that connects the epididymis to the urethra through which sperm are transported during ejaculation.

located on the Y chromosome. When *SRY* was found in individuals with two X chromosomes (normally females), these individuals had male physical features. Furthermore, some individuals with XY sex chromosomes that had female physical features had mutations or alterations in their *SRY* gene. Finally, experiments were done on mice that showed a male mouse would develop when *SRY* was put into a chromosomally female embryo. This evidence proved that *SRY* is the *TDF* gene that triggers the pathway of a developing embryo to become male. While the *SRY* gene triggers the pathway to the development of a male, it is not the only gene responsible for sexual development. Most likely, the *SRY* gene serves to regulate the activity of other genes in this pathway.

Genetic profile

Men and women both have 23 pairs of chromosomes—22 pairs of autosomes and one pair of sex chromosomes (either XX in females or XY in males). The *SRY* gene is located on the Y chromosome. When a man and a woman have a child, it is the man’s chromosomes that determine if the baby will be male or female. This is because the baby inherits one of its sex chromosomes from the mother and one from the father. The mother has only X chromosomes to pass on, while the father can pass on either his X chromosome or his Y chromosome. If he passes on his X chromosome, the baby will be female. If he passes on his Y chromosome (with the *SRY* gene) the baby will be male. Statistically, each pregnancy has a 50% chance of being female and a 50% chance of being male. The Y chromosome is the smallest human chromosome and the SRY region contains a very small number of genes.

Signs and symptoms

Individuals with point mutations or deletions of the *SRY* gene have a condition known as gonadal dysgenesis, XY female type, also called Swyer syndrome. At birth, the individuals with the XY female type of gonadal dysgenesis appear to be normal females (with female inner and outer genitalia); however, they do not develop secondary sexual characteristics at puberty, do not menstruate, and have “streak” (undeveloped) gonads. They have normal stature and an increased incidence of certain neoplasms (gonadoblastoma and germinoma).

Normal development

In normal human sexual development, there are two stages called determination and differentiation. Determination occurs at conception when a sperm from a man fertilizes an egg from a woman. If the sperm has a Y chromosome, the conception will eventually become male. If no Y chromosome is present, the conception will become female.

Though the determination of sex occurs at conception, the differentiation of the developing gonads (future ovaries in the female and testes in the males) does not occur until about seven weeks. Until that time, the gonads look the same in both sexes and are called undifferentiated or indifferent. At this point in development, the embryo has two sets of ducts: the Mullerian ducts that form the fallopian tubes, uterus and upper vagina in females and the Wolffian ducts that form the epididymis, vas deferens, and seminal vesicles in males.

In embryos with *SRY* present, the undifferentiated gonads will develop into the male testes. The testes produce two hormones that cause the differentiation into

maleness. Mullerian inhibiting substance (MIS), also called anti-Mullerian hormone (AMH), causes the Mullerian ducts to regress and the Wolffian ducts to develop into the internal male structures. Testosterone also helps with the development of the Wolffian ducts and causes the external genitals to become male.

When *SRY* is not present, the pathway of sexual development is shifted into female development. The undifferentiated gonads become ovaries. The Mullerian ducts develop into the internal female structures and the Wolffian ducts regress. The external genitals do not masculinize and become female.

SRY and male development

How the *SRY* gene causes an undifferentiated gonad to become a testis and eventually determine the maleness of a developing embryo is not completely understood. What scientists believe happens is that *SRY* is responsible for “triggering” a pathway of other genes that cause the gonad to continue to develop into a testis. The SRY protein is known to go into the nucleus of a cell and physically bend the DNA. This bending of DNA may allow other genes to be turned on that are needed in this pathway. For example, anti-Mullerian hormone is thought to be indirectly turned on by *SRY*.

It is also thought that a threshold exists that must be met at a very specific time for *SRY* to trigger this pathway. This means that enough SRY protein must be made early in development (before seven weeks) to turn an undifferentiated gonad into a testis. If enough SRY is not present or if it is present too late in development, the gonad will shift into the female pathway.

Other genes in sex development

Several other genes have been found that are involved in the development of human sex, including the gene *SOX9*. Mutations or alterations in this gene can cause a condition called camptomelic dysplasia. People with camptomelic dysplasia have bone and cartilage changes. *SOX9* alterations also cause male to female sex reversal in most affected individuals (male chromosomes and female features). It is not known how *SRY*, *SOX9*, and other genes in the sexual developmental pathway interact to turn an undifferentiated gonad into a testis or an ovary.

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Stargardt disease

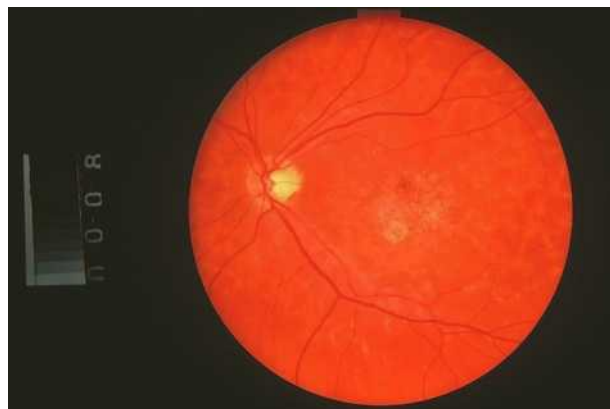
Definition

Stargardt disease (STGD) is an inherited vision disorder with macular degeneration that typically affects younger people.

Description

STGD is the most common form of inherited macular degeneration (or dystrophy), a disorder of the retina, that affects younger people. The condition is also known as Stargardt macular dystrophy, juvenile macular degeneration, macular dystrophy with flecks, and fundus flavimaculatus.

Common symptoms of STGD include progressive loss of central vision, problems identifying and differentiating colors, and difficulty seeing fine details clearly.



A retinal photograph showing Stargardt disease. (Kokell/BSIP SA/Alamy)

Genetic profile

There are different types of STGD. The most common form is Type 1, which is associated with autosomal recessive inheritance. In this type, there may be no family history of the condition, and it usually affects only one generation. A couple has a 25% chance of having another affected son or daughter once a child is diagnosed with STGD Type 1. This type of STGD is associated with mutations in the *ABCA4* (or *ABCR*) gene, which is located on chromosome 1. This gene is involved in moving vitamin A compounds naturally to and from cells in the retina; these cells are often impaired in STGD.

Other rarer forms of macular dystrophy with symptoms nearly identical to STGD have been called Stargardt-like macular dystrophy Types 2, 3, and 4. These are associated with autosomal dominant inheritance. In these types, a family history of the condition is quite common and STGD may be present in several generations of a family tree. A parent with these macular dystrophies has a 50% chance of having an affected son or daughter. Some of these individuals have been found to have mutations in the *ELOVL4* gene on chromosome 6.

Demographics

STGD is found worldwide, affecting males and females equally. The incidence for Type 1 is estimated to be between 1 in 1,600 and 1 in 15,000 individuals. In all, it accounts for 7% of all retinal dystrophies.

STGD Type 1 is usually diagnosed in individuals under the age of 20 when decreased central vision is the first problem noticed. In contrast, Stargardt-like macular dystrophies and age-related macular degeneration typically first show up in adulthood.

Signs and symptoms

Each person with STGD experiences symptoms differently. STGD affects the macula, a specialized portion of the retina that is highly responsible for the ability to see straight in front, notice colors, and see fine details. The macula is normally full of photoreceptors called cone cells. Cone cells help process the light rays that naturally hit the retina. In STGD, these cone cells slowly begin to die and lose function. In addition, the macula's appearance may begin showing abnormal yellow-white flecks that are shaped irregularly in people who have STGD.

Problems with central vision may be an early sign of STGD. The progression of this varies from person to person, and is impossible to predict. In addition, one's ability to see clearly (visual acuity) becomes progressively worse over time. This can progress from near-normal visual acuity to legal blindness. By the age of 50 years,

KEY TERMS

Dystrophy—Progressive abnormal changes in a tissue or organ.

Fluorescein angiography—Procedure to look at the blood vessel system of the eye. Fluorescein, a dye, is injected and photographs are taken as the dye passes through the eye's blood vessels.

Fundus—The interior back wall of the eyeball.

Macular degeneration—Progressive condition that affects the macula, a small portion of the retina at the back of the eye.

Mutation—Small change in the sequence of a gene.

Photoreceptor—Cells at the back of the eye that process the light that hits them; examples are cone and rod cells.

Retina—Structure at the back of the eye with multiple layers, containing different types of cells.

about half of people with STGD have visual acuity equal to or worse than that of legal blindness. Unfortunately, the reduced visual acuity in STGD cannot usually be corrected with prescription eyeglasses or contact lenses.

In later stages of STGD, color vision can be impacted. People may have trouble identifying colors or distinguishing them from one another. Rarely, people may experience difficulty with brightly lit conditions, blind spots in their vision, and problems with adjusting to dark environments.

Diagnosis

A diagnosis is most commonly made based on a person's symptoms. However, genetic testing is available to those suspected to have the condition. A few laboratories offer molecular testing of the *ABCA4* and *ELOVL4* genes on a clinical basis. Still others offer testing of these genes as part of a research study.

A young person who complains of problems with central vision or has poor visual acuity that cannot be corrected should be tested for STGD. A combination of various visual investigations can help rule out other diagnoses and identify visual problems that are consistent with STGD.

A detailed eye examination with an ophthalmologist can help determine one's visual acuity and general eye health. The physician may want to track the visual acuity over time to determine whether it can be corrected with prescription eyeglasses or contact lenses. The

ophthalmologist may also order visual tests to get more information about a diagnosis.

Testing of the visual fields can determine how much is being seen from left to right, and up and down. The full field of vision is studied to identify any blind spots or clarify whether the central vision is affected.

Fluorescein angiography (FA) can be helpful to determine whether blood flow is normal throughout the back of the eye. These detailed photographs of the eye's blood vessels can help identify any circulatory problems at the back of the eye, as well as changes in the retina's structure.

Fundus photographs can be taken to document changes in the eye structure, shape, and color. In STGD, this can sometimes show the yellowish-white flecks on the retina, which may actually fade with time. Sometimes there are other color changes in the retina of people with STGD as well.

An electroretinogram (ERG) tests how well the photoreceptors in the retina are functioning. Specifically for STGD, this test is very good at identifying how well the cone cells are working. It can also show how a person with STGD progressively loses working cone cells.

An electro-oculogram is similar to an ERG in that it studies retinal function and health. However, it is also meant to study the natural connection that exists between the eye and brain. This pathway must function normally in order for people to recognize an image that their eye sees. For STGD, this type of test can further document the cone cell abnormalities or loss.

STGD should not be confused with age-related macular degeneration (AMD), a relatively common condition in individuals often past the age of 50 years. Though the symptoms may be very similar, AMD has not been found to be associated with mutations in the *ABCA4* or *ELOVL4* genes.

Treatment and management

There is no cure for STGD, or known way to stop the disease progression altogether. However, some things can help maintain good retinal function and health.

It is felt that a diet rich in leafy green vegetables and fish may be good for the retina. In addition, certain fish contain omega-3 fatty acids, such as docosahexaenoic acid (DHA), that is naturally found in the retina in very high concentrations. Eating a diet of fish like salmon, tuna, mackerel, or whitefish twice a week should naturally provide good DHA levels. Otherwise, good fish oil capsules containing DHA and other omega fatty acids can be obtained with a prescription or purchased at specialty health stores.

Multivitamins containing vitamins A, E, and C may be useful. These have antioxidant properties, which may be protective for the eyes. However, large doses of certain vitamins may be toxic, and affected individuals should speak to their doctors before taking supplements.

Protecting the eyes from harmful ultraviolet rays is essential to cone cell health. People with STGD should wear good sunglasses outdoors and especially when over water or near snow on a bright, sunny day.

Smoking has been associated with deteriorating retinal health. Even quitting smoking late in life can make a positive impact on eye health.

Low vision aids can be helpful for those in school or at work. Binocular lens and magnifying screens, large-print reading materials, closed-circuit television, and other tools can be helpful and are often available from organizations supporting those with vision loss.

Living with a chronic vision problem makes a significant impact on a person's life and family. It is often helpful for families to have a social worker connect them to helpful resources. Others may find genetic counseling, psychotherapy, or meeting other individuals with STGD through support groups helpful.

Prognosis

Life expectancy is normal in STGD. A person's vision loss is progressive, but the rate of this is unpredictable. Research and future treatments continue to offer hope for those with this type of macular dystrophy.

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Canadian National Institute for the Blind (CNIB), 1929 Bayview Ave., Toronto, ON, Canada M4G 3E8, (800) 563-2642, info@cnib.ca, <http://cnib.ca/en/Pages/default.aspx>

Foundation Fighting Blindness (Canada), 890 Yonge St., 12th Floor, Toronto, ON, Canada M4W 3P4, (416) 360-4200 or (800) 461-3331, (416) 360-0060, info@ffb.ca, <http://www.ffb.ca>

Foundation Fighting Blindness (FFB), 7168 Columbia Gateway Dr., Suite 100, Columbia, MD 21046, (410) 423-0600 or (800) 683-5555, info@FightBlindness.org, <http://www.blindness.org>

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Steinert disease see **Myotonic dystrophy**

Stein-Leventhal syndrome see **Polycystic ovary syndrome**

Stem cells

Definition

Stem cells are cells from the adult or embryo that can develop into many different types of cells and have the ability to replicate themselves.

Description

Types of stem cells

Stem cells can be found in every organ and tissue of the body. They have the ability to develop into many different cell types. There are four types of stem cells:

1. Embryonic stem cells. Embryonic stem cells are pluripotent, which means that they can make copies of themselves indefinitely and can develop into any type of cell in the body. In humans, they first develop into neuroectoderm and mesendoderm precursor cells. Neuroectoderms develop into nerve cells. Mesendoderms develop into all the other cells of the body that makeup organs, muscles, blood and bone. Embryonic cells for research, come from three-to-five-day-old embryos donated from in vitro fertilization procedures (IVF).
2. Perinatal stem cells. Stem cells have been found in the amniotic fluid that surrounds the baby and in umbilical cord blood. These stem cells are pluripotent cells and act like embryonic stem cells.
3. Adult stem cells. A few of these stem cells are found in most tissues. They have a more limited ability to develop into other types of cells.

4. Induced pluripotent adult stem cells. These are adult stem cells whose genes have been changed so that they act like embryonic stem cells. They can make copies of themselves and can develop into most types of cell in the body. Induced pluripotent adult stem cells have limitations. Scientists have not yet been able to develop an adult pluripotent stem cell that can develop into any type of cell.

Stem cell uses

The first stem cells, discovered in 1981, were embryonic stem cells from mice. In 1998 scientists were first able to isolate and grow human embryonic stem cells in the lab. In 2006 researchers first created induced pluripotent adult stem cells. Ever since the discovery of stem cells, researchers have been investigating ways to use stem cells to cure disease, create new organs, and repair damaged tissue.

Stem cell treatments for cancer

Stem cells from the blood are already being used to help replace blood cells damaged by cancer and cancer treatments. Blood stem cells develop into different cells as they mature. They develop into platelets that help your blood clot, red blood cells which deliver oxygen to your body and white blood cells that fight off illness.

Stem cells and mature blood cells can be damaged by cancer and cancer treatment. The stem cells can be replaced with stem cells from healthy donors (allogeneic) or from a person's own stem cells (autologous).

During an allogenic transplant the patient first gets matched to a donor who has a similar genetic makeup. This can help prevent rejection of the donated cells. Alternatively, stem cells from donated umbilical cord blood can be used. The allogenic transplant is done after the patient has treatment like radiation or chemotherapy



A color-enhanced scanning electron microscope image of a stem cell and its processes. (MedicalRF/Science Source)

that destroys the patient's own stem cells. The donor stem cells will be transplanted to the patient's blood stream through an IV. The donor stem cells will then develop into mature and healthy blood cells.

During an autologous transplant, healthy stem cells will be taken from the patient's bone marrow or blood and then frozen. Once the patient's cancer treatment is completed, their stem cells will be returned to the blood stream. The stem cells will eventually develop back into mature blood cells.

Research on how diseases occur

Scientists watch how stem cells mature into different cells of the body and organs and tissues. This allows them to gain a better understanding of how diseases develop and research what causes genetic defects in cells. It can also allow them to discover why certain cells become cancerous.

Regenerative medicine

Regenerative medicine involves methods to repair or replace damaged cells tissues or organs. A lot of research in the field of regenerative medicine involves the use of stem cells. Most researchers believe that stem cells will one day routinely be grown in the lab, manipulated to develop into a specific cell like heart muscle or nerve cells, and then transplanted into diseased or damaged tissue. Stem cells may also one day be used to create organs, which would reduce our reliance on often expensive and difficult-to-obtain donor organs.

Scientists have already demonstrated that they can manipulate stem cells from the blood to grow into cells that can be injected into the heart and repair damage from heart attacks. The use of stem cells to repair damaged tissue would be particularly helpful for tissue like nerve cells or cartilage in the nose, ears, and joints since it does not regenerate on its own.

Gene therapies

Gene therapy involves treating a disease by adding, removing, or changing the genetic material in the cells of a patient. It is often used to treat genetic disease by correcting an abnormal gene that is not functioning properly. Somatic gene therapy involves adding, removing, or changing the genetic material in tissue or cells. This results in the production of a naturally occurring protein that is lacking or not functioning correctly in an individual patient.

Gene therapy can be done using mature cells or stem cells. The advantage of using stem cells is that they can self renew, last longer outside of the body, and differentiate into different cell types.

KEY TERMS

Cell—Building block that provides structure to the body and performs all the functions of the body. Cells contain genetic information and can copy themselves. The four main types of cells are: skin, nerve, muscle and connective tissue.

Gene—A gene is the unit of information on DNA that contains the instructions for making a protein.

Genome—The complete set of genetic instructions of an organism.

Induced pluripotent stem cells—Adult stem cells whose genes have been changed so that they act like embryonic stem cells. They can make copies of themselves indefinitely and can develop into many types of cell.

Pathogenic variant—Any change in the sequence of a genome that causes disease.

Pluripotent stem cells—Can develop into any type of cell in the body and have the ability to replicate themselves.

Protein—Proteins are the building blocks for life. They guide the development and functioning of the body.

Stem cells—Cells that can transform into any different type of cell and can make copies of themselves indefinitely.

Tissue—Made up of cells that have a common function. The four types of tissue are: connective, epithelial (skin), muscle and nervous tissue.

Variant—Change in the sequence of a genome.

Although gene therapy can be done directly in the body (in vivo), gene therapy using stem cells is typically done outside of the body (ex vivo). In ex vivo gene therapy, cells are genetically modified in the lab and then transplanted back into the body.

Gene therapies using stem cells can be done using donor stem cells or stem cells from the patient. Using stem cells from the patient is advantageous since it can be hard to find donors that are a close genetic match. Also, using ones own cells reduces the risk that the body will reject the stem cells as foreign. Because of these challenges, researchers often prefer using gene therapy on stem cells derived from the patient.

Gene therapy using stem cells can be used to treat many genetic conditions. It is particularly useful for conditions where the body is not producing enough of a

certain type of protein. For example, successful clinical trials have been done on Fabry disease. Fabry disease is caused by a genetic defect that reduces the amount of functioning GLA protein. This protein normally breaks down certain types of fats. When GLA is not functioning correctly, then these fats can accumulate in the organs causing problems in the kidneys, heart and brain.

In one gene therapy trial, blood stem cells were removed from patients with Fabry disease. A functioning gene was inserted into the stem cells that allowed them to create normal GLA. The newly modified stem cells were then transplanted back into each patient. All participants in the trial began producing near normal amounts of fully functioning GLA within one week and were able to stop their other treatments.

Another trial involved nine patients with leukodystrophy, a severe degenerative disease that affects the nerve cells and typically causes death in childhood. Participants in this trial all had a form of leukodystrophy that results from pathogenic variants in the gene that produces the protein arylsulphatase A. As a result, this protein was deficient in their body. Blood stem cells were removed from trial participants. A normal arylsulphatase A gene and another gene that boosts the production of arylsulphatase A were added to the stem cells. The stem cells were then reintroduced into the participants. Participants who started this trial before the onset of symptoms, ended up with no symptoms or just mild symptoms.

Gene therapy can also be used to grow normal tissue from skin cells. Scientists at the University of Modena in Italy used gene therapy on stem cells to treat a child with epidermolysis bullosa. Epidermolysis bullosa is a genetic condition that can cause severe blisters. The child who was treated had blisters over 80% of his body. Skin stem cells from the child were modified so that they had a normal epidermolysis bullosa gene. These cells were grown into skin tissue and grafted onto the child. This resulted in normal skin tissue that did not blister.

In addition to fixing genetic disease, gene therapy using stem cells can be used to produce better cells. For example, researchers at Harvard University are researching modifying stem cells so that they can produce insulin for people with Type 1 diabetes. Researchers have also potentially cured a man with HIV by transplanting donor cells with a gene variant in the CCR5 receptor. This variant prevents HIV from gaining access to cells. Researchers are looking to replicate this by creating pluripotent stem cells which have a variant in the CCR5 receptor.

Testing new drugs for safety and effectiveness

Scientists can use certain types of stem cells to test whether drugs are safe and effective before testing them

QUESTIONS TO ASK YOUR DOCTOR

- Would stem cell treatment help treat my disease?
- Are there any stem cell clinical trials available for my disease?
- What are the risks of this trial?

directly on people. Researchers also use stem cells to create tissue that potential medications can be tested on. In order for the testing to be accurate, the cells and tissue need to have similar properties to the cells that will eventually be targeted by the drug.

Cord blood banking and donation

Cord blood from the umbilical cord is rich in stem cells. These cells are capable of transforming into many different cells types. These stem cells can be used for research or to treat disease. Some parents store cord blood in case their children eventually need treatment that requires stem cells. Others donate the cord blood so that it can be used in research or to help treat disease in others. There are both public and private cord blood banks that will store cord blood.

Controversies in stem cell research

Some people are concerned about the ethics of using stem cells from human embryos in research. The NIH developed guidelines for stem cell research in 2009. These guidelines determine how stem cells may be used in research and how they may be donated. They also state that stem cells from embryos can only be used when the embryo is no longer needed and the donor has agreed to the donation.

Although adult stem cells can replace embryonic stem cells in some situations, they cannot always be used. They are not as versatile and stable as embryonic stem cells. They cannot currently be manipulated to create all cell types, which limits their use in treatment of diseases. Adult stem cells also are more likely to have genetic variants due to factors like environmental exposure. These variants could cause problems when transplanted into a recipient.

Challenges in stem cell research

One of the biggest risks of using pluripotent stem cells to treat disease is that they can form tumors after transplantation. This is because the methods that create pluripotent cells can result in genetic variants that can

lead to cancer. Researchers are focused on strategies to reduce this risk.

Immune rejection of stem cells is also a risk. This risk is greatest if donor cells are used. Using pluripotent cells derived from the patient reduces, but does not eliminate, the risk of an immune response. In some cases this is due to the viral components that are often used in the development of pluripotent cells. These viral components can trigger an immune response. Even pluripotent cells developed without viruses can trigger a mild immune response due to modifications that can happen in the transformation to pluripotent stem cells.

Studies have found that rare genetic variants in healthy donors may be passed on to recipients undergoing cancer therapy. Drugs designed to prevent an immune reaction in the recipient, can allow the cells with the rare variant to replicate and cause health problems such as other cancers and heart disease.

Stem cells are not immortal and have a limited lifespan. Some have a lifespan of months while others have a lifespan of years. This means that stem cell treatments may need to be repeated in some cases. Also as these stem cells age, they are less able to repair tissues and may become more susceptible to developing cancer.

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Steroid-resistant nephrotic syndrome type 2/Galloway-Mowat syndrome

Definition

Steroid-resistant nephrotic syndrome (SRNS) type 2 and Galloway-Mowat syndrome (GMS) are rare congenital nephrotic syndromes inherited in an autosomal recessive pattern and characterized by severe proteinuria, hypoproteinemia, and edema manifesting shortly after birth. Galloway-Mowat syndrome, named for the two Scottish physicians who reported on a family with two children affected by the syndrome in 1968, includes abnormalities of the central nervous system and digestive tract as well as loss of kidney function. Its alternate name is microcephaly-hiatal hernia-nephrotic syndrome. SRNS type 2 is also called nephrotic syndrome 2, hereditary nephrotic syndrome, and nephrotic syndrome, idiopathic, steroid-resistant. Although both disorders are inherited in the same pattern, they are caused by mutations in two different genes: the *NPHS2* gene on chromosome 1 in SRNS type 2 and the *WDR73* gene on chromosome 15 in Galloway-Mowat syndrome.

Description

SRNS type 2 is characterized by childhood-onset indications of disturbed kidney function: large amounts of protein in the urine (proteinuria), high levels of albumin in the urine that may be visible as whitish foam (albuminuria), low levels of protein in the blood

KEY TERMS

Albuminuria—Abnormally high levels of albumin (the most abundant protein in blood) in the urine. Albuminuria may be visible as white foam in the urine.

Bowman's capsule—A cup-shaped sac that surrounds the glomerulus in the kidney and receives the fluid (filtrate) from the blood filtered by the glomerulus.

Cerebellum—A portion of the brain consisting of two cerebellar hemispheres connected by a narrow vermis. The cerebellum is involved in control of skeletal muscles and plays an important role in the coordination of voluntary muscle movement.

Edema—Abnormal accumulation of fluid beneath the skin and within body cavities. Pitting edema refers to the persistence of a pit or indentation that remains after the examiner releases finger pressure on the patient's skin.

End-stage renal disease (ESRD)—A potentially fatal condition that occurs when the kidneys can no longer effectively filter urine and excrete waste products from the body.

Focal segmental glomerulosclerosis (FSGS)—Formation of scar tissue in the filtering unit of the kidney. "Focal" means that only some of the glomeruli are affected; "segmental" means that only a segment or section of an affected glomerulus is damaged.

Glomerulus—A structure in the kidney composed of blood vessels that are actively involved in the filtration of the blood.

Hiatal hernia—A structural defect in the digestive tract in which the upper part of the stomach protrudes (herniates) through an opening or weak area in the diaphragm into the chest.

Hyperreflexia—Having overactive or overresponsive reflexes.

Hypoalbuminemia—An abnormally low level of albumin in the blood.

Hypotonia—Low or poor muscle tone, resulting in floppy limbs.

Loss-of-function mutation—Any mutation that causes a gene to lose its ability to encode a protein either partially or completely.

Microcephaly—Abnormal smallness of the head; it is often associated with intellectual disability.

Nephrotic syndrome—A kidney disorder characterized by high levels of protein in the urine, low levels of albumin in the blood, and edema (abnormal accumulation of fluid in the body). It may be caused by genetic mutations, infections, certain medications, or such other disorders as diabetes and cancer.

Podocytes—Specialized cells in the Bowman's capsule of the kidney that wrap around the capillaries in the glomerulus and serve to prevent large protein molecules from passing into the urine while allowing water and small molecules like salt to pass through.

Proteinuria—An abnormally high level of protein in the urine, defined as higher than 3.5 grams per day in adults or higher than 40 mg/m² per hour in children.

(hypoproteinemia), high levels of cholesterol and lipids (fats) in the blood, susceptibility to infections, and retention of fluid in the body (edema). The edema may be severe enough to show pitting (persistence of a dent or pit in the fluid-swollen skin after the doctor removes finger pressure on the skin). The hallmark of SRNS type 2 is that unlike other forms of nephrotic syndrome, it does not respond to treatment with steroid medications, the basic form of therapy for nephrotic syndrome. SRNS type 2 usually progresses to end-stage renal disease (ESRD).

GWS is evident at birth by congenital abnormalities of the infant's skull and abdomen. The head is unusually small (microcephaly), and the facial features may be malformed. The child may also have abnormalities of the brain tissue itself, such as the absence of the inner layer of the cerebellum, abnormally small folds in the outer

layer of brain tissue (microgyria), and the absence or partial lack of myelin (a fatty substance that facilitates the transmission of electrical impulses through the nervous system by serving as an insulator) in the cerebrum and brain stem.

In addition to the craniofacial deformities and neurological abnormalities, the infant with GMS usually has a hiatal hernia—a condition in which part of the stomach protrudes (herniates) through an abnormal opening in the diaphragm into the chest. Other symptoms may include poor muscle tone (hypotonia), abnormally strong reflexes (hyperreflexia), seizures, developmental delays, and intellectual disability. Abnormalities in the kidneys, such as the formation of scar tissue in some of the glomeruli of the kidneys (focal glomerulosclerosis) or the formation of cysts within the kidney tissue, lead to the

same symptoms of nephrotic syndrome as are found in SRNS type 2: proteinuria, albuminuria, and edema. These renal symptoms may become evident shortly after the child's birth, or they may not appear until he or she is two to three years old.

Genetic profile

Both syndromes are inherited in an autosomal recessive pattern, which means that the offspring needs to inherit two copies of the mutated gene—one from each parent—in order to develop the symptoms of the disorder. SRNS type 2 is caused by a mutation in the *NPHS2* gene on the long arm of chromosome 1 at 1q25. This gene codes for a protein called podocin, which is critical in maintaining the integrity of podocytes, specialized cells in the Bowman's capsule of the kidney that cover the basement membrane of each glomerulus and prevent the passage of albumin and other large protein molecules into the urine. Mutations in the *NPHS2* gene lead to weaknesses in the podocytes and consequent leakage of large amounts of albumin, immunoglobulins, and other proteins into the patient's urine. It is the loss of immunoglobulins from the blood that results in the patient's increased susceptibility to infections. As the level of albumin in the blood drops, fluid that is normally retained in the blood begins to accumulate in body tissues instead, resulting in the edema that marks nephrotic syndrome. Eventually, scarring (focal segmental glomerulosclerosis) may occur in some of the glomeruli, thus accelerating loss of kidney function.

An international team of researchers reported in early 2015 that recessive mutations in the *CRB2* gene on the long arm of chromosome 9 at 9q33.3 are also associated with SRNS type 2. Like *NPHS2*, this gene also appears to be essential to the normal functioning of podocytes and the prevention of loss of protein in the urine.

GWS is caused by loss-of-function mutations in the *WDR73* gene on the long arm of chromosome 15 at 15q25.2. This gene encodes a protein that contains multiple WD40 repeats, which are structural patterns that contain between 40 and 60 amino acids. The function of the protein encoded by the *WDR73* gene was unknown as of 2015, but it appears to be important in prolonging cell survival and maintaining cell structure. The protein is known to be expressed in embryonic kidney tissue as well as in the cerebral cortex and the hippocampus in the brain, which explains why mutations in the *WDR73* gene result in abnormalities of the central nervous system, as well as the kidneys.

Demographics

Both disorders are rare. The prevalence of SRNS type 2 in the general population was unknown as of

2015, but it has been reported in consanguineous families in Turkey and elsewhere, as well as in families in the United Kingdom, Hungary, Israel, Brazil, Italy, France, and Germany.

Prior to late 2014, only about 20 cases of GWS had been reported in the medical literature since the disorder was first identified in 1968. In 2014, a group of researchers in Pennsylvania and Ohio reported on a group of 30 children from various Amish families in the eastern United States who were diagnosed with GWS. The Old Order Amish have a high rate of consanguineous marriages, which explains the increased risk of autosomal recessive genetic disorders among them. GWS has also been identified in Turkish and Moroccan families that allowed marriage between first cousins.

As far as is known, both disorders affect males and females equally and may appear in members of all races and ethnic groups.

Signs and symptoms

The signs and symptoms of SRNS type 2 may appear shortly after birth or not until early childhood, but symptoms typically progress rapidly to end-stage renal disease. Although children with SRNS type 2 do not have the craniofacial abnormalities found in GWS, their loss of kidney function will usually be apparent in the form of edema, abnormally high blood pressure readings, high levels of blood cholesterol, frequent infections, and severe proteinuria on urine tests.

The signs and symptoms of GWS may appear at birth in the form of low birth weight and visible craniofacial abnormalities that include a sloping forehead; a small midface; an unusually small jaw; large, low-set, or floppy ears; cataracts in the eyes; drooping eyelids (ptosis); clenched hands with unusually slender fingers; and hypotonia. Repeated vomiting in early infancy and failure to thrive due to the loss of nutrients may lead to suspicion of hiatal hernia. Delayed motor development, seizures, and intellectual disability are usually apparent by two to three years of age.

Diagnosis

SRNS type 2 is suspected when the child is evaluated for proteinuria, edema, high levels of blood cholesterol, high blood pressure, and other signs of nephrotic syndrome but fails to respond to corticosteroid therapy. A kidney biopsy may be done to look for evidence of scarring in the glomeruli, but the definitive diagnosis is provided by molecular genetic testing for mutations in the *NPHS2* gene.

QUESTIONS TO ASK YOUR DOCTOR

- Have you ever treated a patient with either of these rare congenital nephrotic syndromes?
- If so, did the patient obtain a kidney transplant?
- What treatment would you recommend for the neurological symptoms of Galloway-Mowat syndrome?
- Do you think that gene therapy may offer a potential cure for these disorders?

GMS is suspected at birth on the basis of visible craniofacial abnormalities, while the presence of a hiatal hernia can be confirmed by x-ray imaging. Failure to sit up or walk on the normal timetable, seizures, and intellectual disability will usually become apparent after the first year of life. Loss of kidney function will be evident in the passage of foamy urine, abnormal results on urine tests, and pitting edema in the child's skin. A kidney biopsy may be performed to look for the presence of scar tissue (focal sectional glomerulonephrosis) or cysts in some of the glomeruli of the kidneys. The definitive diagnosis of GMS is provided by molecular genetic testing for mutations in the *WDR73* gene.

Treatment and management

The only curative treatment for either of these autosomal recessive congenital nephrotic syndromes is kidney transplantation. Low-sodium and low-protein diets may be recommended, along with diuretics to control the edema and antibiotics to manage infections, but these measures will not affect the underlying cause of the loss of kidney function. Children with GMS who develop seizures may be given anticonvulsant drugs, but the choice of these drugs and their dosage must be decided on an individual basis, as some antiseizure drugs may interact with other medications given to treat GMS.

Children with SRNS type 2 may be given angiotensin-converting-enzyme (ACE) inhibitors to lower blood pressure, as well as diuretics to reduce edema and antibiotics to treat infections. As loss of kidney function progresses, however, patients with SRNS type 2 will require hemodialysis or kidney transplantation. Some patients develop a recurrence of the disorder even after kidney transplantation.

Prognosis

The prognosis of SRNS type 2 is poor. With careful management, some patients can live into their early 20s, but most patients die during the first decade of life.

The prognosis of GMS is also poor; most affected children die within the first ten years of life of end-stage renal disease. The oldest known patient with the disorder died at age 28.

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ORGANIZATIONS

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- National Kidney Foundation, 30 E. 33rd St., New York, NY 10016, (800) 622-9010 or (855) 653-2273, (212) 689-9261, info@kidney.org, <https://www.kidney.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>
- NephCure Kidney International, 150 S. Warner Rd., Suite 402, King of Prussia, PA 19406, (866) 637-4287, info@nephcure.org, <http://nephcure.org>

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Stickler syndrome

Definition

Stickler syndrome is a disorder caused by a genetic malfunction in the tissue that connects bones, heart, eyes, and ears.

Description

Stickler syndrome, also known as hereditary arthropathopathy, is a multisystem disorder that can affect

the eyes and ears, skeleton and joints, and craniofacies. Symptoms may include myopia, cataracts, and retinal detachment; hearing loss that is both conductive and sensorineural; midfacial underdevelopment and cleft palate; and mild spondyloepiphyseal dysplasia and/or arthritis. The collection of specific symptoms that make up the syndrome were first documented by Gunnar B. Stickler, et al., in a 1965 paper published in *Mayo Clinic Proceedings* titled “Hereditary Progressive Arthro-Ophthalmopathy.” The paper associated the syndrome’s sight deterioration and joint changes. Subsequent research has redefined Stickler syndrome to include other symptoms.

Genetic profile

Stickler syndrome is associated with mutations in three genes: *COL2A1* (chromosomal locus 12q13), *COL11A1* (chromosomal locus 1p21), and *COL11A2* (chromosomal locus 6p21). It is inherited in an autosomal dominant manner where the majority of individuals with Stickler syndrome inherit the abnormal allele from one parent. The prevalence of new gene mutations that cause Stickler syndrome is unknown. Individuals with Stickler syndrome have a 50% chance of passing on the abnormal gene to each offspring.

The syndrome can manifest itself differently within families. If the molecular genetic basis of Stickler syndrome has been established, molecular genetic testing can be used for clarification of each family member’s genetic status and for prenatal testing.

A majority of cases are attributed to *COL2A1* mutations, all of which are known to cause Stickler syndrome as a result in the formation of a premature termination codon within the type-II collagen gene. Mutations in *COL11A1* have only recently been described and *COL11A2* mutations have been identified only in patients lacking ocular findings.

Although the syndrome is associated with mutations in the *COL2A1*, *COL11A1*, and *COL11A2* genes, no linkage to any of these three known loci can be established in some rare cases with clinical findings consistent with Stickler syndrome. It is presumed that other, as yet unidentified, gene mutations also account for Stickler syndrome.

Genetically related disorders

There are a number of other phenotypes associated with mutations in *COL2A1*. Achondrogenesis type I is a fatal disorder characterized by absence of bone formation in the vertebral column, sacrum, and pubic bones, by the shortening of the limbs and trunk, and by a prominent abdomen. Hypochondrogenesis is a milder variant of achondrogenesis. Spondyloepiphyseal dysplasia congenita,

a disorder with skeletal changes more severe than in Stickler syndrome, manifests in significant short stature, flat facial profile, myopia, and vitreoretinal degeneration. Spondyloepimetaphyseal dysplasia type Strudwick is another skeletal disorder that manifests in severe short stature with severe protrusion of the sternum and scoliosis, cleft palate, and retinal detachment. A distinctive radiographic finding is irregular sclerotic changes, described as dappled, which are created by alternating zones of osteosclerosis and osteopenia in the metaphyses (ends) of the long bones. Spondyloperipheral dysplasia is a rare condition characterized by short stature and radiographic changes consistent with a spondyloepiphyseal dysplasia and brachydactyly. Kniest dysplasia is a disorder that manifests in disproportionate short stature, flat facial profile, myopia and vitreoretinal degeneration, cleft palate, backward and lateral curvature of the spine, and a variety of radiographic changes.

Other phenotypes associated with mutations in *COL11A1* include Marshall syndrome, which manifests in ocular hypertelorism, hypoplasia of the maxilla and nasal bones, flat nasal bridge, and small upturned nasal tip. Unlike Stickler syndrome, the flat facial profile of Marshall syndrome is usually evident into adulthood. Manifestations include hypoplasia of the nasal sinuses and a thickened calvarium. Ocular manifestations include high myopia, fluid vitreous humor, and early-onset cataracts. Sensorineural hearing loss is common and sometimes progressive. Cleft palate is seen both as an isolated occurrence and as part of the Pierre-Robin sequence (micrognathia, cleft palate, and glossoptosis). Other manifestations include short stature, early-onset arthritis, and skin manifestations that may include mild hypotrichosis and hypohidrosis.

Phenotypes associated with mutations in *COL11A2* include autosomal recessive oto-spondylometaphyseal dysplasia, a disorder characterized by flat facial profile, cleft palate, and severe hearing loss. Anocular Stickler syndrome caused by *COL11A2* mutations is similar to this disorder. Weissenbach-Zweymuller syndrome has been characterized as a neonatal form of Stickler syndrome but it is a separate entity from Stickler syndrome. Symptoms include midface hypoplasia with a flat nasal bridge, small upturned nasal tip, micrognathia, sensorineural hearing loss, and rhizomelic limb shortening. Radiographic findings include vertebral coronal clefts and dumbbell-shaped femora and humeri. Catch-up growth after age two or three is common and the skeletal findings become less apparent in later years.

Demographics

No studies have been done to determine Stickler syndrome prevalence. An approximate incidence of Stickler

syndrome among newborns is estimated based on data on the incidence of Pierre-Robin sequence in newborns. One in 10,000 newborns has Pierre-Robin sequence, and 35% of these newborns subsequently develop signs or symptoms of Stickler syndrome. These data suggest that the incidence of Stickler syndrome among neonates is approximately 1 in 7,500.

Signs and symptoms

Stickler syndrome may affect the eyes and ears, skeleton and joints, and craniofacial characteristics. It may also be associated with coronary complications.

Ocular symptoms

Nearsightedness is a common symptom of Stickler syndrome. High myopia is detectable in newborns. Common problems also include astigmatism and cataracts, and risk of retinal detachment is higher than normal. Abnormalities of the vitreous humor, the colorless, transparent jelly that fills the eyeball, are also observed. Type 1, the more common vitreous abnormality, is characterized by a persistence of a vestigial vitreous gel in the space behind the lens, and is bordered by a folded membrane. Sparse and irregularly thickened bundles throughout the vitreous cavity characterize type 2, which is much less common. These vitreous abnormalities can cause sight deterioration.

Auditory symptoms

Hearing impairment is common and some degree of sensorineural hearing loss is found in 40% of patients. The degree of hearing impairment is variable and may be progressive. Typically the impairment is in the high tone frequency and is often subtle. Conductive hearing loss is also possible. It is known that the impairment is related to the expression of type II and IX collagen in the inner ear, but the exact mechanism for it is unclear. Hearing impairment may be secondary to the recurrent ear infections often associated with cleft palate, or it may be secondary to a disorder of the ossicles of the middle ear.

Skeletal symptoms

Skeletal manifestations include short stature relative to unaffected siblings, early-onset arthritis, and abnormalities at ends of long bones and vertebrae. Radiographic findings are consistent with mild spondyloepiphyseal dysplasia. Some individuals have a physique similar to Marfan syndrome, but without tall stature. Young patients may exhibit joint laxity but it diminishes or even resolves completely with age. Early-onset arthritis is common and generally mild, mostly resulting in joint stiffness. Arthritis

KEY TERMS

Cleft palate—A congenital malformation in which there is an abnormal opening in the roof of the mouth that allows the nasal passages and the mouth to be improperly connected.

Dysplasia—The abnormal growth or development of a tissue or organ.

Glossoptosis—Downward displacement or retraction of the tongue.

Micrognathia—Small lower jaw with recession of lower chin.

Mitral valve prolapse—A heart defect in which one of the valves of the heart (which normally controls blood flow) becomes floppy. Mitral valve prolapse may be detected as a heart murmur but there are usually no symptoms.

Otitis media—Inflammation of the middle ear, often due to fluid accumulation secondary to an infection.

Phenotype—The physical expression of an individual's genes.

Spondyloepiphyseal dysplasia—Abnormality of the vertebra and epiphyseal centers that causes a short trunk.

is sometimes severe, leading to joint replacement as early as the third or fourth decade.

Craniofacial findings

Several facial features are common with Stickler syndrome. A flat facial profile referred to as a “scooped-out” face results from underdevelopment of the maxilla and nasal bridge, which can cause telecanthus and epicanthal folds. Flat cheeks, flat nasal bridge, small upper jaw, pronounced upper lip groove, small lower jaw, and palate abnormalities are possible, all in varying degrees. The nasal tip may be small and upturned, making the groove in the middle of the upper lip appear long. Micrognathia is common and may compromise the upper airway, necessitating tracheostomy. Midfacial hypoplasia is most pronounced in infants and young children, and older individuals may have a normal facial profile.

Coronary findings

Mitral valve prolapse may be associated with Stickler syndrome, but studies are still inconclusive about the connection.

Diagnosis

Stickler is believed to be a common syndrome in the United States and Europe, but only a fraction of cases are diagnosed since most patients have minor symptoms. Misdiagnosis may also occur because symptoms are not correlated as having a single cause. More than half of patients with Stickler syndrome are originally misdiagnosed, according to one study.

While the diagnosis of Stickler syndrome is clinically based, clinical diagnostic criteria have not been established. Patients usually do not have all symptoms attributed to Stickler syndrome. The disorder should be considered in individuals with clinical findings in two or more of the following categories:

- **Ophthalmologic.** Congenital or early-onset cataract, myopia greater than -3 diopters, congenital vitreous anomaly, and rhegmatogenous retinal detachment. Normal newborns are typically hyperopic ($+1$ diopter or greater), and so any degree of myopia in an at-risk newborn, such as one with Pierre-Robin sequence or an affected parent, is suggestive of the diagnosis of Stickler syndrome. Less common ophthalmological symptoms include paravascular pigmented lattice degeneration and cataracts.
- **Craniofacial.** Midface hypoplasia, depressed nasal bridge in childhood, anteverted nares (tipped or bent nasal cavity openings), split uvula, cleft hard palate, micrognathia, and Pierre-Robin sequence.
- **Audiologic.** Sensorineural hearing loss.
- **Joint.** Hypermobility, mild spondyloepiphyseal dysplasia, and precocious osteoarthritis.

It is appropriate to evaluate at-risk family members with a medical history and physical examination and ophthalmologic, audiologic, and radiographic assessments. Childhood photographs may be helpful in the evaluation of adults since craniofacial findings may become less distinctive with age.

Molecular genetic testing

Mutation analysis for *COL2A1*, *COL11A1*, and *COL11A2* is available. Detection is performed by mutation scanning of the coding sequences. Stickler syndrome has been associated with stop mutations in *COL2A1* and with missense and splicing mutations in all of the three genes. Because the meaning of a specific missense mutation within the gene coding sequence may not be clear, mutation detection in a parent is not advised without strong clinical support for the diagnosis.

Clinical findings can influence the order for testing the three genes. In patients with ocular findings, including type 1 congenital vitreous abnormality and mild

QUESTIONS TO ASK YOUR DOCTOR

- What is the genetic basis for Stickler syndrome?
- What tests or other criteria are used to diagnose Stickler syndrome?
- What treatments are available for this condition, and how effective are these treatments?
- What provisions should a family make for a child who has been diagnosed with Stickler syndrome to provide the best medical and emotional care at home?

hearing loss, *COL2A1* may be tested first. In patients with typical ocular findings including type 2 congenital vitreous anomaly and significant hearing loss, *COL11A1* may be tested first. In patients with hearing loss and craniofacial and joint manifestations but without ocular findings, *COL11A2* may be tested first.

Prenatal testing

Before considering prenatal testing, its availability must be confirmed and prior testing of family members is usually necessary. Prenatal molecular genetic testing is not usually offered in the absence of a known disease-causing mutation in a parent. For fetuses at 50% risk for Stickler syndrome, a number of options for prenatal testing may exist. If an affected parent has a mutation in the gene *COL2A1* or *COL11A1*, molecular genetic testing may be performed on cells obtained by chorionic villus sampling at 10–12 weeks gestation or amniocentesis at 16–18 weeks gestation. Alternatively, or in conjunction with molecular genetic testing, ultrasound examination can be performed at 19–20 weeks gestation to detect cleft palate. For fetuses with no known family history of Stickler syndrome in which cleft palate is detected, a three-generation pedigree may be obtained, and relatives who have findings suggestive of Stickler syndrome should be evaluated.

Treatment and management

Individuals diagnosed with Stickler syndrome, and individuals in whom the diagnosis cannot be excluded, should be followed for potential complications.

Evaluation by an ophthalmologist familiar with the ocular manifestations of Stickler syndrome is recommended. Individuals with known ocular complications may prefer to be followed by a vitreoretinal specialist. Patients should avoid activities that may lead to traumatic

retinal detachment, such as contact sports. Patients should be advised of the symptoms associated with a retinal detachment and the need for immediate evaluation and treatment when such symptoms occur. Individuals from families with Stickler syndrome and a known *COL2A1* or *COL11A1* mutation who have not inherited the mutant allele do not need close ophthalmologic evaluation.

A baseline audiogram to test hearing should be performed when the diagnosis of Stickler syndrome is suspected. Follow-up audiologic evaluations are recommended in affected persons since hearing loss can be progressive.

Radiological examination may detect signs of mild spondyloepiphyseal dysplasia. Treatment is symptomatic, and includes over-the-counter anti-inflammatory medications before and after physical activity. No preventive therapies currently exist to minimize joint damage in affected individuals. In an effort to delay the onset of arthropathy, physicians may recommend avoiding physical activities that involve high impact to the joints, but no data support this recommendation.

Infants with Pierre-Robin sequence need immediate attention from otolaryngology and pediatric critical care specialists. Evaluation and management in a comprehensive craniofacial clinic that provides all the necessary services, including otolaryngology, plastic surgery, oral and maxillofacial surgery, pediatric dentistry, and orthodontics, is recommended. Tracheostomy may be required, which involves placing a tube in the neck to facilitate breathing.

Middle ear infections (otitis media) may be a recurrent problem secondary to the palatal abnormalities, and ear tubes may be required. Micrognathia (small jaw) tends to become less prominent over time in most patients, allowing for removal of the tracheostomy. In some patients, however, significant micrognathia persists and causes orthodontic problems. In these patients, a mandibular advancement procedure may be required to correct jaw misalignment.

Cardiac care is recommended if complaints suggestive of mitral valve prolapse, such as episodic tachycardia and chest pain, are present. While the prevalence of mitral valve prolapse in Stickler syndrome is unclear, all affected individuals should be screened since individuals with this disorder need antibiotic prophylaxis for certain surgical procedures.

Prognosis

Prognosis is good under physician care. It is particularly important to receive regular vision and hearing exams. If retinal detachment is a risk, it may be advisable

to avoid contact sports. Some craniofacial symptoms may improve with age.

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ORGANIZATIONS

- Stickler Involved People, 15 Angelina, Augusta, KS 67010, (316) 256-5194, sip@sticklers.org, <http://www.sticklers.org>
- Stickler Syndrome Support Group, PO Box 371, Walton-on-Thames, UK KT12 2YS, 44-01932 267635, <http://www.stickler.org.uk>

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Sturge-Weber syndrome

Definition

Sturge-Weber syndrome (SWS) is a condition involving specific brain changes that often cause seizures and mental delays. It also includes port wine-colored birthmarks (or "port-wine stains"), usually found on the face.

Description

The brain finding in SWS is leptomeningeal angioma, which is a swelling of the tissue surrounding the brain and spinal cord. These angiomas cause seizures in

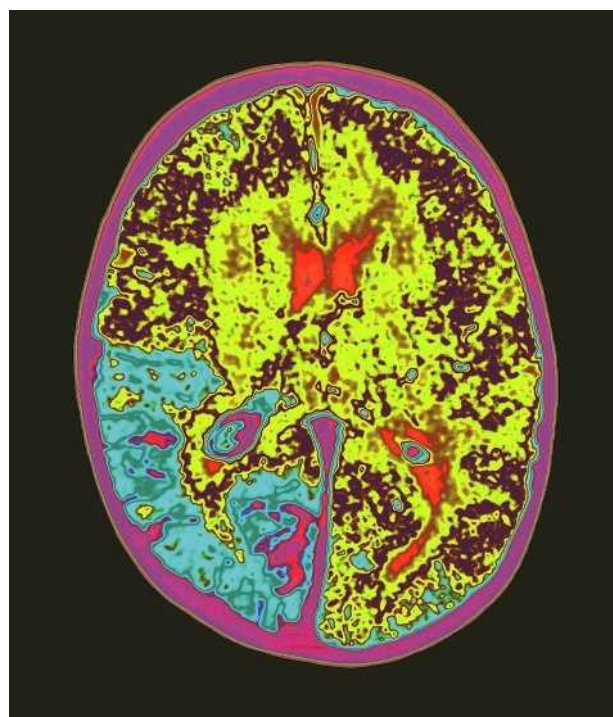
approximately 90% of people with SWS. A large number of affected individuals are also mentally delayed.

Port-wine stains are present at birth. They can be quite large and are typically found on the face near the eyes or on the eyelids. Vision problems are common, especially if a port-wine stain covers the eyes. These vision problems can include glaucoma and vision loss.

Facial features, such as port-wine stains, can be very challenging for individuals with SWS. These birthmarks can increase in size with time, and this may be particularly emotionally distressing for the individuals, as well as their parents. A state of unhappiness about this is more common during middle childhood and later than it is at younger ages.

Genetic profile

The genetics behind Sturge-Weber syndrome are still unknown. Interestingly, in other genetic conditions involving changes in the skin and brain (such as neurofibromatosis and tuberous sclerosis) the genetic causes are well described. It is known that most people with SWS are the only ones in their family with the condition; there is usually not a strong family history of the disease. However, the gene known to cause SWS is still not known.



MRI scan of a brain with Sturge-Weber syndrome. The front of the brain is at the top. Red-colored areas indicate fluid-filled ventricles. The blue area is where the brain has become calcified. (Mehau Kulyk/Science Source)

KEY TERMS

Calcification—A process in which tissue becomes hardened due to calcium deposits.

Choroid—A vascular membrane that covers the back of the eye between the retina and the sclera and serves to nourish the retina and absorb scattered light.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Glaucoma—An increase in the fluid eye pressure, eventually leading to damage of the optic nerve and ongoing visual loss.

Leptomeningeal angioma—A swelling of the tissue or membrane surrounding the brain and spinal cord, which can enlarge with time.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Port-wine stain—Dark-red birthmarks seen on the skin, named after the color of the dessert wine.

Sclera—The tough white membrane that forms the outer layer of the eyeball.

For now, SWS is thought to be caused by a random, sporadic event.

Demographics

Sturge-Weber syndrome is a sporadic disease that is found throughout the world, affecting males and females equally. The total number of people with Sturge-Weber syndrome is not known, but estimates range between 1 in 400,000 to 1 in 40,000.

Signs and symptoms

People with SWS may have a larger head circumference (measurement around the head) than usual. Leptomeningeal angiomas can progress with time. They usually only occur on one side of the brain, but can exist on both sides in up to 30% of people with SWS. The angiomas can also cause great changes within the brain's white matter. Generalized wasting, or regression, of portions of the brain can result from large angiomas. Calcification of the portions of the brain underlying the angiomas can also occur. The larger and more involved the angiomas are, the greater the expected amount of

mental delays in the individual. Seizures are common in SWS, and they can often begin in very early childhood. Occasionally, slight paralysis affecting one side of the body may occur.

Port-wine stains are actually capillaries (blood vessels) that reach the skin's surface and grow larger than usual. As mentioned earlier, the birthmarks mostly occur near the eyes; they often occur only on one side of the face. Though they can increase in size over time, port-wine stains cause no direct health problems for the person with SWS.

Vision loss and other complications are common in SWS. The choroid of the eye can swell, and this may lead to increased pressure within the eye in 33%–50% of people with SWS. Glaucoma is another common vision problem seen in SWS, and is more often seen when a person has a port-wine stain that is near or touches the eye.

In a 2000 study about the psychological functioning of children with SWS it was noted that parents and teachers report a higher incidence of social problems, emotional distress, and problems with compliance in these individuals. Taking the mental delays into account, behaviors associated with attention-deficit hyperactivity disorder (ADHD) were noted; as it turns out, about 22% of people with SWS are eventually diagnosed with ADHD.

Diagnosis

Because no genetic testing is available for Sturge-Weber syndrome, all diagnoses are made through a careful physical examination and study of a person's medical history.

Port-wine stains are present at birth, and seizures may occur in early childhood. If an individual has both of these features, SWS should be suspected. A brain MRI or CT scan can often reveal a leptomeningeal angioma, brain calcifications, as well as any other associated white matter changes.

Treatment and management

Treatment of seizures in SWS by antiepileptic medications is often an effective way to control them. In the rare occasion that an aggressive seizure medication therapy is not effective, surgery may be necessary. The general goal of the surgery is to remove the portion of the brain that is causing the seizures, while keeping the normal brain tissue intact. Though most patients with SWS only have brain surgery as a final attempt to treat seizures, some physicians favor earlier surgery because this may prevent some irreversible damage to the brain (caused by the angiomas).

QUESTIONS TO ASK YOUR DOCTOR

- What is the status of current research on the genetic basis of Sturge-Weber syndrome?
- How common is Sturge-Weber syndrome in the general population and in any populations at special risk?
- Should individuals with Sturge-Weber be subject to regular medical monitoring and, if so, what kind of tests should be conducted?
- Are there sources on the Internet that can provide me with additional information about this disorder?

Standard glaucoma treatment, including medications and surgery, is used to treat people with this complication. This can often reduce the amount of vision loss.

There is no specific treatment for port-wine stains. Because they contain blood vessels, it could disrupt blood flow to remove or alter the birthmarks.

Prognosis

The prognosis for people with SWS is directly related to the amount of brain involvement for the leptomeningeal angiomas. For those individuals with smaller angiomas, prognosis is relatively good, especially if they do not have severe seizures or vision problems.

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ORGANIZATIONS

Sturge-Weber Foundation, PO Box 418, Mount Freedom, NJ 07970, (973) 895-4445 or (800) 627-5482, (973) 895-4846, swf@sturge-weber.org, <http://www.sturge-weber.org/home.html>

Deepti Babu, MS

Summitt syndrome see **Carpenter syndrome**

Super Enhancers (SE)

Definition

Enhancers are short regions of DNA that activate the expression (transcription) of their associated genes. These regions of about 50–1,500 nucleotide base pairs (the building blocks of DNA) bind proteins called transcription factors. The binding of these factors to enhancer sequences promotes the transcription of genes into RNAs, which subsequently may be translated to produce the corresponding proteins. Super enhancers (SEs) are clusters of enhancers that are responsible for determining and maintaining cell types. Variations or mutations (changes) in the DNA sequences of SEs appear to be associated with the development of various diseases, including autoimmune disorders and cancers.

Description

The hundreds of different types of cells in the human body share the same DNA sequence (genome); however, the specific genes that are expressed (transcribed) in the cells determine their cell type or identity. To a large extent, the regulation of this differential gene expression in different types of cells is controlled by enhancers. Enhancers are DNA sequences that are typically a few hundred base pairs in length. These enhancer sequences bind multiple transcription factors and activators and RNA polymerase II, the enzyme that copies (transcribes) the DNA of a gene into RNA that may be translated to produce the protein encoded by the gene. There are approximately one million enhancers in the human genome, of which tens of thousands are estimated to be active in a given cell type. Enhancers are very important, not just for controlling the expression of cell-type-specific genes, but also because many of the variations in DNA sequences that are associated with diseases occur in enhancers.

SEs are also called “stretch enhancers” because they are formed from multiple enhancers that are clustered or “stretched” together by the densely packed binding of proteins, including “master” transcription factors and the

mediator coactivator complex. SEs differ from typical enhancers in important ways:

- They are much larger.
- They are much more densely packed with transcription factors and other proteins that differ from those that bind to typical enhancers.
- They bind very high levels of a complex of proteins called the mediator coactivator complex, which is important for activating gene transcription.
- They are in particularly close proximity to the genes they regulate.
- They promote much more active transcription of their associated genes.
- They are associated with genes that encode cell-type-specific transcription factors—transcription factors that are only active in specific cell types. In contrast, typical enhancer-associated genes tend to be active in many different types of cells.
- They are very susceptible to perturbation that results in the loss of bound proteins and results in changes in gene transcription activity.

SEs are very powerful molecular “switches” that promote high-level expression (transcription) of genes that determine and maintain cell type (cell identity). Scientists can locate SEs in the genomes of specific types of cells by looking for regions of DNA that are open and accessible for the binding of regulatory proteins, rather than tightly coiled and protected by chromosomal proteins called histones. By identifying the transcription factors that bind to SEs in different cell types, researchers can determine which factors control the cell-specific activation of genes that maintain the functions of specific cell types.

In addition to associating with genes that control cell type and cell-type-specific functions, SEs tend to be acquired by genes that encode potential master transcription factors and regulatory RNAs that do not make proteins. SEs bind unusually high amounts of RNA polymerase II and its associated cofactors and chromatin regulators (proteins that make the DNA in chromosomes available for transcription), which are responsible for transcribing enhancer RNAs (eRNAs) from enhancer sequences. These eRNAs may also be involved in gene activation.

Embryonic stem cells (ESCs)

ESCs are cells from the earliest stages of embryonic development and can develop or differentiate into any type of cell in the body. Thus, they are a major focus of scientific investigations. In ESCs, SEs are bound by transcription factors, cofactors, chromatin regulators, and other proteins required for gene transcription. SEs are

associated with genes that define and control cell differentiation. ESC master transcription factors, such as Oct4, Sox2, Nanog, Klf4, and Esrrb, bind to (occupy) enhancers and recruit the mediator coactivator complex to form SEs. Mediator and the master transcription factors recruit RNA polymerase II to transcribe genes that are important for establishing and maintaining the ESC state and for embryonic development. Transcription of the genes that produce the Oct4, Sox2, and Nanog master transcription factor proteins are themselves regulated by SEs.

Although many additional transcription factors occupy both typical enhancers and SEs in ESCs, a 2013 study found that SEs have high levels of various other proteins compared with typical enhancers, including a wide variety of cofactors and chromatin regulators. These are involved in activating genes, modifying histones and nucleosomes (chromosome structures), and looping enhancers to put them into proximity to each other and to the genes that they activate. Differentiation of ESCs into specific cell types is accompanied by changes in the proteins that bind to SEs; this “turns off” or inactivates some SE-associated genes. Reduced levels of Oct4 or mediator in an SE result in a greater loss of the associated gene expression compared to other enhancers. This loss of master transcription factors may be the mechanism by which gene-expression patterns are switched as ESCs differentiate into specific types of cells.

Genetic disorders

Genetic variations (mutations) that are associated with disease are very common in SEs of disease-related cell types. Changes in single nucleotides in the DNA sequence, called single-nucleotide polymorphisms (SNPs), are associated with the development of many diseases and disorders. Many of these disease-associated SNPs are located within SEs of relevant cell types. Because SEs drive the expression of cell-identity genes, it is possible that the altered expression of these genes resulting from mutations in SEs contributes to various diseases.

Autoimmune disorders

Autoimmune disorders are diseases in which immune system cells attack the body’s own proteins rather than foreign proteins and microorganisms that pose a threat. It has been difficult to identify susceptibility genes associated with autoimmune disorders, but enhancers have been suspected of playing a role. In part, this is because many of the mutations that have been identified as associated with autoimmune disorders are not located within DNA that codes for proteins. Because SEs are particularly powerful enhancers of gene transcription that act as genetic

KEY TERMS

Autoimmune disorder—A disorder that occurs when the body’s tissues are attacked by its own immune system, as in RA.

Cytokine—A protein associated with inflammation that, at high levels, may be toxic to nerve cells in the developing brain.

Embryonic stem cells (ESCs)—Cells from early-stage embryos that have the capacity to differentiate into any cell type (pluripotency).

Enhancer—A DNA sequence that binds transcription factors to promote gene activity (transcription).

Mediator coactivator complex—A large protein complex that binds to super enhancers to activate genes.

Oncogene—A gene that allows the uncontrolled division and proliferation of cells that lead to tumor formation and usually to cancer.

Rheumatoid arthritis (RA)—A chronic autoimmune disease marked by inflammation of the membranes surrounding joints.

Single-nucleotide polymorphisms (SNPs)—Single-nucleotide variant (SNV); a variation or point mutation in a single-nucleotide building block of DNA.

T cells—Immune system cells that originate in the thymus gland and are involved in autoimmune disorders.

Transcription factor—A factor that activates the transformation of DNA to RNA (the next step is translation, in which RNA is changed into protein).

switches, researchers have wondered if they could be involved in autoimmunity.

In 2015, a research group headed by John J. O’Shea, scientific director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, reported the discovery of an SE that appears to be an important regulator of immune system genes and may play a role in autoimmune diseases. O’Shea and his colleagues examined SEs in T cells, a type of immune cell that is an important factor in the autoimmune disease rheumatoid arthritis (RA). RA causes painful swelling and inflammation of the joints. The researchers found that many of the identified mutations in T cells that were known to be associated with RA or other autoimmune diseases were located in SEs. Specifically, SEs were controlling the production of immune system proteins called cytokines and their

receptors, which facilitate communication between T cells and other cells to launch immune responses. When the researchers treated human T cells with tofacitinib, a drug used in the treatment of RA, they discovered that the drug altered the expression of genes that were under the control of SEs, without significantly affecting the expression of genes that were not under SE control. Thus, tofacitinib may exert its anti-RA effects by inhibiting the activity of genes that are being controlled by malfunctioning SEs.

Many autoimmune disorders are believed to be caused by interactions between environmental factors and susceptibility genes. Variations or mutations in the DNA sequences of SEs of such genes are suspected of being involved in at least some autoimmune disorders:

- Type 1 diabetes is caused by the autoimmune destruction of insulin-producing beta cells in the pancreas, a process mediated by T cells. Of the 76 SNPs that have been associated with type 1 diabetes, 67 are in non-protein-coding DNA sequences, especially in the SEs of T helper (Th) cells. Thirteen of the SNPs are in SEs associated with genes that are important for Th cell biology.
- Systemic lupus erythematosus (SLE) is a serious autoimmune disease that can affect the entire body. Of the 72 SNPs that have been associated with SLE, 67 are in non-protein-coding regions, especially in the SEs of a type of immune cell called a B cell, with 22 SNPs in SEs of 16 genes that are important for B cell activity.
- Multiple sclerosis (MS) is an autoimmune disease in which the immune system attacks myelin, the fatty covering of nerve cells that protects the cells and facilitates the transmission of nerve impulses. Damage to myelin from MS interferes with nerve transmission and causes pain, movement difficulties, loss of sensation, and other problems. At least some forms of MS may be associated with mutations or variations in SEs.
- Other autoimmune disorders that may be associated with mutations in SEs include systemic scleroderma, primary biliary cirrhosis, Crohn's disease, Graves' disease, vitiligo, and atrial fibrillation.

The discovery of SNPs in SEs that control the activities of immune system genes that are involved in autoimmune disorders helps explain how susceptibility to these disorders, which often run in families, can be inherited when no mutations have been found in the protein-coding regions of genes that appear to be involved in the disorders.

Alzheimer's disease

Alzheimer's disease is the most common form of dementia. It is characterized by progressive neurodegeneration and loss of cognitive functions. Of the 27 SNPs that have been associated with Alzheimer's disease, five

QUESTIONS TO ASK YOUR DOCTOR

- Could my autoimmune disorder be caused by a mutation in a super enhancer?
- Is genetic testing available for super enhancer mutations?
- Are there targeted drugs available for diseases caused by super enhancers?

occur in SEs in brain tissue. Two of these SNPs are in the SE associated with the *BIN1* gene, whose activity is linked to a risk for developing the disease.

Cancer

Oncogenes are mutated proto-oncogenes that promote cancer development (carcinogenesis). Many important oncogenes in several types of cancer have associated SEs. These SEs are not present in the proto-oncogenes that normally regulate cell growth and development and have not mutated into oncogenes. It appears that acquiring SEs to drive the expression of oncogenes may be an important mechanism in the development of cancer. Cancer cells also have SEs associated with other genes that are important for the growth and pathogenesis of cancer. These SEs are not present in the corresponding noncancerous cells. In fact, a large proportion of genes that have important functions in cancer cell development and pathogenesis appear to have acquired SEs.

DNA translocations (the breakage and rejoining of DNA sequences in different locations), amplifications (increases in the number of copies of DNA sequences), and overexpression of transcription factors appear to account for the acquisition of SEs by cancer cells. For example, multiple myeloma cells often have a translocation that positions a specific SE adjacent to the *MYC* oncogene. Overexpression of the *TAL1* transcription factor in acute lymphoblastic leukemia is also associated with the formation of an SE near the *MYC* oncogene.

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National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIAMS Information Clearinghouse, National Institutes of Health, 1 AMS Circle, Bethesda, MD 20892-3675, (301) 495-4484 or (877) 226-4267, (301) 718-6366, NIAMSinfo@mail.nih.gov, <http://www.niams.nih.gov>

Margaret Alic, PhD

Surdicardiac syndrome see **Jervell and Lange-Nielsen syndrome**

SWI/SNF-related autism syndrome

Definition

SWI/SNF-related autism syndrome is a genetic disorder classified as an autism spectrum disorder or ASD. Children with ASDs have difficulty interacting socially with others; have problems with both verbal and nonverbal communication, including delayed speech; and have restricted repetitive patterns of behavior known as stereotypy. Stereotyped behaviors in ASDs include such actions as hand flapping, head-banging, or rocking back and forth.

SWI/SNF-related autism syndrome is also defined as a form of syndromic autism, which means that the disorder has clinical features in addition to the autism itself. SWI/SNF-related autism syndrome is distinguished by mild to severe intellectual disability and malformed facial features. Other names for the syndrome include Helsmoortel-Van der Aa syndrome (HVDAS) and intellectual disability, autosomal dominant, 28 (MRD28).

Description

Children with SWI/SNF-related autism syndrome have many of the same characteristics as children diagnosed with other ASDs; however, they have more severe developmental delays, mild to severe intellectual disabilities, dysmorphic facial features, visual disorders, and

other neuropsychiatric disorders that include obsessive-compulsive disorder, attention deficit hyperactivity disorder, and anxiety disorders.

Genetic profile

SWI/SNF-associated autism syndrome is inherited in an autosomal dominant pattern, which means that only one copy of the mutated gene is necessary for the disorder to appear in a child. The gene associated with the syndrome is the *ADNP* gene on the long arm of chromosome 20 at 20q13.13. This gene has been the subject of interest of a group of researchers at the University of Antwerp in Belgium who formed the ADNP Research Project after the relationship between the *ADNP* gene and the SWI/SNF complex was reported in 2007. The name of the gene stands for “activity-dependent neuroprotective protein,” and deficiencies in the protein that the gene encodes were found to affect the function of the SWI/SNF complex in chromatin remodeling. Mutations in other genes associated with the SWI/SNF complex were linked to two other syndromes characterized by intellectual disability in 2012.

To understand the relationship between the *ADNP* gene, its protein product, and the SWI/SNF chromatin remodeling complex, it is necessary to review the way in which genetic material is packaged inside a cell and the ways in which this packaging can be rearranged to regulate gene expression; that is, to “turn on” or “turn off” specific genes during development or cell reproduction. The term “SWI/SNF” refers to a group of proteins that associate (form a complex) to remodel (rearrange) the way that DNA is packaged inside a cell. The SWI/SNF complex changes the arrangement of nucleosomes, which are the basic units of DNA packaging. A nucleosome consists of eight proteins called histones, with about 147 base pairs of DNA wound around them somewhat like thread or yarn around a spool. The nucleosomes in turn are arranged like beads on a string to form chromatin, which is the genetic material found in the nucleus of a cell. Chromatin is made up of DNA, RNA, and proteins, and it condenses to form chromosomes during the process of cell division.

In addition to functioning as a tumor suppressor in many human cancers, the SWI/SNF protein complex helps to regulate gene expression (“turning on” specific genes) by making the nucleosomes in the chromatin of a cell more accessible to transcription factors. Transcription factors are proteins that control the rate of transcription (copying) of specific segments of DNA into messenger RNA. The *ADNP* gene encodes a protein that is thought to act as a transcription factor. The researchers who reported on the initial group of ten patients theorize that mutations in the *ADNP* gene interfere with the ability of

the SWI/SNF complex to rearrange the nucleosomes in the cell's chromatin correctly, leading to irregularities in gene expression and disruptions in nerve cell formation and reproduction. Abnormalities in the formation of nerve cells would help to explain the intellectual disability and psychiatric disorders found in SWI/SNF-related autism syndrome. While the functions of the ADNP protein are not completely understood, it is thought to stimulate the growth of certain types of tumor cells while inhibiting the growth of others. Thus mutations in this gene may be linked to an increased risk of cancer as well as intellectual disability.

Demographics

It is not yet clear how common SWI/SNF-related autism syndrome may be worldwide because the syndrome was reported only in 2014 and involved a total of 15 patients studied by three groups of researchers. Fourteen of the 15 patients are Europeans from Belgium, the Netherlands, and the United Kingdom, with the remaining patient being a six-year-old girl in the United States. Given this small number of patients, further research will be needed to determine whether SWI/SNF-related autism syndrome is more common in some racial or ethnic groups than others. The disorder is more likely to appear in males, with eight of the first 10 patients identified being boys.

Signs and symptoms

According to the ADNP Research Project, the major features of SWI/SNF-related autism syndrome include the following:

- behaviors characteristic of an ASD, including stereotypy
- intellectual disability ranging from mild (40% of patients) to severe (40%)
- developmental delays apparent in infancy
- hypotonia (poor muscle tone and muscle weakness)
- *de novo* mutation in the *ADNP* gene in 75% of patients
- delayed motor development
- delayed speech development
- delayed growth, short stature, and a tendency to obesity
- facial deformities: prominent forehead, notched eyelids, drooping eyelids (ptosis), short nose, thin upper lip, absence of a philtrum (vertical groove) in the upper lip
- behavioral disorders: obsessive-compulsive disorder, anxiety disorders, attention-deficit hyperactivity disorder
- recurrent infections

Less common signs and symptoms include the following:

- seizures
- high pain threshold

KEY TERMS

Autism spectrum disorders (ASDs)—A general term for a group of neurodevelopmental disorders characterized by difficulties in social interactions, significant abnormalities in speech patterns, and limited but repetitive interests and activities.

Autosomal dominant—A pattern of inheritance in which only one copy of a defective gene on a nonsex chromosome is required for a disease or inherited trait to develop in an individual.

Autosome—One of the 22 chromosomes that are not involved in determining gender (chromosomes 1 through 22 and not the X or Y chromosome).

Chromatin—A complex found in mammalian cells consisting of DNA, protein, and RNA. Chromatin serves to package DNA into a smaller volume that will fit within the cell to prevent damage to DNA and to control DNA replication and gene expression. It condenses to form chromosomes during the process of cell division.

De novo mutation—A genetic mutation that is seen for the first time in the affected person, not inherited from the parents.

Dysmorphic—An abnormal body structure often associated with a genetic disorder.

Histones—Alkaline proteins found in cell nuclei that organize and wrap strands of DNA into units called nucleosomes.

Hypotonia—Low or poor muscle tone, resulting in floppy limbs.

Nucleosome—A basic unit of DNA packaging consisting of a segment of DNA wrapped around eight histone proteins.

Ptosis—Drooping of the upper eyelid.

Stereotypy—A repetitive movement, gesture, or utterance; examples include head banging, rocking, or repeatedly crossing and uncrossing the legs. Stereotypy is found in persons with intellectual disabilities and some forms of schizophrenia as well as autism spectrum disorders.

Syndromic autism—A term used to describe autism that exists in combination with other clinical features, including physical as well as developmental abnormalities.

Transcription factor—A factor that activates the transformation of DNA to RNA (the next step is translation, in which RNA is changed into protein).

QUESTIONS TO ASK YOUR DOCTOR

- How common is syndromic autism in comparison to ASDs that are not associated with a clinical syndrome?
 - Have you ever seen a case of syndromic autism?
 - Should I have my child tested for mutations in specific genes known to be linked to autism?
 - Do you think there is a genetic link between syndromic autism and an increased risk of cancer?
- visual disturbances: farsightedness, cataracts, or astigmatism
 - mood disorders
 - congenital heart defects

Diagnosis

The diagnosis of autism spectrum disorders is made on the basis of clinical symptoms observed in the child in late infancy or early childhood. The Centers for Disease Control and Prevention and the American Academy of Pediatrics recommend that all children should be screened twice, at 18 months of age and again at 24 months. Screening consists of the use of a questionnaire or checklist to evaluate such signs as the child's failure to respond to his or her name, inability to make eye contact, lack of social skills, stereotyped behaviors, failure to learn language skills or loss of language skills previously attained, unusual preoccupation with certain objects or activities, and tendency to become extremely upset when routines or schedules are changed. The standard instrument used by pediatricians and other medical professionals in evaluating children for autism is the *Autism Diagnostic Observation Schedule*, second edition (ADOS-2); there are also checklists for use by parents available on the Autism Speaks website.

Children who are suspected of being at risk of autism on the basis of the ADOS-2 or other checklists are then given a comprehensive follow-up examination by a group of specialists—most often a child psychiatrist, a neurologist, a psychologist, and a speech-language pathologist. Imaging studies are not useful in diagnosing autism, although the child may be given an electroencephalogram to rule out seizure disorder. The child may also have his or her hearing tested to be sure that delayed speech is not the result of impaired hearing.

As of 2015, genetic testing was available for SWI/SNF-related autism syndrome at two laboratories in the United States, one in South Carolina and the other in California.

Treatment and management

There is no cure for SWI/SNF-related autism syndrome or any other form of syndromic autism. Patients are treated with a combination of special education programs, speech therapy, and medications for those with seizure disorder. All treatments are highly individualized. One patient with visual problems was successfully treated with surgery. It is possible that the identification of more patients with SWI/SNF-related autism syndrome combined with long-term follow-up of the patients already identified will yield more specific treatment recommendations.

Prognosis

The prognosis of SWI/SNF-related autism syndrome depends partly on the severity of the child's intellectual disability. Children with relatively mild intellectual disability may be able to care for themselves and live in sheltered residential settings, but most will require full-time care at home or in institutional settings throughout their lives. As far as is known, the syndrome does not affect the patient's life expectancy, but further research will be needed to determine whether mutations in the *ADNP* gene may increase the child's risk of cancer in adult life.

Resources

BOOKS

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 "What is Autism Spectrum Disorder?" CDC. <https://www.cdc.gov/ncbddd/autism/facts.html> (accessed June 21, 2021).

ORGANIZATIONS

ADNP Research Project. University of Antwerp, Centrum Medische Genetica, Prins Boudewijnlaan 43, Edegem, 2950, +32 (0)3 275 97 56, <http://www.adnpgene.com>

American Academy of Child and Adolescent Psychiatry (AACAP), 3615 Wisconsin Ave. NW, Washington, DC 20016-3007, (202) 966-7300, (202) 966-2891, <http://www.aacap.org>

Autism Society, 4340 East-West Hwy., Suite 350, Bethesda, MD 20814, (301) 657-0881 or (800) 328-8476, info@autism-society.org, <http://www.autism-society.org>

Autism Speaks, 1 E. 33rd St., 4th Floor, New York, NY 10016, (888) 288-4762, (212) 252-8676, familyservices@autismspeaks.org, <https://www.autismspeaks.org>

National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Dr., MSC 2152, 9000 Rockville Pike, Bethesda, MD 20892-2152, (301) 402-0911, <https://www.genome.gov/about-nhgri/Contact>

National Institute of Neurological Disorders and Stroke (NINDS), PO Box 5801, Bethesda, MD 20824, (301) 496-5751 or (800) 352-9424, <http://www.ninds.nih.gov/index.htm>

Rebecca J. Frey, PhD



Talipes see **Clubfoot**

Tangier disease

Definition

Tangier disease is a rare autosomal recessive condition characterized by low levels of high-density lipoprotein cholesterol (HDL-C) in the blood, accumulation of cholesterol in many organs of the body, and an increased risk of arteriosclerosis.

Description

Donald Fredrickson was the first to discover Tangier disease. He described this condition in 1961 in a five-year-old boy from Tangier Island who had large, yellow-orange colored tonsils that were engorged with cholesterol. Subsequent tests on this boy and his sister found that they both had virtually no HDL-C in their bloodstream. Other symptoms of Tangier disease such as an enlarged spleen and liver, eye abnormalities, and neurological abnormalities were later discovered in others affected with this disease.

It was not until 1999 that the gene for Tangier disease, called the *ABCA1* gene, was discovered. This gene is responsible for producing a protein that is involved in the pathway by which HDL removes cholesterol from the cells of the body and transports it to the liver where it is digested and removed from the body.

Cholesterol is transported through the body as part of lipoproteins. Low-density lipoproteins (LDL) and high-density lipoproteins (HDL) are two of the major cholesterol-transporting lipoproteins. Cholesterol attached to LDL (LDL-C) is often called bad cholesterol since it can remain in the bloodstream for a long time, and high levels of LDL-C can increase the risk of clogging of the arteries (arteriosclerosis) and heart disease.

Cholesterol attached to HDL is often called good cholesterol since it does not stay in the bloodstream for a long period of time, and high levels are associated with a low risk of arteriosclerosis.

Research suggests that the ABCA1 protein helps to transport cholesterol found in the cell to the surface of the cell where it joins with a protein called ApoA-1 and forms an HDL-C complex. The HDL-C complex transports the cholesterol to the liver where the cholesterol is digested and removed from the body. This process normally prevents an excess accumulation of cholesterol in the cells of the body and can help to protect against arteriosclerosis.

Genetic profile

Changes in the *ABCA1* gene, such as those found in Tangier disease, cause the gene to produce abnormal ABCA1 protein. The abnormal ABCA1 protein is less able to transport cholesterol to the surface of the cell, which results in an accumulation of cholesterol in the cell. The accumulation of cholesterol in the cells of the body causes most of the symptoms associated with Tangier disease. The decreased efficiency in removing cholesterol from the body can lead to an increased accumulation of cholesterol in the blood vessels, which can lead to a slightly increased risk of arteriosclerosis, and ultimately an increased risk of heart attacks and strokes. The ABCA1 protein defect also results in decreased amounts of cholesterol available on the surface of the cell to bind to ApoA-1 and decreased cholesterol available to form HDL-C. This in turn results in the rapid degradation of ApoA-1 and reduced levels of ApoA-1 and HDL-C in the bloodstream. It also leads to lower levels of LDL-C in the blood.

The *ABCA1* gene is found on chromosome 9. Since we inherit one chromosome 9 from our mother and one chromosome 9 from our father, we also inherit two *ABCA1* genes. People with Tangier disease have inherited one changed *ABCA1* gene from their father and one

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Arteriosclerosis—Hardening of the arteries that often results in decreased ability of blood to flow smoothly.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Biochemical testing—Measuring the amount or activity of a particular enzyme or protein in a sample of blood, urine, or other tissue from the body.

Cholesterol—A fatty-like substance that is obtained from the diet and produced by the liver. Cells require cholesterol for their normal daily functions.

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

DNA testing—Analysis of DNA (the genetic component of cells) in order to determine changes in genes that may indicate a specific disorder.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular

sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Hemolytic anemia—Anemia that results from premature destruction and decreased numbers of red blood cells.

High-density lipoprotein (HDL)—A cholesterol-carrying substance that helps remove cholesterol from the cells of the body and deliver it to the liver where it is digested and removed from the body.

Low-density lipoproteins (LDL)—A cholesterol-carrying substance that can remain in the bloodstream for a long period of time.

Lymph node—A bean-sized mass of tissue that is part of the immune system and is found in different areas of the body.

Mucous membrane—Thin, mucous-covered layer of tissue that lines organs such as the intestinal tract.

Prenatal testing—Testing for a disease such as a genetic condition in an unborn baby.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

Spleen—Organ located in the upper abdominal cavity that filters out old red blood cells and helps fight bacterial infections. Responsible for breaking down spherocytes at a rapid rate.

Thymus gland—An endocrine gland located in the front of the neck that houses and transports T cells, which help to fight infection.

Ureters—Tubes through which urine is transported from the kidneys to the bladder.

changed *ABCA1* gene from their mother, making Tangier disease an autosomal recessive condition.

Parents who have a child with Tangier disease are called carriers, since they each possess one changed *ABCA1* gene and one unchanged *ABCA1* gene. Carriers for Tangier disease do not have any of the symptoms associated with the disease, except for increased levels of HDL-C in their bloodstream and a slightly increased risk of arteriosclerosis. The degree of risk of arteriosclerosis is unknown, and is dependent on other genetic and environmental factors, such as diet. Each child born to parents who are both carriers of Tangier disease has a 25% chance of having Tangier disease, a 50% chance of being

a carrier, and a 25% chance of being neither a carrier nor affected with Tangier disease.

Demographics

Tangier disease is a very rare disorder with less than 100 cases diagnosed worldwide. Tangier disease affects both males and females.

Signs and symptoms

The symptoms of Tangier disease are quite variable but the most common symptoms are enlarged, yellow-colored tonsils, an enlarged spleen, accumulation of

cholesterol in the mucous membranes of the intestines, abnormalities in the nervous system (neuropathy), and an increased risk of arteriosclerosis. Less commonly seen symptoms are an enlarged liver, lymph nodes, and thymus and hemolytic anemia. Cholesterol accumulation has been seen in other organs such as the bone marrow, gall bladder, skin, kidneys, heart valves, ureters, testicles, and the cornea of the eye.

Symptoms involving the tonsils, intestines, and spleen

The unusual appearance of the tonsils is due to an accumulation of cholesterol. Even when the tonsils are removed, small yellow patches at the back of the throat may be evident. The accumulation of cholesterol in the mucous membranes of the intestines results in the appearance of orange-brown spots on the rectum, and can occasionally result in intermittent diarrhea and abdominal pain. The enlargement of the spleen can result in anemia and decreased numbers of certain blood cells called platelets.

Nervous system abnormalities

Cholesterol can accumulate in the nerve cells, which can result in nervous system abnormalities and symptoms such as loss of heat and pain sensation, weakness, increased sweating, burning/prickling sensations, loss of feeling, eye muscle spasms, double vision, drooping eyelids, and decreased strength and reflexes. These symptoms can be mild to severe, and can be temporary or permanent. Most people with Tangier disease have some nervous system dysfunction, but in many cases the symptoms are mild and may be undetectable. Occasionally patients with Tangier disease experience progressive and debilitating nervous system abnormalities.

Arteriosclerosis

Since so few people are known to be affected with Tangier disease it is difficult to precisely predict their risk of developing arteriosclerosis and heart disease. Depending on their age, people with Tangier disease appear to have approximately four to six times increased risk for arteriosclerosis leading to heart disease. People over the age of 30 appear to have a sixfold increased risk. It is possible that Tangier patients are protected from higher risks of arteriosclerosis by lower than average levels of LDL-C in their bloodstream.

Diagnosis

Tangier disease is diagnosed through assessment of clinical symptoms and biochemical testing. A diagnosis of Tangier disease should be considered in anyone with deposits of cholesterol on the cornea, an unexplained enlarged spleen or liver, or neurological abnormalities.

QUESTIONS TO ASK YOUR DOCTOR

- What are the most common signs and symptoms of Tangier disease?
- What are the most serious long-term medical problems with which a person with Tangier disease may have to deal?
- What types of treatment are available for this condition, and what risks are involved with each type of treatment?
- Can you recommend any written material that will provide more information about Tangier disease?

Examination of the throat, tonsils, and rectal mucous membrane should be performed on those suspected to have Tangier disease. Measurements of the total cholesterol—HDL-C, LDL-C, ApoA-1, and triglycerides—should also be performed. Patients with Tangier disease have virtually no HDL-C in their bloodstream and ApoA-1 levels are reduced to 1% – 3% of normal. LDL-C levels are also reduced to approximately 40% of normal and triglyceride levels can be mildly elevated. As of 2001, DNA testing for Tangier disease is not available through clinical laboratories, although DNA testing on a clinical basis should be available in the future. Some laboratories may identify *ABCA1* gene changes in patients as part of their research. Prenatal testing is only available if *ABCA1* gene changes are identified in the parents.

Treatment and management

There is no treatment for Tangier disease, and treatment of decreased HDL-C with medication is usually ineffective. Occasionally, organs such as the spleen and tonsils are removed because of extensive accumulation of cholesterol. Arteriosclerosis may be treated through angioplasty or bypass surgery. Angioplasty involves inserting a small, hollow tube called a catheter with a deflated balloon through the groin or arm and into a clogged artery. The balloon is then inflated, which enlarges the artery and compresses the blockage. Coronary artery disease can also be treated through bypass surgery, which is performed by taking a blood vessel from another part of the body and constructing an alternate path around the blocked part of the artery.

Prognosis

In most cases the prognosis for Tangier disease is quite good. People who develop heart disease may,

however, have a decreased lifespan depending on the severity of the disease and the quality of medical treatment.

Resources

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ORGANIZATIONS

National Tay-Sachs and Allied Diseases Association (NTSAD), 2001 Beacon St., Suite 204, Boston, MA 02135, (617) 277-4463, (800) 906-8723, info@ntsad.org, <http://www.ntsad.org>.

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TAR syndrome

Definition

Thrombocytopenia-absent radius (TAR) syndrome is a rare condition that is apparent at birth. Affected infants are born with incomplete or missing forearms. Typically, the bone on the thumb side of the forearm (radius) is absent, but other bones may be missing or abnormally formed. TAR syndrome also causes life-threatening bleeding episodes due to low levels of platelets in the blood (thrombocytopenia). It is inherited in an autosomal recessive manner.

Description

Dr. S. Shaw first wrote about two siblings (a brother and a sister) with missing forearms and bleeding problems in 1956. Thirteen years later, Dr. Judith Hall gave the name and acronym of TAR syndrome to the disorder. She described three families containing nine individuals. TAR syndrome has also been called the tetraphocomelia-thrombocytopenia syndrome.

KEY TERMS

Cordocentesis—A prenatal diagnostic test, usually done between 16 and 30 weeks of gestation. Using ultrasound guidance, a thin needle is introduced through the abdomen into the amniotic sac. A blood sample is taken directly from the umbilical cord. Tests can then be done on the blood sample.

Intracranial hemorrhage—Abnormal bleeding within the space of the skull and brain.

Tetralogy of Fallot—A congenital heart defect consisting of four (tetralogy) associated abnormalities: ventricular septal defect (VSD—hole in the wall separating the right and left ventricles); pulmonic stenosis (obstructed blood flow to the lungs); the aorta "overrides" the ventricular septal defect; and thickening (hypertrophy) of the right ventricle.

Tetraphocomelia—Absence of all, or a portion of, all four limbs. The hands or feet may be attached directly to the trunk.

Thalidomide—A mild sedative that is teratogenic, causing limb, neurologic, and other birth defects in infants exposed during pregnancy. Women used thalidomide (early in pregnancy) in Europe and in other countries between 1957 and 1961. It is still available in many places, including the United States, for specific medical uses (leprosy, AIDS, cancer).

The forearm is comprised of two bones. The radius is the long bone on the thumb side of the forearm. The ulna is the long bone on the little finger side. In TAR syndrome, the radius is missing on each forearm. Many times the ulna may also be missing or shorter than normal.

As these bone deficiencies are quite obvious at birth, the forearms will look very short. In fact, the hand looks as if it comes directly from the elbow. In more severe cases, the bone of the upper arm is also missing, with the hand connected to the shoulder. Approximately 50% of the time, there are other skeletal abnormalities, particularly in the lower limbs.

Each individual seems to be affected somewhat differently. For instance, some individuals with TAR syndrome might have one arm longer than the other arm; another might have both arms short, and bones missing in the feet; a third person might have all four limbs severely affected. The one constant feature is the absence of the radius bone. The forearm defects cause the hands to



Brian Hinman, a high school student with TAR syndrome, prepares to jump in the water during a swim meet. (*P Images/Laramie Boomerang/Andy Carpenear*)

be bent inward toward the body. However, the four fingers and thumb usually look normal.

The other main feature of the syndrome is thrombocytopenia. Thrombocytopenia means abnormally low levels of platelets in the blood. Platelets are made from cells called megakaryocytes. The megakaryocytes are formed in the red bone marrow, lungs, and spleen. In TAR syndrome, the megakaryocytes are either absent, decreased in number, or not formed properly. Therefore, the platelets are not properly made. The exact reason remains unknown.

When injury occurs, platelets are needed so that the blood can clot. The process is called blood coagulation. The platelets help initiate this process by attaching to the injured tissue, and clumping together, almost like a temporary patch. The platelets then release an enzyme called thromboplastin. Thromboplastin acts to cleave a

particle called fibrinogen (also in the blood) to fibrin. Fibrin is a hard substance that attaches to the injured area, and forms a meshwork (a blood clot). Along with other clotting factors, this permanently stops the bleeding.

In TAR syndrome, the normal process of making platelets is defective. The effect of this is excessive bleeding and bruising. These individuals have frequent nosebleeds and their skin bruises more easily. The platelet problem makes them more prone to bleeding inside the body, such as in the kidney or lungs. Bleeding can also occur inside the brain (intracranial hemorrhage), and be so severe that these infants die from the internal bleeding.

Genetic profile

There have been numerous instances of siblings, each with TAR syndrome. The parents were not affected.

A few families have also been seen where the parents were said to be closely related (i.e., may have shared the same altered gene within the family). For these reasons, TAR syndrome is most likely an autosomal recessive disorder. Autosomal means that both males and females can have the condition. Recessive means that both parents would be carriers of a single copy of the responsible gene. Autosomal recessive disorders occur when a person inherits a particular pair of genes that do not work correctly. The chance that this would happen to children of carrier parents is 25% (1 in 4) for each pregnancy.

It is known that the limbs (arms, legs), the heart, and the precursors of the blood system form between the fourth and eighth week of pregnancy. The birth defects seen in TAR syndrome must occur during this crucial period of development. TAR syndrome is caused by mutations in the *RBM8A* gene.

Demographics

TAR syndrome affects both males and females equally. It most likely occurs in every racial and ethnic group. It is estimated that 1 in every 250,000 infants are born with TAR syndrome. In all, more than 200 individuals with this disorder have been described in the medical literature.

Signs and symptoms

Aside from the limb deficiencies and the thrombocytopenia, the heart can also be affected. Around one-third of these infants are born with heart defects. These are usually found at birth. The heart problems include holes in the atrial chamber of the heart (atrial septal defect) and tetralogy of Fallot. The name tetralogy of Fallot means there are four different defects of the heart. Because of the high risk for excessive bleeding, these infants are not good candidates for heart surgery. Some of them have died from heart failure.

Diagnosis

Diagnosis of TAR syndrome is made with the use of x-rays of the bones, and by testing for low platelet levels in the blood at birth. TAR syndrome can be diagnosed during pregnancy. By using ultrasound (sound waves) at around 16 to 20 weeks of pregnancy, the shortening of the arms can be seen. A second test is then done called cordocentesis. In this procedure, using ultrasound guidance, a thin needle is introduced through the mother's abdomen into the amniotic sac. A blood sample is taken directly from the umbilical cord. With this blood sample, a count of the platelets can be done. If the platelet count is low, along with the short arms (absent radii), the diagnosis of TAR syndrome is made.

QUESTIONS TO ASK YOUR DOCTOR

- How did TAR disease get its name?
- What do scientists know about the genetic basis of this disorder?
- What information can a genetic counselor provide me with about TAR disease?
- What are the problems that a child born with TAR disease will have to deal with in her or his life?

Treatment and management

Surgery is sometimes done in an attempt to straighten and improve the use of their hands. They may wear corrective braces for the forearms. Many of these individuals develop arthritis, especially of the wrists and knees as they get older. This may further limit the use of their hands and legs.

Prognosis

About 40% of these individuals die in infancy, usually due to severe bleeding episodes. Cow's milk allergy or intolerance is a common problem. Stomach infections seem particularly threatening to these infants, and can also trigger the bleeding episodes. The thrombocytopenia is treated with platelet transfusions, which may or may not control the bleeding, and death may occur.

The thrombocytopenia seen in TAR syndrome does improve with age. If these individuals survive the first two years of life, they appear to have a normal lifespan. However, the easy bruising continues throughout life. Many females with TAR syndrome also have abnormal menstrual periods, possibly related to the thrombocytopenia.

However, most individuals with TAR syndrome learn to adapt well to their disability, and lead productive lives.

Resources

BOOKS

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Kevin M. Sweet, MS, CGC

Tay-Sachs disease

Definition

Tay-Sachs disease is a genetic disorder caused by a missing enzyme that results in the accumulation of a fatty substance in the nervous system. This results in disability and death.

Description

Gangliosides are a fatty substance necessary for the proper development of the brain and nerve cells (nervous system). Under normal conditions, gangliosides are continuously broken down, so that an appropriate balance is maintained. In Tay-Sachs disease, the enzyme necessary for removing excess gangliosides is missing. This allows gangliosides to accumulate throughout the brain, and is responsible for the disability associated with the disease.

Risk factors

People at highest risk for Tay-Sachs are those who have a family history of the condition and who are of Jewish or French-Canadian ancestry (from the St. Lawrence River Valley of Quebec) or members of the Cajun population in Louisiana.

Genetic profile

Tay-Sachs is caused by a defective *HEXA* gene, located on chromosome 15. The *HEXA* gene provides

instructions for making an enzyme called beta-hexosaminidase A. Without this enzyme, gangliosides cannot be degraded. They build up within the brain, interfering with nerve functioning. Because it is a recessive disorder, only people who receive two defective genes (one from the mother and one from the father) will actually have the disease. People who have only one defective gene and one normal gene are called carriers. They carry the defective gene and thus the possibility of passing the gene and/or the disease onto their offspring.

When a carrier and a noncarrier have children, none of their children will actually have Tay-Sachs. It is likely that 50% of their children will be carriers themselves. When two carriers have children, their children have a 25% chance of having normal genes, a 50% chance of being carriers of the defective gene, and a 25% chance of having two defective genes. The two defective genes cause the disease itself.

Demographics

Tay-Sachs disease is very rare in the general American population but particularly common among Jewish people of eastern European and Russian (Ashkenazi) origin. About 1 out of every 3,600 babies born to Ashkenazi Jewish couples will have the disease. Tay-Sachs is also more common among certain French-Canadian and Cajun French families.

Signs and symptoms

Classic Tay-Sachs disease strikes infants around the age of six months. Up until this age, the baby will appear to be developing normally. When Tay-Sachs begins to



A retinal photograph showing Tay-Sachs disease. People with this disorder have a cherry-red spot at the back of the eye. (Ralph C. Eagle, Jr./Science Source)

show itself, the baby will stop interacting with other people, and develop a staring gaze. Normal levels of noise will startle the baby to an abnormal degree. By about one year of age, the baby will have very weak, floppy muscles, and may be completely blind. The head will be quite large. Patients also present with loss of peripheral (side) vision, inability to breathe and swallow, and paralysis as the disorder progresses. Seizures become a problem between ages one and two, and the baby usually dies by about age four.

A few variations from this classical progression of Tay-Sachs disease are possible:

- Juvenile hexosaminidase A deficiency. Symptoms appear between ages 2 and 5; the disease progresses more slowly, with death by about 15 years of age.
- Chronic hexosaminidase A deficiency. Symptoms may begin around age 5, or may not occur until age 20–30. The disease is milder. Speech becomes slurred. The individual may have difficulty walking due to weakness, muscle cramps, and decreased coordination of movements. Some individuals develop mental illness. Many have changes in intellect, hearing, or vision.

Diagnosis

Examination

Examination of the eyes of a child with Tay-Sachs disease will reveal a very characteristic cherry-red spot at the back of the eye (in an area called the retina).

Tests

Prenatal tests such as amniocentesis and chorionic villus sampling (CVS) can diagnose the disease before birth. Amniocentesis is usually done between 16 and 18 weeks of pregnancy. In this test, the doctor draws a sample of the fluid that surrounds the fetus. The fluid contains fetal cells, which are tested to see if they contain hexosaminidase A. A carrier will have about half of the normal level of hexosaminidase A present, while a patient with the disease will have none.

Treatment and management

Providing good, supportive care and treating the symptoms as they arise is the only way to treat Tay-Sachs; there is no way to treat the disease itself. Researchers are investigating whether stem cell transplants could help babies with Tay-Sachs. However, as of 2015, stem cell transplantation had not yet been successful in stopping or reversing brain damage, and the treatment also carries a high risk of death. Prevention involves identifying carriers of the disease and providing them with appropriate information concerning the chance of their

QUESTIONS TO ASK YOUR DOCTOR

- What are the treatment options for Tay-Sachs?
- Is stem cell transplant a possible option?
- Should I get tested for Tay-Sachs before I become pregnant if I'm of eastern European and Russian origin?

offspring having Tay-Sachs disease. When the levels of hexosaminidase A are half the normal level, a person is a carrier of the defective gene. Blood tests of carriers reveals reduction of hexosaminidase A.

Prognosis

Children born with infantile Tay-Sachs, even with the best available care, usually die before the age of five. Children born with juvenile Tay-Sachs usually die before the age of 15.

Resources

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- March of Dimes Foundation, 1275 Mamaroneck Ave., White Plains, NY 10605, (914) 997-4488, <http://www.marchofdimes.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

National Tay-Sachs and Allied Diseases Association (NTSAD),
2001 Beacon St., Suite 204, Boston, MA 02135, (617)
277-4463, (800) 906-8723, info@ntsad.org, http://www.
.ntsad.org

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Teratogen

Definition

A teratogen is any environmental influence that adversely affects the normal development of the fetus.

Description

Abnormal fetal development may result from exposure to a teratogen. There are four different teratogen categories: physical agents (radiation and hyperthermia), metabolic conditions affecting the mother, infection, and drugs (like thalidomide) and alcohol.

Physical agents

Hyperthermia

Women whose body temperature is raised while pregnant may have abnormalities result in their fetus. The rise in body temperature can be caused by infection or by spending time in hot areas such as a sauna or hot tub.

Ionizing radiation—mutagens versus teratogens

Any outside agent (like radiation) interfering with the process of development is considered a teratogen. Development is the process in which a tiny mass of undifferentiated cells (the embryo) multiplies and differentiates into the kidney, liver, heart, bones, muscles, and so on. Mutagens, however, are agents that directly affect and disrupt DNA, the genetic blueprint of an organism. Some agents, like radiation, are mutagens and teratogens. Ionizing radiation can cause defects either in development, or it can damage DNA directly.

Metabolic disease

Infants of women with metabolic disorders have increased risks for abnormalities. Diabetic women, for example, are three to four times more likely to have fetuses with congenital abnormalities than infants of mothers without diabetes. The metabolic disease of the mother can have genetic or other causes.

Infection

There are a number of known infectious organisms that are teratogenic to the fetus, some of which cause damage directly and some of which damage the fetus by causing a fever and raising the temperature of the mother.

Alcohol and drugs

Thalidomide

A dramatic example of a teratogen is thalidomide. In the early 1960s, it was shown that more than 7,000 women who took the antinausea drug thalidomide during their pregnancy had children with very short or absent arms and legs. Other abnormalities were also seen in the children, such as the absence of ears, as well as heart and intestinal malformations. Affected infants were born to women who took thalidomide during the critical time period, also known as the period of susceptibility.

Period of susceptibility: The example of thalidomide

Thalidomide also teaches the importance of timing in the action of teratogens. Only a small amount of thalidomide was necessary to cause birth defects, but it had to be taken between 34 and 50 days after conception in order to harm the embryo. The time when teratogens can act, in this case from day 34 to day 50 after conception, is called the period of susceptibility. Since organ development in the unborn child occurs at different times, it was shown that taking thalidomide on different days caused the infants to have a variety of defects (heart vs. ears vs. limb formation). Drugs very often affect specific parts of the process of development. Before, or after, the processes take place, the drug will have no effect. Of course many teratogens, like thalidomide, work on a number of different developmental processes at different times (sometimes they are consecutive times, or they may be nonconsecutive; for example, from days 16 to 20 and days 24 to 48). The period of susceptibility of the fetus to most teratogens is between the third and eighth week after conception.

Dose and duration: The example of alcohol

The most common teratogen, alcohol, illustrates the important concept that the dose of a teratogen (for example, the number of alcoholic drinks a mother has) and duration of exposure to a teratogen (for example, the number of days a mother drinks alcohol) both play an important role in the effect of a teratogen. Alcohol can have a wide range of effects on a fetus, from no mental change or very mild mental changes (usually a small dose of alcohol) to full-blown fetal alcohol syndrome, in which the infant is severely retarded. Even two glasses of alcohol

can be teratogenic to a fetus, but the mental retardation and characteristic facial changes seen in full-blown fetal alcohol syndrome generally requires the mother to drink 2–3 oz. of alcohol per day for a sustained period of time (the exact amount of time is not known) during pregnancy. Thus, dose and duration help determine the severity of a teratogen's effects.

Other factors that affect teratogens

Although the dose and duration are important in determining how much of an effect alcohol will have on the fetus, other factors have an impact too. When normal mice and mutant mice are given the same dose of a particular teratogen, the mutant mice are affected much more severely. This means that in humans, the genetic makeup of the fetus helps determine to what extent the teratogen will affect the fetus. A fetus with one particular set of genes might be severely affected by the mother drinking one glass of alcohol, while another fetus may be unaffected by the first or even second glass of alcohol. The outcome of teratogens probably depends on a combination of factors: the mother's condition (genetic or otherwise), the genetic background of the fetus, and the dose and duration of the teratogen. However, the importance of each factor probably varies greatly from teratogen to teratogen and from individual to individual.

Although the discussion of these teratogenic concepts has revolved around examples from the category of drugs and alcohol, the concepts may be applied to any of the categories of teratogens.

Demographics

Exact numbers of infants affected by teratogens are difficult to estimate. *Langman's Medical Embryology* states 4%–6% of all infants will have major developmental or genetic abnormalities. This source estimates that of the children with major abnormalities, 10% can be attributed to teratogens, 20%–25% can be attributed to genetic and environmental influences, and 40%–60% of the abnormalities are due to unknown causes (possibly teratogenic). That means as many as 95% of all major birth disorders may involve teratogens.

Diagnosis

The diagnosis varies from teratogen to teratogen. Some genetic diseases and teratogens can present with the same abnormalities and symptoms. If the gene causing the disorder has been isolated and is well understood, the difference between a genetic and a teratogenic disorder may be established. Many abnormalities in children go unexplained. In these cases, teratogen exposure should be considered.

Treatment, prevention, and the period of susceptibility

Treatment options and how well they work vary widely according to the teratogen. The best course is to prevent teratogen exposure, or reduce the exposure as much as possible. Prevention is complicated because very often women may not realize they are pregnant until the middle of the period of susceptibility. Substances that are not harmful to an adult, like the derivatives of retinoic acid found in a number of skin creams, alcohol, and many prescription drugs, can be extremely harmful to the fetus. Retinoic acid, for example, has a period of susceptibility from days 20–35 after conception—a time when many women might not realize they are pregnant.

Thus, women who are engaging in activities that can lead to pregnancy and want to avoid any potential damage to their fetus should attempt to avoid teratogenic substances (including a large number of over-the-counter, prescription, and illegal drugs). Alternatively, women can also prevent most damage to the fetus by closely monitoring their pregnancy status and avoiding teratogens as soon as pregnancy occurs.

Partial list of teratogens

Drugs and chemicals:

- alcohol
- aminoglycosides
- aminopterin
- antithyroid agents
- bromine
- cortisone
- diethylstilbestrol (DES)
- diphenylhydantoin
- heroin
- lead
- methylmercury
- penicillamine
- retinoic acid (Isoretinoin, Accutane)
- tetracycline
- thalidomide
- trimethadione
- valproic acid
- warfarin

Physical agents:

- hyperthermia (fever, sauna)
- ionizing radiation (x-rays)

KEY TERMS

Development—The process whereby undifferentiated embryonic cells replicate and differentiate into limbs, organ systems, and other body components of the fetus.

Maternal—Relating to the mother.

Mutagen—An environmental influence that causes changes in DNA.

Period of susceptibility—The time when teratogens can cause harm to the developing fetus.

Infectious organisms:

- Coxsackie virus
- Cytomegalovirus
- Herpes simplex virus
- Parvovirus
- Rubella
- Toxoplasma gondii
- Treponema pallidum (syphilis)

Metabolic conditions in the mother:

- autoimmune disease
- diabetes
- malnutrition
- phenylketonuria

Resources

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ORGANIZATIONS

Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

Michael V. Zuck, PhD

Testicular feminization syndrome see
Androgen insensitivity syndrome

Thalidomide embryopathy

Definition

The term "thalidomide embryopathy" (TE) is used to describe a specific pattern of birth defects caused by a mother's use of the drug thalidomide during her pregnancy. The drug is able to cross the placenta and reaches the developing embryo, causing parts of the embryo's body to form abnormally. The most common birth defects observed in infants with TE are structural abnormalities of the arms, legs, ears, and eyes, although other organs may also be affected. The most harmful time to use thalidomide is during the first three to six weeks of pregnancy.

Description

Thalidomide was originally marketed in Germany in October 1957 as a safe, inexpensive, and effective sedative. Its use was later expanded to include treatment of insomnia, anxiety, upset stomach, and morning sickness during pregnancy. Prior to its release onto the market, thalidomide had been tested in rodents and had been deemed safe; human studies were not performed. It was made available in at least 46 countries. However, the drug was never approved for marketing in the United States due to concerns about the medication's potential side effects, one of which, peripheral neuropathy, was first recognized in 1960. Symptoms of peripheral neuropathy, or nerve damage, include burning, numbness, or tingling in the arms, legs, hands, or feet. The damage may not be reversible even after stopping the medication. Early in the 1960s, an increased number of infants with severe abnormalities of the arms and legs were observed in Germany, Great Britain, and Australia. Once it became clear that the mothers of these infants had taken thalidomide while pregnant, a connection was made between the drug and the birth defects. In 1961, the drug was withdrawn from the worldwide market. It has since become known as a powerful human teratogen, a drug or other agent proven to cause birth defects. The experience with thalidomide also led to greater overall attention to the potential effects of drug and other environmental exposures on a developing fetus,



Freddie Astbury, affected by thalidomide after his mother was prescribed it to help with morning sickness, was born with stunted arms and legs. (Paul Cooper/Rex Features/AP Images)

and to improved legislation regarding testing requirements before a new drug is released to the public.

Although the use of thalidomide decreased dramatically after 1961, it remained available in the United States and other countries on a “compassionate use” basis: physicians could obtain special permission to treat ill patients they believed could significantly benefit from the drug. Over time, it became clear that thalidomide is effective in the treatment of a number of medical conditions. This surprising resurgence of thalidomide has, in turn, led to concern over the possibility of another generation of children born with thalidomide-related birth defects. The manufacturer of thalidomide, Celgene Corporation, is working in close partnership with the U.S. Food and Drug Administration (FDA) to tightly control the use of the drug and to maintain close follow-up on all individuals to whom it is prescribed. The drug is marketed under the brand name Thalomid.

Limb abnormalities are the most readily identified, and most well-known, type of birth defect caused by prenatal thalidomide exposure. However, other types of physical problems may also occur in an exposed infant. In addition to limb abnormalities, TE may include abnormalities of the ears, eyes, kidneys, heart, intestinal tract, and nervous system. Mental retardation has been reported in approximately 5% of older individuals with TE.

Genetic profile

TE is not an inherited medical condition. However, thalidomide is a known teratogen. Therefore, women who use this medication while pregnant are at risk of having infants with physical, and possibly mental, birth defects. A woman who does not use thalidomide during pregnancy cannot have a child with TE. It is still not

entirely clear how thalidomide causes birth defects. One hypothesis is that the drug prevents formation of new blood vessels. Research is continuing in this area.

Demographics

It is estimated that 10,000–12,000 infants were born with birth defects consistent with TE following its initial period of use in the late 1950s to early 1960s. According to the Teratology Society 1998 Public Affairs Symposium, approximately 40%, or roughly 5,000, of the affected individuals survived.

In July 1998, the FDA approved the use of thalidomide in the United States, under a very tightly controlled protocol, for the treatment of erythema nodosum leprosum (ENL), a painful skin complication of leprosy. The drug has been available in South America, an area where leprosy is more common than in the United States. Reports of thalidomide-affected South American infants were published as recently as 2015.

Medical researchers are studying whether or not thalidomide may be effective in the treatment of other medical conditions, including certain skin and immunologic disorders, certain complications associated with human immunodeficiency virus (HIV) infection, and certain cancers. Although pregnancies among female patients with any of these conditions may be rare, unintended pregnancies will occur and will be at risk for fetal abnormalities if the mothers are taking thalidomide.

Signs and symptoms

TE includes a spectrum of physical abnormalities, all of which may occur at various levels of severity. An affected individual may not have every type of birth defect. All affected infants, however, have been exposed to thalidomide in early pregnancy, a time when the organs and body of an embryo are rapidly developing. Although use of thalidomide at any point in pregnancy is strongly discouraged, women who use the drug during the first six weeks of pregnancy are at the greatest risk of having children with birth defects. Rigorous control of the drug is necessary since many pregnancies are unplanned and may go unrecognized until after the drug exposure has occurred.

The clinical features of TE include the following.

Limb defects

The most well-known type of abnormality is referred to as phocomelia. Phocomelia occurs when most of the bones in the arms or legs are missing, and the hand or foot is attached directly to the body, similar to a flipper. Radial aplasia, or absence of the thumb and connecting bone in the forearm (radius), is another common abnormality.

Abnormalities of the digits include a triphalangeal thumb (three small bones in the thumb, rather than two, such that the thumb looks like a finger), or an absent (hypoplastic) thumb only. Similar defects of the legs may also occur. Frequently, affected infants have abnormalities on both sides of their bodies, involving all four extremities.

Ears

Malformations of the ears are common. These range from complete absence of the ear (severe microtia, also sometimes referred to in the medical literature as anotia) to mild changes in the appearance of the external ear. Abnormalities of the inner ear frequently cause deafness. Inner ear malformations may occur even if the external ear appears normal.

Eyes

A range of eye abnormalities have been reported, including a very small eye (microphthalmos), glaucoma, strabismus, cataract, and abnormal production of tears.

Other

- Structural heart defects.
- Kidney malformations, most often an absent or misplaced kidney.
- Abnormalities of the intestinal system.
- Structural defects of the spine and chest.
- Central nervous system abnormalities, such as mental handicap, described in a small percentage of older individuals with TE.
- Paralysis of the nerves of the face on either one side, both sides equally, or both sides but asymmetrically.
- An increased risk for early infant death, particularly among those infants with severe abnormalities of their internal organs.

Diagnosis

Exposure to thalidomide during the first six weeks of pregnancy poses a significantly increased risk of having a child with TE. It is important to note that the exact dosage of the drug during this period is irrelevant. Thalidomide is rapidly broken down in the mother's body and is therefore able to reach her developing embryo quickly. There is no direct genetic test to accurately diagnose all thalidomide-related birth defects before delivery. However, prenatal ultrasound examinations may be used to identify major structural abnormalities, such as those involving the limbs, heart, kidneys, and intestinal tract. A careful physical examination by a knowledgeable and experienced physician(s) is warranted after birth to document the nature and severity of any thalidomide-induced

KEY TERMS

Cataract—A clouding of the eye lens or its surrounding membrane that obstructs the passage of light, resulting in blurry vision. Surgery may be performed to remove the cataract.

Embryo—The earliest stage of development of a human infant, usually used to refer to the first eight weeks of pregnancy. The term *fetus* is used from roughly the third month of pregnancy until delivery.

Erythema nodosum leprosum—A complication of leprosy characterized by development of small, painful swellings due to inflammation of a blood or lymph vessel. It is often accompanied by inflammation of a nerve or nerves, causing decreased function of the affected area.

Glaucoma—An increase in the fluid eye pressure, eventually leading to damage of the optic nerve and ongoing visual loss.

Immunologic—Related to immunology, the study of how the body's immune system fights disease. Many immunologic disorders are characterized by the body's use of antibodies.

Insomnia—An inability to either fall or stay asleep, particularly at a time of day when sleep is expected. A number of medications are available, and may be used, for treatment.

Leprosy—A chronic, contagious skin and nervous system disease that leads, in the more serious form, to numbness, muscle weakness, and paralysis. Leprosy is sometimes referred to as Hansen's disease.

Placenta—The organ responsible for oxygen and nutrition exchange between a pregnant mother and her developing baby.

Sedative—Medication that has a soothing or tranquilizing effect.

Strabismus—An improper muscle balance of the ocular muscles resulting in crossed or divergent eyes.

birth defects. Additional studies, such as hearing evaluations, are also indicated.

Treatment and management

Management of the individual with TE is primarily symptomatic. Specialized medical care, such as heart surgery, may be necessary in certain situations, and should be determined on a case-by-case basis. Deaf individuals may require hearing aids and/or will need to learn sign

QUESTIONS TO ASK YOUR DOCTOR

- Is my child a candidate for a hearing aid or devices to assist with mobility?
- Could my child be helped by physical or occupational therapy?
- If I do not take thalidomide again, is there a continued risk of having another child with TE?
- How long does it take for thalidomide to be completely out of my system?

language. Severe limb abnormalities may lead to the use of a wheelchair or other device to assist in mobility.

In order to try to minimize the number of future children born with TE, the drug manufacturer and the FDA implemented the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program in 1998. The goals of the program are threefold: (1) to limit the risk of fetal exposure to thalidomide; (2) to enforce universal compliance of patients, physicians, and pharmacists with the designated components of the program; and (3) to support appropriate, controlled use of the drug. To achieve this, the S.T.E.P.S. program requires informed consent from all patients to whom the drug will be given. Face-to-face counseling, a patient information booklet, and a videotape are all used to review the potential benefits and side effects of the medication. Plans for birth control (contraception) and/or abstinence from sexual intercourse are also discussed. All women of childbearing age must agree to a pregnancy test prior to receiving their medication and at frequent intervals during treatment. Two methods of birth control are additionally required. Physicians who will be prescribing thalidomide must be registered in the S.T.E.P.S. program and must agree to follow each step of the program. Prescriptions may only be filled at registered pharmacies. No more than a one-month supply of the medication may be provided at one time; there are no automatic refills. It is recommended that women receive only a one-week supply, particularly during the first four weeks of treatment. Weekly refills are granted only with proof from a physician of a negative pregnancy test. In the event that a woman becomes pregnant, or suspects that she may be pregnant, an immediate referral is made for medical evaluation. Follow-up care is provided, and a database of all patients taking thalidomide is maintained.

Despite this unprecedented level of strict control, the S.T.E.P.S. program is unlikely to completely prevent the birth of *every* child in the United States with TE. Other countries in which the drug has been approved for use

have been encouraged to develop similar methods to follow outcomes of pregnancies exposed to thalidomide. In the meantime, research is continuing to find drugs that will be as effective as thalidomide without the same dangers to embryonic development.

Prognosis

There is no data addressing long-term survival rates among individuals with TE. Nonetheless, the presence and severity of thalidomide-related birth defects, particularly those involving the heart, would be expected to have the greatest impact on longevity. Severe heart malformations that cannot be corrected by surgery are likely to lead to early death. In the absence of such abnormalities, a normal lifespan is anticipated.

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ORGANIZATIONS

- March of Dimes, 1275 Mamaroneck Ave., White Plains, NY 10605, (914) 997-4488, <http://www.marchofdimes.org>
- Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>
- U.S. Food and Drug Administration (FDA), 10903 New Hampshire Ave., Silver Spring, MD 20993, (888) 463-6332, <http://www.fda.gov>

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Thanatophoric dysplasia

Definition

Thanatophoric dysplasia is one of the most common and most severe forms of dwarfism. Affected infants have marked shortening of their arms and legs, a small chest,



X-ray of a newborn baby with thanatophoric dysplasia. (Scott Camazine/Science Source)

and a relatively large head. Most die within a few days after birth; longer-term survivors have been reported but are rare.

Description

Thanatophoric dysplasia (TD) was first described in 1967 to refer to infants with a severe form of dwarfism who died within the first hours of life. The word “thanatophoric” is derived from the Greek word “thanatophorus,” which means “death-bringing.” The term “thanatophoric dwarfism” is occasionally used, but the word “dysplasia,” which refers to any disorder in growth, has become the preferred terminology.

Two distinct types of TD were delineated in 1987. Affected infants are divided based on their particular combination of physical features and skeletal findings. While all individuals with TD have micromelia, or abnormally small or short arms and legs, differences in the length and shape of the long bones of the thigh (femur) can be used to distinguish between TD types 1 (TD1) and 2 (TD2). Infants with TD1 have curved, “telephone-receiver”-like femurs. In contrast, the femurs of infants with TD2 are longer and straighter.

The presence of skull abnormalities is another important distinction between the two types: infants with TD2 typically have a severe abnormality of the bones of the skull, referred to as cloverleaf skull or *kleeblattschadel* anomaly. The skull of a normal infant is composed of several segments of bone, some of which are completely joined together or fused by the time of delivery. Their lines of fusion are referred to as sutures. Some sutures are only partially fused, leaving soft, skin-covered openings that will gradually close over the first year of life. Premature closure of these sutures leads to a condition called craniosynostosis. Craniosynostosis can cause an abnormal skull shape and if not eventually corrected by surgery, prevents normal growth of the brain. The most extreme form of craniosynostosis, as seen in infants with TD2, causes a severely abnormal skull whose shape resembles that of a cloverleaf. Although milder forms of craniosynostosis may be found in infants with TD1, cloverleaf skull is not typically present.

Other bone abnormalities occur in both TD types 1 and 2, including an abnormal shape of and spacing between the bones in the spine (vertebrae), shortened ribs, and small pelvic bones. Most of the other organs of the body, with the exception of the brain, are normal, although occasional abnormalities of the kidneys have been reported. A variety of abnormal changes in the structure of the brain have been described. The few cases of children with TD who have survived past infancy have been severely mentally and physically handicapped.

The most common cause of death among individuals with TD is respiratory insufficiency. The small chest and limited growth of the lungs are the primary reasons for the breathing problems seen in TD. However, associated abnormalities of the central nervous system are most likely also involved since these interfere with the body’s ability to regulate normal breathing.

Genetic profile

Both types of thanatophoric dysplasia occur as sporadic, autosomal dominant conditions. Only one copy of the altered gene causing TD needs to be present in order for the condition to occur. Males and females are equally likely to be affected. The parents of an affected child do not have TD and are normal. Thus, in most cases, it is likely that a new genetic mutation that causes TD occurred in either the egg or sperm cell that gave rise to that particular pregnancy. Such a mutation cannot be made to happen; it occurs simply by chance. There is a very low risk of recurrence, or chance of another affected child in a future pregnancy. Unfortunately, families have been described with more than one child with TD. The most likely explanation in these families is gonadal mosaicism.

Gonadal mosaicism occurs when an adult has a mixed population of normal and abnormal cells in his or her gonads (testes or ovaries), but all of the other cells in that individual's body are presumably normal. Most sperm or egg cells from these gonads would be normal and would not have a TD mutation; however, an unknown percentage would carry the mutation. As a result, even though the parents would be normal, he or she could, with the same or a different partner, have another child with TD. It is virtually impossible to prove whether or not a parent has gonadal mosaicism. Even so, all parents of an affected child are counseled that gonadal mosaicism in one of them is a possibility.

Thanatophoric dysplasia is caused by mutations in the fibroblast growth factor receptor 3 gene (*FGFR3*), located on the short arm of chromosome 4 at band 16.3 (abbreviated as 4p16.3). The fibroblast growth factors are a family of important proteins in the human body that are involved in the production of new cells and new blood vessels as well as in the healing of wounds. Mutations in each of the fibroblast growth factor genes (*FGFR1*, 2, and 3) have been linked to a variety of genetic conditions. The *FGFR3* protein is primarily found in cartilage and the central nervous system. Different mutations in the *FGFR3* gene have been associated with other skeletal dysplasias, most notably achondroplasia and hypochondroplasia.

As might be expected, different mutations in *FGFR3* have been found in patients with TD1 versus those with TD2. A wider variety of mutations have been identified among infants with TD1. One predominant mutation has been present in nearly all cases of TD2 studied so far. Regardless of the specific mutation, the net effect of each of the mutations in both TD1 and TD2 is the same: the linear growth of bone is prevented, resulting in very short, small bones.

Demographics

Thanatophoric dysplasia is the most common lethal skeletal dysplasia, with an estimated incidence of 1 in 35,000–50,000 births. It has been described in all races and ethnic groups.

Signs and symptoms

Infants with TD are typically identified either during pregnancy or at the time of birth. Affected pregnancies are often complicated by polyhydramnios, or excess amniotic fluid around the fetus. As a result, the mother often appears more pregnant than she actually is. It is common for a prenatal ultrasound examination to be performed to rule out a fetal birth defect as the cause. The serious limb abnormalities typical of TD are often

KEY TERMS

Achondroplasia—An autosomal dominant form of dwarfism caused by a defect in the formation of cartilage at the ends of long bones. Affected individuals typically have short limbs, a large head with a prominent forehead and flattened profile, and a normal-sized trunk.

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks of gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Hypochondroplasia—An autosomal dominant form of dwarfism where physical features are similar but milder than those of achondroplasia. Affected individuals have mild short stature and a normal facial appearance.

identified in this way. Polyhydramnios may also lead to an increased chance of early labor and premature delivery. The pregnant woman may require more intensive monitoring of her pregnancy.

At birth, newborns with TD typically have a very large head with a prominent forehead, a flattened bridge of the nose, and prominent, bulging eyes. Their limbs are extremely short and are often held extended out from the rest of the body. The neck is short, the chest is narrow, and the belly appears unusually large, giving an overall resemblance to a pear. The shape of the skull may be abnormal due to either cloverleaf skull or a milder form of craniosynostosis. Newborns are often rather floppy, or hypotonic, with poor muscle tone and absent primitive neurologic reflexes. Breathing is very difficult due to the small chest and lungs, often leading to the use of a ventilator to prolong survival.

The physical appearance of individuals with TD who survive the neonatal period does not dramatically change over time. Affected children remain very small and have

QUESTIONS TO ASK YOUR DOCTOR

- What type of supportive measures will be most helpful?
- How can I best determine if a future pregnancy will result in a child with TD?
- What is your level of certainty that my child has either TD1 or TD2?
- At what point should I have genetic testing?

limited potential to walk or move about unaided. Intellectual disability due to structural brain malformations has been reported. Seizures and hearing loss frequently develop.

Diagnosis

Prenatal diagnosis of TD is possible based on ultrasound examination, usually during the second half of pregnancy. However, it is important to realize that many of the physical abnormalities seen in fetuses with TD such as an enlarged head and shortened long bones, may also be found in fetuses with other forms of skeletal dysplasia. Consequently, while ultrasound may suggest a diagnosis of a skeletal dysplasia, it may not be possible to confirm a diagnosis of TD until after birth.

Upon delivery, a careful examination of the infant should be performed to look for many of the more obvious external features of TD. Radiologic studies are extremely important, particularly to distinguish between TD1 and TD2. X-ray will confirm the marked shortening of the long bones, identify curved or straight femurs, document the shape and appearance of the spinal vertebrae, and reveal the extent of craniosynostosis. An autopsy, including x-rays, is highly recommended on any stillborn infant with TD to confirm the diagnosis. Mutation studies by analysis of the *FGFR3* gene are being used more often to confirm a diagnosis of TD and to determine TD type. Perhaps the greatest benefit of direct genetic testing is for those parents who have been told by a prenatal ultrasound examination that their unborn child has a serious bone dysplasia. An amniocentesis for additional genetic studies may be offered. Further clarification of the diagnosis allows for more refined counseling regarding the infant's likely prognosis. Termination of the pregnancy may be an option for some couples. For those couples wishing to continue an affected pregnancy, plans can be made for the remaining prenatal care, especially given the risk for polyhydramnios and/or early labor and

delivery. Careful consideration may be given as to the level of intervention and medical care desired for the infant after birth.

Knowledge of the specific TD mutation is also helpful in planning care for any future pregnancy. Despite the sporadic nature of TD, a couple with a history of one affected child has a small risk of having a second affected child due to the possibility of gonadal mosaicism. Prenatal testing in a new pregnancy, such as chorionic villus sampling (CVS) or amniocentesis, may be offered to look for a TD mutation. However, in order for this to be possible the TD mutation in the previous child must have been determined.

Studies are ongoing to assess whether or not three-dimensional ultrasound, in contrast to the current, much more widely available, two-dimensional ultrasound, may be used to accurately prenatally diagnose TD and other skeletal dysplasia. If effective, additional prenatal studies could become less common; however, early results have shown no significant improvement in the detection or diagnosis of TD and related disorders. The present standard of care therefore remains a prenatal ultrasound examination, if available, physical evaluations after delivery, and identification of the underlying genetic mutation, whenever possible.

Treatment and management

The treatment and care of an infant with TD is mainly supportive. The poor prognosis associated with TD should be discussed. Infants who survive the newborn period will require intensive, ongoing medical care.

Prognosis

Nearly all infants with TD, both types 1 and 2, die either at the time of delivery or shortly thereafter due to severe respiratory distress. Aggressive medical treatment after birth cannot always help affected infants live even a short amount of time. Prolonged survival has been reported but is highly unusual. Survival is associated with poor growth and development, and with continuing, serious respiratory problems.

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ORGANIZATIONS

Little People of America, 250 El Camino Real, Suite 211, Tustin, CA 92780, info@lpaonline.org, <http://www.lpaonline.org>

Magic Foundation, 6645 W. North Ave., Oak Park, IL 60302, (708) 383-0808, (800) 362-4423, ContactUs@magicfoundation.org, <https://www.magicfoundation.org>

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Thomsen disease see **Myotonia congenita**

Thoracic aortic aneurysms

Definition

An aneurysm is an abnormal bulge or ballooning in an artery wall caused by a weakness in the wall. A thoracic aortic aneurysm is one that occurs in the upper part of the aorta in the chest above the heart. It is also called thoracic aortic aneurysm and dissection (TAAD), because a large aneurysm can burst or infiltrate the artery wall (dissection) and cause life-threatening bleeding. Familial TAAD runs in families and can be caused by mutations in various genes.

Description

The aorta is the largest artery in the body. It carries oxygen-rich blood from the heart through the chest and abdomen to the rest of the body. Most aneurysms occur in the aorta. Thoracic aortic aneurysms occur in the aorta in the chest, and abdominal aortic aneurysms occur in the portion of the aorta that runs through the abdomen. An aortic rupture is a burst aneurysm that causes bleeding within the body. An aortic dissection occurs when pumped blood splits the layers of a weakened artery wall and allows blood to leak between the layers. Most deaths



X-ray of the chest of a 68-year-old woman with an aortic aneurysm (upper center). (SPL/Science Source)

from aortic aneurysms are caused by ruptures and dissections. Small, slow-growing thoracic aortic aneurysms may never cause a problem, but large, fast-growing aneurysms can cause life-threatening rupture or dissections.

Thoracic aortic aneurysms are most often caused by atherosclerosis (hardening of the arteries), which is more common in people with high cholesterol or long-term high blood pressure (hypertension) and in smokers. More than 70% of people with thoracic aortic disease have uncontrolled hypertension. Age-related changes to the artery wall, inflammation of the aorta, syphilis, and injuries from falls or motor-vehicle accidents are also risk factors for TAAD.

Familial TAAD is caused by inherited problems with the aorta. Familial TAAD can cause the aorta to weaken and stretch (aortic dilatation), which can lead to an aneurysm or aortic dissection. Aortic aneurysms and dissections can rupture and/or reduce blood flow to the brain and other vital organs. Other arteries may also be affected. TAAD can also be caused by inherited connective-tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome.

Genetic profile

About 20% of TAADs are familial and can be caused by mutations in several different genes. Familial TAAD is inherited in an autosomal dominant pattern, which

means that an individual need only inherit one mutated gene from an affected parent to develop TAAD, even if the second gene, inherited from the other parent, is normal. However, some people who inherit a TAAD-associated gene mutation never develop aortic abnormalities—a phenomenon known as reduced penetrance and indicating that the corresponding normal gene is able to compensate for the defect.

Between 14% and 20% of people with familial TAAD have mutations in the *ACTA2* gene. This gene produces a protein called smooth muscle alpha-2 actin, which is an important component of the vascular smooth muscle cells (SMCs) that form layers in the walls of the aorta and other arteries. Smooth muscle alpha-2 actin forms the protein core of structures called sarcomeres that enable muscles to contract and the arteries to hold their shape while blood pumps through them. The *ACTA2* (ACTin, Alpha2, smooth muscle, aorta) gene mutations that cause familial TAAD change single amino acids (building blocks) in the smooth muscle alpha-2 actin protein. This results in an abnormal protein that interferes with sarcomere function and results in stretching of the arteries as the blood is pumped through. Because the blood pumped directly from the heart to the aorta has the most force, the aorta is especially vulnerable to stretching. This can result in dilatation, aneurysms, and dissections. Whereas mutations in *ACTA2* disrupt the thin filaments in the SMC contractile complex, mutations in the *MYH11* gene, which produces myosin heavy chain 1 in smooth muscle, disrupt the thick filaments in the SMC contractile complex. In both cases, the ability of SMCs to contract in response to blood pressure is reduced.

About 2.5% of people with familial TAAD have mutations in the *TGFBR2* gene that produces a protein called transforming growth factor-beta (TGR-beta) receptor type 2. This receptor binds TGR-beta on the surfaces of cells, causing the receptor to transmit signals to the inside of the cell to control cell growth and division (proliferation) and differentiation into specific types of cells. The TGR-beta receptor 2 is also involved in the formation of the extracellular matrix that fills the spaces between cells. Mutations in *TGFBR2* change the structure of the receptor, which disrupts signaling within the cell and impairs cell growth and development, resulting in aortic abnormalities.

In 2013, researchers identified a rare mutation in the *PRKG1* gene. This mutation changes a single amino acid in an enzyme called type 1 cGMP-dependent protein kinase (PKG-1) and causes familial TAAD. The PKG-1 enzyme controls SMC relaxation when it is activated by binding the nucleotide cGMP. The majority of affected individuals in four families had acute aortic dissections at relatively young ages, some as young as 17. The amino

KEY TERMS

ACTA2—The gene that encodes smooth muscle alpha-2 actin; up to 20% of familial thoracic aortic aneurysms and dissections (TAADs) are caused by mutations in the *ACTA2* gene.

Aorta—The largest artery in the body that carries blood through the trunk to branch arteries throughout the body.

Aortic dilatation—Weakening and stretching of the aorta that can occur with TAAD-associated gene mutations and lead to an aneurysm or aortic dissection.

Aortic dissection—A splitting of the layers of the aorta wall that causes blood to leak between the layers.

Autosomal dominant—A pattern of genetic inheritance in which only one abnormal gene is needed to express the trait or disorder.

Penetrance—The proportion of individuals who actually exhibit a trait for which they have gene or gene variant.

Smooth muscle cells (SMCs)—The layered cells in the wall of the aorta and other arteries.

acid change causes the protein to be always active, even in the absence of cGMP. This is known as a gain-of-function mutation. This constant PKG-1 activity decreases contraction of vascular SMCs by removing phosphate groups from myosin, an important muscle protein. Like other TAAD mutations, the *PRKG1* mutation is inherited in an autosomal dominant manner and appears to be very rare. It changes a highly conserved amino acid in the PKG-1 protein, meaning that this particular amino acid is present at the same position in the protein in a wide variety of organisms and suggesting that it is essential for protein structure and/or function.

In 2015, researchers identified mutations in the *MAT2A* gene that can cause autosomal dominant TAAD. The *MAT2A* gene produces a protein called methionine adenosyltransferase II alpha (MAT IIalpha). The two identified mutations were single changes in a building block (nucleotide) of the DNA sequence of the *MAT2A* gene that changed single amino acids in the protein. There are very few variations in the human *MAT2A* gene, and the two identified changes occur in amino acids that are evolutionarily conserved in the MAT IIalpha enzyme. These two mutations are believed to disrupt the enzymatic activity of the MAT IIalpha protein.

Other genes in which mutations can cause TAAD include:

- MYLK (myosin, light-chain kinase)
- TGFBR1 (transforming growth factor, beta receptor 1)
- TGFBR2 (transforming growth factor, beta 2)
- SMAD3
- FBN1

Genetic testing may be available for identified TAAD gene mutations. It is thought that mutations in other as-yet-unidentified genes may also cause rare cases of familial TAAD.

Demographics

Although aortic aneurysms are common worldwide, they usually have no symptoms unless they rupture, so their prevalence is difficult to determine. Ruptured aortic aneurysms and dissections cause nearly 30,000 deaths in the United States every year. About two-thirds of aortic dissections occur in males.

At least 20% of all TAAD are believed to be familial. The other 80% are not inherited but rather are caused by damage to the aorta wall from aging, smoking, injury, or disease. Although TAAD usually appears to be inherited in an autosomal dominant pattern, its occurrence is variable, even within affected families, and penetrance is lower in females. Mutations in the *ACTA2* gene account for 14%–20% of familial TAAD. Mutations in the *TGFBR2* gene account for about 2.5% of cases. Mutations in each of the other identified TAAD-associated genes appear to account for smaller percentages of familial TAAD.

Signs and symptoms

The development of familial TAAD varies, even within the same family. Aortic abnormalities may develop in childhood, adulthood, late in life, or not at all. Aortic dilatation usually appears first, although sometimes dissection occurs with little or no dilatation.

Aortic aneurysms can develop slowly over many years and usually have no symptoms until the aneurysm leaks or expands. Symptoms start suddenly when an aneurysm grows rapidly or ruptures or aortic dissection occurs. However, depending on the size, rate of growth, and location of the aneurysm and whether it presses against other structures, symptoms may include:

- pain in the chest, back, neck, or jaw
- swelling in the head, neck, or arms
- difficult or painful swallowing
- hoarseness
- shortness of breath

- wheezing or high-pitched breathing
- chronic cough
- coughing up of blood
- clammy skin
- nausea and vomiting
- rapid heart rate
- feeling of impending doom

An aortic dissection generally causes sudden, severe chest or back pain. It can also cause:

- pale skin color
- very faint pulse
- numbness or tingling in one or more limbs
- paralysis

Although familial TAAD is not generally associated with other signs and symptoms, some people in affected families have mild features of Marfan syndrome or Loeys-Dietz syndrome, including:

- tall stature
- stretch marks on the skin
- joint hypermobility (unusually large range of motion)
- a sunken or protruding chest

Some people with familial TAAD have:

- brain or abdominal aortic aneurysms
- congenital (present at birth) heart abnormalities
- a soft out-pouching in the lower abdomen called an inguinal hernia
- purple skin discoloration called livedo reticularis caused by abnormalities in the tiny blood vessels of the skin
- increased risk of blockages in smaller arteries that can lead to a heart attack or stroke

Diagnosis

Thoracic aortic aneurysms can be diagnosed with imaging tests, but they are usually discovered during testing performed for other reasons. These include a chest x-ray, echocardiogram, or a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the chest. A CT scan will reveal the size of the aorta and the exact location of the aneurysm. An aortogram—x-rays taken after the aorta is injected with a dye—can identify aneurysms, as well as any branches of the aorta that may be involved.

Because aneurysms do not usually cause symptoms unless they rupture or a dissection occurs, and physical examinations are usually normal, ultrasound screening is recommended for people between the ages of 65 and 75 who have a family history of TAAD, as well as for men who have ever smoked.

QUESTIONS TO ASK YOUR DOCTOR

- Should I be screened for thoracic aortic aneurysms, since they run in my family?
- Is genetic testing available for thoracic aortic aneurysms?
- What are the symptoms of thoracic aortic aneurysms?
- What are the chances that I will pass thoracic aortic aneurysm and dissection on to my children?

Treatment and management

Treatment of thoracic aortic aneurysm depends on its size and how fast it is growing. No treatment other than “watchful waiting” may be prescribed if the aneurysm is small and slow growing. Medications can also be prescribed. A ruptured aneurysm or aortic dissection usually requires emergency surgery. If an aneurysm is discovered that is at risk of rupture, it may be repaired in a planned surgery. The type of surgery depends on the location of the aneurysm.

If an aneurysm is larger than 5–6 cm (2 in.) and is in the ascending aorta that leads from the heart toward the head or in the middle curved part of the aorta called the aortic arch, the aorta is usually replaced with a plastic or fabric graft. This is major surgery through the middle of the chest bone and requires a heart-lung machine.

If an aneurysm is in the descending thoracic aorta that extends downward and is more than 6 cm (2 in.), the aorta is replaced with a fabric graft. This is major surgery performed on the left side of the chest and possibly reaching to the abdomen. Sometimes endovascular stenting can be used for a descending thoracic aneurysm. This is a less invasive method that does not require cutting into the chest; rather, a tiny metal or plastic tube is inserted into the aorta to hold it open.

Prognosis

The prognoses for thoracic aortic aneurysms depend on the presence of other medical problems such as heart disease, hypertension, or diabetes. Aortic surgery carries the risk of serious complications, and 5%–10% of patients die soon after aortic surgery. Aneurysm stenting sometimes damages blood vessels supplying the leg, which may require a second surgery.

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ORGANIZATIONS

American Heart Association, 7272 Greenville Ave., Dallas, TX 75231, (800) 242-8721, (888) 474-VIVE, <http://www.heart.org>

Centers for Disease Control and Prevention, 1600 Clifton Rd., Atlanta, GA 30329-4027, (800) 232-4636, <http://www.cdc.gov>

Marfan Foundation, 22 Manhasset Ave., Port Washington, NY 11050, (516) 883-8712, (800) 8-MARFAN, (516) 883-8040, <http://www.marfan.org>

National Heart, Lung, and Blood Institute, NHLBI Health Information Center, PO Box 30105, Bethesda, MD 20824-0105, (301) 592-8573, <http://www.nhlbi.nih.gov>

Society of Thoracic Surgeons, 633 N. St. Clair St., Fl. 23, Chicago, IL 60611, (312) 202-5800, (312) 202-5801, <http://www.sts.org>

Margaret Alic, PhD

Thoracic aortic aneurysm and dissection (TAAD) see **Thoracic aortic aneurysms**

Thyroid hormone resistance syndrome

Definition

Thyroid hormone resistance syndrome refers to a disorder in which the individual’s body tissues have reduced responsiveness to the active form of thyroid hormone, triiodothyronine, or T3. Tissues respond when thyroid hormone receptors, which are proteins within cells, become activated by binding thyroid hormone. There are three

basic types of thyroid receptors (TRs): thyroid receptor alpha-1, most commonly found in heart and skeletal muscle; thyroid receptor beta-1, predominantly found in the brain, liver, and kidney; and thyroid receptor beta-2, primarily limited to the hypothalamus and the pituitary gland in the brain.

These thyroid hormone receptors are encoded by two different genes, *THRA* and *THRB*, respectively. The fact that the three major types of hormone receptors are found in different proportions in different organs explains why some body tissues (for example, tissues with normal alpha receptors) can show signs of thyroid hyperactivity while other tissues (for example, those with mutations in the beta receptors) may have features of thyroid underactivity.

Although thyroid hormone resistance syndrome has been recognized since 1967, it was only in the late 1980s that a mutation in the thyroid hormone receptor gene, beta (*THRB*) was discovered to be the cause of most cases of the disorder. Researchers identified both autosomal dominant and autosomal recessive forms of thyroid hormone resistance syndrome. More recently, in 2012 and 2013, geneticists began to see patients with thyroid resistance syndrome who lacked mutations in the *THRB* gene but did have mutations in the thyroid hormone receptor gene, alpha (*THRA*).

Description

Thyroid hormones and the thyroid feedback system

To understand the characteristic features of thyroid hormone resistance syndrome, it is helpful first to have an overview of the process of thyroid hormone secretion and activation. Under normal circumstances, the level of thyroid hormone in the bloodstream and body tissues is kept fairly constant by a feedback system. Secretion of thyroid hormone begins in the hypothalamus of the brain, a small structure located just above the brainstem. The hypothalamus secretes a hormone called thyrotropin-releasing hormone or TRH. TRH in return stimulates the release of thyroid-stimulating hormone (TSH) from the anterior lobe of the pituitary gland, which is located below the hypothalamus at the base of the brain. The pituitary gland in human adults is a small gland about the size of a pea.

Thyroid-stimulating hormone signals the thyroid gland itself to produce two forms of thyroid hormone: thyroxine or T4; and triiodothyronine or T3. The ratio of T4 to T3 is about 20 to 1. T4 is a prohormone—the relatively inactive precursor of T3, which is the form of thyroid hormone that is active in the body's target tissues. T4 is converted into T3 within the cells by various enzymes.

When the levels of T4 and T3 in the blood rise to a certain point, they inhibit the production of TSH in the pituitary gland, which in turn inhibits the release of the thyroid hormones from the thyroid gland. As the blood levels of the thyroid hormones drop, the pituitary gland begins to release more TSH, stimulating the thyroid gland to produce more thyroid hormones. The thyroid system is an example of a closed-loop feedback process.

Thyroid hormone resistance

In thyroid hormone resistance syndrome, mutations in either of the two genes that code for thyroid receptor proteins—*THRB* and *THRA*—impair the ability of the cells in the target tissues to take in the hormone across the cell membrane or to metabolize it. Patients identified with thyroid hormone resistance syndrome have a range of different signs and symptoms, depending on which thyroid receptor gene has a mutation and whether the inheritance pattern is autosomal dominant or autosomal recessive.

Genetic profile

About 85% of known cases of thyroid hormone resistance syndrome are associated with mutations in the *THRB* gene on the short arm of chromosome 3 at 3p24.2.

Thyroid hormone resistance, autosomal dominant, beta

Also known as generalized thyroid hormone resistance or GTHR, this form of the disorder is inherited in an autosomal dominant manner, which means that only one copy of the mutated gene is needed for the affected person to develop the characteristic features of the disorder. These may include goiter, abnormal patterns of bone growth and maturation, deafness, and an abnormally rapid heartbeat (tachycardia). The disorder is suspected when a thyroid function test indicates high levels of thyroxine and triiodothyronine in the bloodstream along with normal or slightly elevated levels of thyroid-stimulating hormone. This finding results from disruption of the normal thyroid feedback system in that the pituitary gland does not respond to the high levels of thyroid hormones in the blood but continues to produce TSH.

Thyroid hormone resistance, autosomal recessive, beta

Also known as Refetoff syndrome after its discoverer, this form of thyroid hormone resistance was the first one identified in 1967, although it was not then known to be caused by a genetic mutation. The signs and symptoms of this form of thyroid resistance syndrome are similar to those of the autosomal dominant form, with the exception of the fact that patients' laboratory test results indicate significantly

KEY TERMS

Adenoma—A benign tumor that develops in glandular tissue. A thyroid adenoma may produce large amounts of thyroid hormone that disrupt the normal thyroid feedback system.

Analogue—A drug or other chemical compound that resembles another in structure or constituents but has different effects.

Endocrine gland—Any gland that secretes its products directly into the bloodstream rather than through a duct. The hypothalamus, pituitary, and thyroid are all endocrine glands.

Euthyroid—Having normal thyroid gland function.

Exophthalmos—The bulging of the eye forward from the orbit. It is a symptom of abnormally high levels of thyroid hormone.

Goiter—A swelling of the neck or larynx caused by enlargement of the thyroid gland.

Hypothalamus—A structure in the brain just above the brainstem that secretes thyrotropin-releasing hormone (among other functions) to stimulate the pituitary gland.

Pituitary gland—An endocrine gland located at the base of the hypothalamus. The anterior portion of the pituitary gland secretes thyroid-stimulating hormone

(TSH) in response to thyrotropin-releasing hormone (TRH) from the hypothalamus. The pituitary gland is also called the hypophysis.

Prohormone—A precursor of a more active hormone. Thyroxine is the prohormone of triiodothyronine.

Receptor—A molecule in or on the surface of a cell that recognizes and binds with specific molecules, such as hormones, neurotransmitters, or drugs.

Tachycardia—An abnormally rapid heartbeat in an adult at rest (that is, not exercising), usually regarded as 100 beats per minute or faster.

Thyroid-stimulating hormone (TSH)—A hormone produced in the anterior lobe of the pituitary gland that stimulates the thyroid gland to produce thyroxine and triiodothyronine. It is also known as thyrotropin.

Thyrotropin-releasing hormone (TRH)—A hormone produced by the hypothalamus that stimulates the pituitary gland to release TSH.

Thyroxine (T4)—The major form of thyroid hormone circulating in the blood. It is converted in the liver and the thyroid gland itself into triiodothyronine, the most active thyroid hormone.

Triiodothyronine (T3)—The most active and final form of thyroid hormone.

elevated levels of thyroid-stimulating hormone as well as high levels of thyroxine and triiodothyronine.

Thyroid hormone resistance, alpha

This form of thyroid hormone resistance syndrome was first reported in 2012 and 2013 by two groups of researchers in the United Kingdom and the Netherlands. It is caused by mutations in the *THRA* gene on the long arm of chromosome 17 at 17q11.2 and is thought to be inherited in an autosomal dominant pattern. Patients with this mutation show delayed bone development, malformations of the skeleton, mental retardation, constipation, and anemia. Laboratory test results indicate low-to-normal levels of thyroxine; normal-to-high levels of triiodothyronine; an abnormally low T4 to T3 ratio; normal levels of thyroid-stimulating hormone; and anemia.

Demographics

Thyroid hormone resistance syndrome is rare worldwide, estimated to occur once in every 40,000 to 50,000 live births. About 3,500 cases had been reported worldwide as of 2015. The syndrome affects males and females

equally. As of 2015, it was also thought to affect all races and ethnic groups equally.

Signs and symptoms

Thyroid hormone resistance, autosomal dominant, beta

Patients with this form of thyroid hormone resistance syndrome may be euthyroid (showing normal thyroid gland function) along with a goiter (swelling in the neck) and high levels of thyroid hormone in the blood. The goiter results from the thyroid gland's extra production of thyroid hormones. Children with this form of thyroid hormone resistance syndrome may have delayed speech development and be diagnosed with attention-deficit hyperactivity disorder (ADHD). Patients with this form of the syndrome will respond to the administration of thyrotropin-releasing hormone or TRH.

Thyroid hormone resistance, autosomal recessive, beta

Patients with the autosomal recessive form of thyroid hormone resistance due to mutations in the *THRB* gene

typically have some symptoms of hyperthyroidism, including bulging eyes (exophthalmos) as well as goiter. Infants with this form of the syndrome are often small for their gestational age or may have a low birth weight at time of birth. They may also have hearing impairments.

Thyroid hormone resistance, alpha

Patients with this form of thyroid hormone resistance syndrome have abnormalities of skeletal growth, including unusually short stature and an abnormally large head (macrocephaly) with coarse facial features. They may show signs of hypothyroidism, including a low rate of metabolism and weight gain. Patients also have some gastrointestinal symptoms, most often constipation. Children may have relatively high birth weight, and mild or moderate mental retardation. Patients are also usually anemic and have high blood cholesterol levels.

Diagnosis

Thyroid hormone resistance syndrome can be diagnosed at almost any age, although thyroid function test results will be abnormal from birth. In older children and adults, the diagnosis of the various forms of thyroid hormone resistance syndrome begins with a patient history, including indications of mental retardation and such neurological symptoms as ADHD or delayed speech. The history-taking is followed by an office examination of the patient's facial features, heart rate, and skeletal abnormalities, if any. The next step is a thyroid function test: a blood test for the levels of the two thyroid hormones, the ratio between them, and the level of thyroid-stimulating hormone. A complete blood count will also be done to evaluate the patient for anemia.

If the results of the thyroid function test suggest the presence of thyroid hormone resistance, other tests will be performed to ensure that the abnormal levels of TSH are not caused by a thyroid-secreting adenoma in the pituitary gland. This type of adenoma is a slow-growing benign tumor in the pituitary gland that secretes excessive amounts of TSH. Two types of tests that are done to exclude a pituitary adenoma are an MRI of the patient's brain and a thyrotropin-releasing hormone test. This second test involves an initial test of the patient's blood hormone levels followed by an injection of TRH and a second blood test an hour later.

Lastly, the diagnosis can be confirmed by molecular genetic testing for mutations of the *THRB* and *THRA* genes. There were three laboratories (in Germany, Portugal, and the United States) that offered tests for mutations in the *THRA* gene as of 2015. There were 14 laboratories worldwide that offer testing for the autosomal dominant form of thyroid hormone resistance associated with mutations of

QUESTIONS TO ASK YOUR DOCTOR

- Which type of thyroid hormone resistance syndrome do I have?
- Will I need genetic testing, or will the results of a thyroid function test be adequate for a diagnosis?
- Which treatments will you recommend? What are their long-term side effects, if any?
- How likely am I to pass on my mutation to my children?

the *THRB* gene and seven laboratories that offer testing for the autosomal recessive form of the disorder.

Treatment and management

Treatment and management depends on the type of thyroid hormone resistance and the severity of the patient's symptoms. Some patients have abnormal blood test results but no external symptoms and do not need any treatment. Children, however, should be monitored to make sure that they are growing and developing at a normal rate.

Patients with mutations in the *THRA* gene were treated with levothyroxine tablets as of 2015. Levothyroxine is a synthetic form of T₄ and is converted in the patient's body to T₃, the active form of thyroid hormone. According to the researchers who first identified mutations in the *THRA* gene, therapy with levothyroxine brings the patients' blood levels of thyroid hormone back to normal and relieves constipation, but does not affect mental functioning or short stature.

Patients with tachycardia are treated with beta-blockers, a class of drugs that can slow the heartbeat in patients with abnormally high blood levels of thyroid hormone.

A drug known as tiratricol or TRIAC, which is an analogue of thyroid hormone, is used in the United Kingdom and France to treat thyroid hormone resistance syndrome. It is not, however, approved for sale in the United States and Canada because of its misuse in the late 1990s as a weight-loss aid. The Utah-based manufacturer agreed to stop distributing any product containing tiratricol in 2000.

Prognosis

Thyroid hormone resistance syndrome is not a life-threatening disorder and is not known to shorten patients' lifespans. Mutations in the *THRA* gene and the autosomal dominant form of thyroid resistance associated with *THRB* mutations can obviously have a severe impact on

a child's intellectual and social development as well as growth in height and physical coordination.

Because administration of synthetic thyroid hormone can affect an unborn child, women diagnosed with thyroid hormone resistance syndrome should consult their physician before they become pregnant, and should be carefully monitored throughout pregnancy.

Thyroid hormone resistance syndrome is known to increase the risk of osteoporosis in both males and females; thus adult patients diagnosed with the syndrome should have their bone density monitored.

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ORGANIZATIONS

American Thyroid Association (ATA), 6066 Leesburg Pike, Suite 550, Falls Church, VA 22041, (703) 998-8890, (703) 998-8893, thyroid@thyroid.org, <http://www.thyroid.org>
Endocrine Society, 2055 L St. NW, Suite 600, Washington, DC 20036, (202) 971-3636, (888) 363-6274, (202) 736-9705, <http://www.endocrine.org>

Rebecca J. Frey, PhD

Tourette syndrome

Definition

Tourette syndrome is an inherited disorder of the nervous system characterized by a variable expression of unwanted movements and noises (tics).



X-ray of a 25-year-old man with Tourette syndrome, showing electrodes implanted in his brain to stimulate the thalamus in an attempt to improve the symptoms. (Zephyr/Science Source)

Description

The first references in the literature to what might today be classified as Tourette syndrome largely described individuals who were wrongly believed to be possessed by the devil. In 1885, Gilles de la Tourette, a French neurologist, provided the first formal description of this syndrome. He described the disorder as an inherited neurological condition characterized by motor and vocal tics.

Although vocal and motor tics are the hallmark of Tourette syndrome, other symptoms such as the expression of socially inappropriate comments or behaviors, obsessive-compulsive disorder, attention-deficit disorder, self-injuring behavior, depression, and anxiety also appear to be associated with Tourette syndrome. Most research suggests that Tourette syndrome is an inherited disorder, although a gene responsible for Tourette syndrome has not yet been discovered.

Genetic profile

The cause of Tourette syndrome is unknown, although some studies suggest that the tics associated with Tourette syndrome are caused by an increased amount of a neurotransmitter called dopamine. A neurotransmitter is a chemical found in the brain that helps to transmit information from one brain cell to another. Other studies suggest that the defect in Tourette syndrome involves another neurotransmitter called serotonin, or involves other chemicals required for normal functioning of the brain. It is clear that genetic factors are involved in the occurrence of Tourette syndrome because studies of

identical twins (twins who share all the same genes) show that about 85% of the time that one is affected, the other is also affected. One theory is that Tourette syndrome is an autosomal dominant disorder with decreased penetrance. This theory has not been proven and may not be true in all families. An autosomal dominant disorder results from a change in one copy of a pair of genes. Individuals with an autosomal dominant disorder have a 50% chance of passing on the changed gene to their children. Decreased penetrance means that not all people who inherit the changed gene will develop symptoms. There is some evidence that females who inherit the Tourette syndrome gene have a 70% chance of exhibiting symptoms, and males have a 99% chance of having symptoms.

Other theories about the cause of Tourette syndrome include the presence of a single gene in combination with other genetic or environmental changes that cause the condition. Some studies have indicated that it is unlikely that there is one genetic change alone that is responsible for causing Tourette syndrome. It is possible that Tourette syndrome has different causes in different individuals. Linkage analysis has been performed by several researchers to identify genes that may be associated with Tourette syndrome. In linkage analysis, researchers determine if people with Tourette syndrome have more markers (identifiable DNA sequences) associated with particular genes in common than would be expected by chance. These studies have indicated several chromosomal locations of interest, including locations on chromosome 2, 4, 5, 7, 8, 10, 11, 13, 17, and 19. In addition, individuals with Tourette syndrome features from different families have been reported to have chromosomal rearrangements that involve chromosome breaks in chromosomes 2, 6, 8, 7, and 18q. The areas where the chromosome broke in these families are under further investigation. More research is needed to establish the cause of Tourette syndrome.

Researchers are also interested in determining if the sex of the parent passing on a particular genetic change for Tourette syndrome influences the occurrence or severity of symptoms. Researchers also want to determine how having a family history of Tourette syndrome in both parents affects the chance for, and the severity of, the condition in their children.

Demographics

Tourette syndrome is found in all populations and all ethnic groups, but is three to four times more common in males than in females and is more common in children than in adults. The exact frequency of Tourette syndrome is unknown, but estimates range from 1 to 10 in 1,000 children or adolescents.

Signs and symptoms

Motor and vocal tics

The principal symptoms of Tourette syndrome include simple and complex motor and vocal tics. Simple motor tics are characterized by brief muscle contractions of one or more limited muscle groups. An eye twitch is an example of a simple motor tic. Complex motor tics tend to appear more complicated and purposeful than simple tics and involve coordinated contractions of several muscle groups. Some examples of complex motor tics include the act of hitting oneself and jumping. Copropraxia, the involuntary display of unacceptable/obscene gestures, and echopraxia, the imitation of the movement of another individual, are other examples of complex motor tics.

Vocal tics are actually manifestations of motor tics that involve the muscles required for vocalization. Simple vocal tics include stuttering, stammering, abnormal emphasis of part of a word or phrase, and inarticulate noises such as throat clearing, grunts, and high-pitched sounds. Complex vocal tics typically involve the involuntary expression of words. Perhaps the most striking example of this is coprolalia, the involuntary expression of obscene words or phrases, which occurs in less than one-third of people with Tourette syndrome. The involuntary echoing of the last word, phrase, sentence, or sound vocalized by oneself (phalilalia) or of another person or sound in the environment (echolalia) are also classified as complex tics.

The type, frequency, and severity of tics exhibited vary tremendously between individuals with Tourette syndrome. Tourette syndrome has a variable age of onset, and tics can start anytime between infancy and age 18. Initial symptoms usually occur before the early teens, and the mean age of onset for both males and females is approximately seven years of age. Most individuals with symptoms initially experience simple muscle tics involving the eyes and the head. These symptoms can progress to tics involving the upper torso, neck, arms, hands, and occasionally the legs and feet. Complex motor tics are usually the latest-onset muscle tics. Vocal tics usually have a later onset than motor tics. In some rare cases, people with Tourette syndrome suddenly present with multiple, severe, or bizarre symptoms. Not only is there extreme variability in clinical symptoms between individuals with Tourette syndrome, but individuals commonly experience a variability in type, frequency, and severity of symptoms within the course of their lifetime. Adolescents with Tourette syndrome often experience unpredictable and variable symptoms, which may be related to fluctuating hormone levels and decreased compliance in taking medications. Adults often experience a decrease in symptoms or a complete end to symptoms.

A number of factors appear to affect the severity and frequency of tics. Stress appears to increase the frequency and severity of tics, while concentration on another part of the body that is not taking part in a tic can result in the temporary alleviation of symptoms. Relaxation, following attempts to suppress the occurrence of tics, may result in an increased frequency of tics. An increased frequency and severity of tics can also result from exposure to drugs such as steroids, cocaine, amphetamines, and caffeine. Hormonal changes such as those that occur prior to the menstrual cycle can also increase the severity of symptoms.

Other associated symptoms

People with Tourette syndrome are more likely to exhibit nonobscene, socially inappropriate behaviors such as expressing insulting or socially unacceptable comments or socially unacceptable actions. It is not known whether these symptoms stem from a more general dysfunction of impulse control that might be part of Tourette syndrome.

Tourette syndrome appears to also be associated with attention-deficit disorder (ADD). ADD is a disorder characterized by a short attention span and impulsivity and, in some cases, hyperactivity. Researchers have found that 21%–90% of individuals with Tourette syndrome also exhibit symptoms of ADD, whereas 2%–15% of the general population exhibit symptoms of ADD.

People with Tourette syndrome are also at higher risk for having symptoms of obsessive-compulsive disorder (OCD). OCD is a disorder characterized by persistent, intrusive, and senseless thoughts (obsessions) or compulsions to perform repetitive behaviors that interfere with normal functioning. A person with OCD, for example, may be obsessed with germs and may counteract this obsession with continual hand washing. Symptoms of OCD are present in 1.9%–3% of the general population, whereas 28%–50% of people with Tourette syndrome have symptoms of OCD.

Self-injurious behavior (SIB) is also seen more frequently in those with Tourette syndrome. Approximately 34%–53% of individuals with Tourette syndrome exhibit some form of self-injuring behavior. The SIB is often related to OCD, but can also occur in those with Tourette syndrome who do not have OCD.

Symptoms of anxiety and depression are also found more commonly in people with Tourette syndrome. It is not clear, however, whether these symptoms are symptoms of Tourette syndrome or occur as a result of having to deal with the symptoms of moderate to severe Tourette syndrome.

People with Tourette syndrome may also be at increased risk for having learning disabilities and personality disorders and may be more predisposed to behaviors such as aggression, antisocial behaviors, severe temper

KEY TERMS

Attention-deficit disorder (ADD)—Disorder characterized by a short attention span, impulsivity, and, in some cases, hyperactivity.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Coprolalia—The involuntary expression of obscene words or phrases.

Copropexia—The involuntary display of unacceptable/obscene gestures.

Decreased penetrance—Individuals who inherit a changed disease gene, but do not develop symptoms.

Dysphoria—Feelings of anxiety, restlessness, and dissatisfaction.

Echolalia—Involuntary echoing of the last word, phrase, or sentence that is spoken by someone else or by sounds in the environment.

Echopraxia—The imitation of the movement of another individual.

Linkage analysis—A type of genetic study used to identify genes that cause specific diseases.

Neurotransmitter—Chemical in the brain that transmits information from one nerve cell to another.

Obsessive-compulsive disorder (OCD)—Disorder characterized by persistent, intrusive, and senseless thoughts (obsessions) or compulsions to perform repetitive behaviors that interfere with normal functioning.

Phalilalia—Involuntary echoing of the last word, phrase, sentence, or sound vocalized by oneself.

Tic—Brief and intermittent involuntary movement or sound.

outbursts, and inappropriate sexual behavior. Further controlled studies need to be performed, however, to ascertain whether these behaviors are symptoms of Tourette syndrome. Individuals with Tourette syndrome are more likely to get migraine headaches and to have sleep disorders, such as difficulty falling asleep, staying asleep, or having unusual movements during sleep.

Diagnosis

Tourette syndrome cannot be diagnosed through a blood test. The diagnosis is made through observation

and interview of the patient and discussions with other family members. The diagnosis of Tourette syndrome is complicated by a variety of factors. The extreme range of symptoms of this disorder makes it difficult to differentiate Tourette syndrome from other disorders with similar symptoms. Diagnosis is further complicated by the fact that some tics appear to be within the range of normal behavior. For example, an individual who only exhibits tics such as throat clearing and sniffing may be misdiagnosed with a medical problem such as allergies. In addition, bizarre and complex tics such as coprolalia may be mistaken for psychotic or “bad” behavior. Diagnosis is also confounded by individuals who attempt to control tics in public and in front of healthcare professionals and deny the existence of symptoms. Although there is disagreement over what criteria should be used to diagnose Tourette syndrome, one aid in the diagnosis is the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5). The DSM-5 outlines suggest diagnostic criteria for a variety of conditions, including Tourette syndrome, such as:

- Presence of both motor and vocal tics at some time during the course of the illness.
- The occurrence of multiple tics nearly every day through a period of more than one year, without a
- remission of tics for a period of greater than three consecutive months.
- Symptoms cause distress or impairment in functioning.
- Age of onset prior to 18 years of age.
- The symptoms are not due to medications or drugs and are not related to another medical condition.

Some physicians critique the DSM-IV criteria, citing that they do not include the full range of behaviors and symptoms seen in Tourette syndrome. Others criticize the criteria since they limit the diagnosis to those who experience a significant impairment, which may not be true for individuals with milder symptoms. For this reason, many physicians use their clinical judgment as well as the DSM-IV criteria as a guide to diagnosing Tourette syndrome.

Treatment and management

There is no cure for Tourette syndrome, and treatment involves the control of symptoms through educational and psychological interventions, behavioral training, and/or medications. The treatment and management of Tourette syndrome vary from patient to patient and should focus on the alleviation of the symptoms that are most bothersome to the patient or that cause the most interference with daily functioning.

QUESTIONS TO ASK YOUR DOCTOR

- Would my child benefit from psychotherapy?
- What side effects could result from taking Ritalin and Clonidine?
- Are there early signs of medication side effects?
- What educational interventions do you recommend?

Psychological and educational interventions

Psychological treatments such as counseling are not generally useful for the treatment of tics, but can be beneficial in the treatment of associated symptoms such as obsessive-compulsive behavior and attention-deficit disorder. Counseling may also help individuals to cope better with the symptoms of this disorder and to have more positive social interactions. Psychological interventions may also help people cope better with stressors that can normally be triggers for tics and negative behaviors. The education of family members, teachers, and peers about Tourette syndrome can be helpful and may foster acceptance and prevent social isolation.

Behavioral training

A variety of behavioral training techniques has been suggested and tried in people with Tourette syndrome. Some of these include conditioning techniques (training a person to respond to a particular stimulus with a particular behavior), awareness training, biofeedback training (learning how to control one's involuntary nervous system), and habit reversal. Relaxation therapies have been tried with short-term success. The effectiveness of behavioral training as a whole is not clear.

Medications

Many people with mild symptoms of Tourette syndrome never require medications. Those with severe symptoms may require medications for all or part of their lifetime. The most effective treatment of tics associated with Tourette syndrome involves the use of drugs such as Haloperidol, pimozide, sulpiride, and tiapride, which decrease the amount of dopamine in the body. Unfortunately, the incidence of side effects, even at low dosages, is quite high. The short-term side effects can include sedation, dysphoria, weight gain, movement abnormalities, depression, and poor school performance. Long-term side effects can include phobias, memory difficulties, and

personality changes. These drugs are therefore better candidates for short-term rather than long-term therapy.

Tourette syndrome can also be treated with other drugs such as clonidine, clonazepam, and risperidone, but the efficacy of these treatments is unknown. In many cases, treatment of associated conditions such as ADHD and OCD is often more of a concern than the tics themselves. Clonidine used in conjunction with stimulants such as Ritalin may be useful for treating people with Tourette syndrome who also have symptoms of ADHD. Stimulants should be used with caution in individuals with Tourette syndrome since they can sometimes increase the frequency and severity of tics. OCD symptoms in those with Tourette syndrome are often treated with drugs such as Prozac, Luvox, Paxil, and Zoloft.

In many cases, the treatment of Tourette syndrome with medications can be discontinued after adolescence. Trials should be performed through the gradual tapering-off of medications and should always be done under a doctor's supervision.

Surgical treatments

Several areas of the brain have been targeted for surgical approaches to the treatment of severe tic disorders. In addition, deep brain stimulation (using sound waves to stimulate certain areas of the brain) has been suggested as treatment, as there has been some success with this treatment in other movement disorders. Clinical trials are needed to determine the effectiveness and safety of this treatment for possible use in the future.

Prognosis

The prognosis for Tourette syndrome in individuals without associated psychological conditions is often quite good, and only approximately 10% of people with Tourette syndrome experience severe tic symptoms. Approximately 46% of individuals with Tourette syndrome will experience a decrease in the frequency and severity of tics, and another 26% will experience a complete end of symptoms by late adolescence. Fourteen percent will have no change and 14% will have an increase in symptoms. There does not appear to be a definite correlation between the type, frequency, and severity of symptoms and the eventual prognosis. Patients with severe tics may experience social difficulties and may isolate themselves from others for fear of shocking and embarrassing them. People with Tourette syndrome who have other symptoms such as obsessive-compulsive disorder, attention-deficit disorder, and self-injurious behavior usually have a poorer prognosis.

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ORGANIZATIONS

National Institute of Neurological Disorders and Stroke (NINDS), PO Box 5801, Bethesda, MD 20824, (301) 496-5751, (800) 352-9424, <http://www.ninds.nih.gov>

Tourette Association of America, 42–40 Bell Blvd., Bayside, NY 11361, (718) 224-2999, (718) 279-9596, <http://www.tsa-usa.org>

Tourette Canada, 5945 Airport Rd., Suite 175, Mississauga ON Canada L4V 1R9, (800) 361-3120, (905) 673-2255, (800) 387-0120, (905) 673-2638, <http://www.tourette.ca>

Sonja Rene Eubanks, MS, CGC

Translation see **Chromosomal abnormalities**

Treacher Collins syndrome

Definition

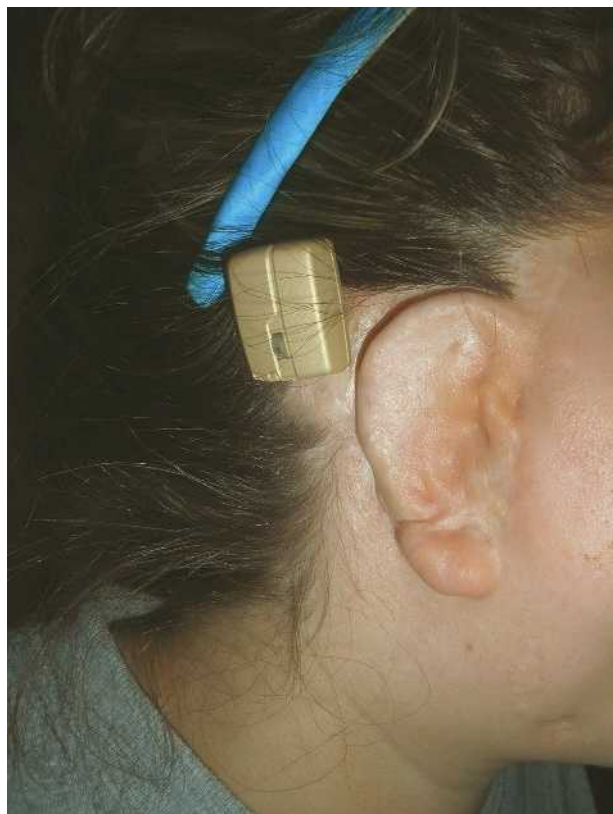
Treacher Collins syndrome (TCS) is a genetic disorder involving abnormal facial development. Individuals with TCS have underdevelopment of the jawbone, cheekbones, ears, and eye area. These features range widely from mild to severe. Intelligence and lifespan are usually normal.

Description

TCS was first described by E. Treacher Collins in 1900 after observation of two individuals with similar facial abnormalities. In 1949, Franceschetti and Klein gave TCS another name, mandibulofacial dysostosis. TCS is also sometimes called Franceschetti-Kleinsyndrome or Franceschetti syndrome.

The features of TCS result from a problem in early embryonic development. After an embryo forms, there are cells that are unspecialized and have the ability to develop into any type of cell in any part of the body (neural crest cells). Early in development, the neural crest cells travel to different areas of the embryo and specialize to become a specific type of cell for a specific organ or body part. The branchial arches are the areas where neural crest cells specialize to develop the bone structure and features of the face. In individuals with TCS there is thought to be an error in the movement of the neural crest cells to the branchial arches or in the specialization of those cells once they reach the branchial arches. The result is underdevelopment of the facial bones, eyes, and ears.

Individuals with mild features of TCS may go undiagnosed. Sometimes adults do not know they have TCS until they have a child with more noticeable features. This can cause feelings of guilt for the parent. Children with



The ear and hearing aid of Lidia DiFrancesco, a woman affected by Treacher Collins syndrome. She was born with no chin, cheekbones, or ears; she also had small, droopy eyes and her jaw was too far back. She was deaf, had no tear ducts, and could hardly breathe. She underwent 20 surgeries including rib grafts to create ears and a scalp graft to make cheekbones. (James Ambler/Barcroft Media/Getty Images)

KEY TERMS

Coloboma—An abnormality on the upper or lower eyelid that often gives the lid a droopy appearance.

Craniofacial—Relating to or involving both the head and the face.

Tracheostomy—An opening surgically created in the trachea (windpipe) through the neck to improve breathing.

more moderate to severe features of TCS look strikingly different and may be teased or shunned. These children are at risk for psychological stress and low self-esteem. Even adults with TCS who are productive and successful may battle issues of social stigma and low self-esteem regarding their facial differences.

Genetic profile

TCS is an autosomal dominant condition. Children of an affected parent have a 50% chance of inheriting the disorder. Males and females are affected equally. The severity of symptoms ranges widely, even among members of the same family. Therefore, the severity of a child's features cannot be predicted by the features of the affected parent.

About 40% of babies born with TCS have one affected parent. The other 60% are assumed to have a new, sporadic gene mutation (alteration). If a child has a new mutation (one that is not carried by the parents) then his or her siblings will have an extremely low chance of also having TCS. When a baby with TCS is born to seemingly normal parents, it is important to examine both parents carefully for mild features of TCS in order to give them accurate recurrence risks.

The gene for TCS is on chromosome 5 and is called *TCOF1*. This gene produces a protein that has been named treacle. Disease-causing *TCOF1* mutations result in absent or inactive treacle. The exact role of treacle is not known but it is thought to be involved in early embryo neural crest cell movement or specialization in the branchial arches.

Demographics

TCS is rare and affects an estimated 1 in 25,000 to 50,000 live births.

Signs and symptoms

TCS is described as a craniofacial condition because its features are all related to the head and face. The overall

head size may be smaller than average (microcephaly). The outer corners of the eyes slant downward. There may be colobomas on the lower eyelids, giving the lids a droopy appearance. The bridge of the nose is usually wide. Most individuals with TCS have underdeveloped cheekbones (malar bones), which give that area of the face a flat or sunken appearance. The lower jaw and chin are usually small and retroverted (jawbone points downward toward the neck instead of pointing out perpendicular to the neck). Many individuals also have a large mouth. Cleft palate (with or without cleft lip) is seen in one-quarter to one-third of patients with TCS.

Ear abnormalities are also common in TCS. The ears may be low-set, small, misshapen, or absent. For this reason, hearing loss or deafness is a common feature of TCS. The hearing loss is usually due to abnormalities in the middle ear structures rather than the outer ear structures.

Infants with moderate or severe malar bone underdevelopment may have compressed airways. These babies can have problems breathing after birth and may need a respirator or tracheostomy. A small, retroverted jaw and chin can cause feeding problems that may warrant a feeding tube.

The severity of features present at birth remains constant throughout life. TCS does not get progressively better or worse as an individual ages.

Diagnosis

The diagnosis of TCS is usually made by physical examination and identification of the typical facial features. Computerized tomography (CT) scans can be used to determine the degree of underdevelopment of the facial bone structure.

There are other syndromes that have facial appearances that resemble TCS. A complete physical examination of other body systems can help to establish a diagnosis of TCS. TCS can be distinguished from Nager syndrome and Miller syndrome if no abnormalities are present in the hands or arms. TCS can be distinguished from oculoauriculovertebral (OAV) conditions (for example, Goldenhar syndrome) because facial involvement is bilateral (affecting both sides of the face) and the spinal column is normal.

If there are several people in a family with TCS, genetic linkage studies can be performed. Linkage studies require blood samples from many family members, both affected and unaffected. Markers on the *TCOF1* gene are analyzed and compared to determine which gene version is shared by affected family members. The disease-causing gene should be present in all affected family members and absent from all unaffected members. Linkage studies can be performed on an unborn baby to

QUESTIONS TO ASK YOUR DOCTOR

- Do you have any suggestions regarding plastic surgery?
- At what specific points in my child's life should the surgeries be performed?
- What are the risks versus benefits of the surgeries?
- Do you recommend that my child undergo a hearing evaluation?

determine if the baby inherited the family's disease-causing gene. Prenatal ultrasound can also be used to look for facial features of TCS. While there have been reports of prenatal diagnosis of TCS with ultrasound only, babies with mild features may appear normal. Detection may also depend on the skill of the physician performing the ultrasound and his or her experience with features of TCS.

Treatment and management

Newborn infants with severe TCS may require a ventilator, tracheostomy, or feeding tube if life-threatening breathing or feeding problems exist. A cleft palate can be repaired with surgery. Hearing aids can help individuals with hearing loss.

For most individuals, the problems of TCS are largely cosmetic. Plastic surgery can help to rebuild the bone structure of the face, which may improve appearance as well as breathing and feeding. Surgeons can use bone grafts to build up the underdeveloped cheekbones. The jawbone can be "lengthened" and its angle repositioned. The bridge of the nose can be narrowed. Ears can be reconstructed using cartilage from the ribcage. Surgery can also be performed on the eye area.

This reconstruction may take multiple surgeries at different ages. Each individual must be evaluated for his or her unique features and needs. Surgeries are timed with facial growth and emotional needs and maturity of the patient.

Prognosis

A small percentage of newborns with TCS will have life-threatening breathing difficulties, and infant deaths can occur. However, the majority of individuals with TCS have a normal lifespan.

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ORGANIZATIONS

- FACES: The National Craniofacial Association, PO Box 11082, Chattanooga, TN 37401, (423) 266-1632, (800) 332-2373, faces@faces-cranio.org, <http://www.faces-cranio.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Amie Stanley, MS

Trichorhinophalangeal syndrome

Definition

Trichorhinophalangeal syndrome, or Langer-Giedion syndrome (LGS), is characterized by skeletal abnormalities and dysmorphic (distinctive) facial features. Most people with LGS also have intellectual disability.

Description

LGS affects mostly the skeletal system and facial structure. Since the features include abnormalities in the hair (tricho), nose shape (rhino), and fingers and toes (phalangeal), the technical name for LGS is trichorhinophalangeal syndrome.

Genetic profile

LGS is not usually passed through generations in a family. However, the condition is considered a contiguous-gene syndrome. This means that it is caused by the loss of functional copies of two genes near each other on chromosome 8. Research suggests that another gene may be involved. Genetic counseling is suggested for anyone considering pregnancy who has a relative with this condition.

Demographics

About 50 cases of Langer-Giedion syndrome have been reported in the literature. Males are affected three times more often than females.

Signs and symptoms

Craniofacial features associated with Langer-Giedion syndrome include a bulbous, pear-shaped nose; a small jaw; a thin upper lip; and large ears. The hair is usually sparse, and the head is small in 60% of individuals with LGS. Mild to severe intellectual disability is present in 70% of people; it often affects speech more than other skills.

Skeletal features include exostoses—spiny growths on the bone—which occur before age five and usually increase in number until the skeleton matures. Compression of nerves or blood vessels, asymmetric limb growth, and limitation of movement are problems that can result from the exostoses. Scoliosis—a curvature of the spine—is found in some people, as well as thin ribs. Short stature is often seen as a result of epiphyses—cone-shaped bone ends. Longitudinal bone growth appears to be slowed. Short and/or curved fingers are common. Loose skin often occurs, but that tends to improve with age.

Features of LGS that are less commonly seen include loose joints and low muscle tone. Others are wandering eye (exotropia), droopy eyelid, widely spaced eyes, fractures in the bones, birthmarks that increase with age, hearing loss, heart or genito-urinary abnormalities, and webbing of the fingers.

Diagnosis

The criteria for diagnosis of LGS are a bulbous, pear-shaped nose and epiphyses and exostoses. These signs are probably all related to abnormal bone growth, but researchers do not yet understand the link to intellectual disability and hair abnormalities. The distinctive facial features may be recognized at birth. Changes in the epiphyses are recognizable through x-ray by age three, and exostoses are visible by age five. Chromosome

KEY TERMS

Contiguous gene syndrome—A genetic syndrome caused by the deletion of two or more genes located next to each other.

Craniofacial—Relating to or involving both the head and the face.

Epiphysis—The end of long bones, usually terminating in a joint.

Exostose—An abnormal growth (benign tumor) on a bone.

Intellectual disability—Significant impairment in intellectual function and adaptation in society. Usually associated with an intelligence quotient (IQ) below 70.

Philtrum—The center part of the face between the nose and lips that is usually depressed.

Short stature—Shorter than normal height; can include dwarfism.

analysis will likely reveal an abnormality in a certain region of chromosome 8.

There are no reports of prenatal diagnosis of this condition. To provide accurate genetic counseling regarding prognosis and risk of recurrence, it is important to distinguish this condition from others that are similar to it, such as trichorhinophalangeal syndrome, type 1.

Treatment and management

The treatment for LGS is tailored to each person. Exostoses may need to be surgically removed if they are causing problems with nerves or blood vessels. If the two leg lengths are different, corrective shoes may be helpful. Orthopedic devices such as braces or, more rarely, surgery may be indicated in severe cases of skeletal abnormality. Plastic surgery to alter specific features, such as the ears or nose, has been chosen by some people.

The risk of cancer at the site of the exostoses is not known but may be higher.

Special education for mentally retarded individuals is indicated. A focus on speech development may be appropriate.

Prognosis

Langer-Giedion syndrome does not alter lifespan. Complications from associated abnormalities such as intellectual disability, however, can cause problems. Asymmetry of the limbs can interfere with their function

and cause pain. Psychological effects due to physical abnormalities may also be experienced.

Resources

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ORGANIZATIONS

National Institute on Deafness and Other Communication Disorders, 31 Center Dr., MSC 2320, Bethesda, MD 20892, (301) 496-7243, (301) 402-0018, nidcdinfo@nidcd.nih.gov, <http://www.nidcd.nih.gov>

Trichorhinophalangeal Syndrome Association (TRPSA), 6585 Dawn Way E, Inver Grove Heights, MN 55076, (651) 450-0788, TRPSA@comcast.net, http://trpsa.org/trpsa_wp

Amy Vance, MS, CGC

Triosephosphate isomerase deficiency

Definition

Triose phosphate isomerase (TPI) deficiency is a rare non-sex-linked (autosomal) disorder that is a result of an insufficient amount of the enzyme triose phosphate isomerase. This disorder is inherited as an autosomal recessive trait and is known to be caused by homozygous or compound heterozygous mutations in the *TPII* gene.

Description

Triose phosphate isomerase is an enzyme involved in the breakdown of glucose into the energy required to sustain cellular metabolism. Glucose is first converted into

the chemical pyruvate. Pyruvate then enters the tricarboxylic acid cycle (TCA cycle) to produce ATP, the chemical form of energy used by the cells. Glucose is broken down to the chemical pyruvate via a chemical pathway that involves 10 enzymes. TPI is the fifth enzyme in this reaction chain. The two major products of the reaction proceeding the TPI reaction are D-glyceraldehyde-3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP). These two chemicals are isomers, which means that they have the same chemical formulas but different chemical structures. TPI is the enzyme that converts DHAP into GAP. This conversion (isomerization) is important because only GAP is used in the subsequent steps in the reaction pathway to the essential pyruvate molecules.

Under normal physiological conditions, DHAP is produced in much greater quantities than GAP (approximately 20:1). Therefore, it is essential that TPI convert the DHAP to GAP to increase the overall efficiency of pyruvate production from glucose. Individuals affected with TPI deficiency have extremely low levels of TPI activity because the enzyme that they do produce is not properly formed and, thus, is highly inefficient.

Genetic profile

The gene that is responsible for the production of TPI has been localized to a region on chromosome 12. There are many different mutations in this gene that lead to TPI deficiency. In every case, very slight changes in the chemical structure of TPI occur such that the TPI produced is less effective than a normal TPI molecule, especially when the body is hot, either from the weather or from exercise.

Demographics

TPI deficiency is extremely rare. As of 2015, approximately 40 cases had been reported. The documented rarity of this disorder does not seem to coincide with the observed frequency of reduced TPI activity in the population.

In a 1996 study of unselected individuals of Caucasian and Japanese descent, a Japanese researcher found that approximately 5 out of every 1,000 individuals had TPI activity that was only half of the normal TPI activity. In a separate study, it was estimated that 9 in 1,713 Caucasians and 7 in 168 African Americans showed these low levels of TPI activity. One possible explanation is that complete TPI deficiency is an embryo-lethal condition. In other words, if complete TPI deficiency is inherited at conception, the embryo is miscarried before the mother even knows that conception has occurred.

All of the mutations in the gene responsible for the production of TPI are expressed as recessive traits. This

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Thermolabile—Heat-sensitive. A thermolabile protein is a protein that easily loses its shape when heated even only slightly.

Transversion—A genetic term referring to a specific substitution of one base pair for another. There are only four possible transversions: guanine for cytosine, cytosine for guanine, adenine for thymine, or thymine for adenine.

Triose phosphate isomerase—Abbreviated TPI, this is the enzyme responsible for the conversion of dihydroxyacetone phosphate (DHAP) into D-glyceraldehyde-3-phosphate (GAP). DHAP and GAP are the two major products of a step in the multi-step process that converts glucose into ATP to supply the body with the energy it needs to sustain itself. Only GAP can continue in this process, but DHAP is produced in much higher quantities. People with TPI deficiency cannot change DHAP into GAP as efficiently as unaffected people, resulting in insufficient amounts of ATP from glucose to maintain normal cell function.

means that a child will inherit a mutation on the TPI1 gene from both parents. Also, if one child has been born affected with TPI deficiency, the likelihood that a second child of the same parents will also be affected is 25%.

Signs and symptoms

TPI deficiency affects primarily the circulatory and nervous systems. Disorders of the circulatory system include at least four separate forms of anemia (a lack of properly functioning red blood cells) that cause a lack of oxygen transport to the tissues and organs of the body. Disorders of the neurologic system include developmental delay and degenerative neurologic disorder with spasticity, a condition in which the nervous system progressively degenerates and the affected person suffers from spasticity similar to that seen in people with multiple sclerosis. Because of the malformations of the red blood cells in TPI deficiency affected individuals, the liver, the organ that is responsible for cleaning the blood, often becomes overworked. This causes jaundice (an

QUESTIONS TO ASK YOUR DOCTOR

- What supportive measures can I offer my child?
- Have there been any advancements in transfusion research?
- How feasible is an enzyme replacement?
- How often should my child's blood be tested?

abnormal yellowing of the skin and the whites of the eyes). Heart failure is also quite common and is often the cause of death in TPI deficiency patients.

People affected with TPI deficiency are generally highly susceptible to recurrent infections. This tendency is believed to be due to a depression of the immune system caused by improper blood function.

Diagnosis

If a family history of the disease leads to suspicion, TPI deficiency can be detected prenatally by a test of umbilical cord blood. A device recognized by the Food and Drug Administration is available to measure the activity of TPI on red blood cells taken in a sample. This device provides a definitive test for TPI deficiency. A blood test indicating extremely elevated levels of DHAP is also indicative of TPI deficiency.

Another blood test that can be performed is an autohemolysis test. This test allows TPI deficiency to be differentially diagnosed from certain other enzymatic deficiencies. In this test, samples of blood are drawn and incubated at body temperature for 48 hours. After this time, the amount of breakdown of the red blood cells is recorded. One sample is left untreated, one sample has added glucose, and a third sample has added ATP. If the untreated sample shows higher than normal breakdown of the red blood cells but those samples treated with glucose or ATP show a lessened breakdown of red blood cells, this is indicative of TPI deficiency. If glucose, but not ATP, slows the breakdown of the red blood cells, this indicates a diagnosis of G6PD deficiency. If ATP, but not glucose, slows the breakdown of the red blood cells, this indicates a diagnosis of pyruvate kinase deficiency. G6PD and pyruvate kinase are two other enzymes involved in the breakdown of glucose to pyruvate to ATP.

Treatment and management

No treatment is currently available for TPI deficiency. Studies are ongoing to determine the feasibility

of bone marrow transplants and enzyme replacement therapies. In 1999, TPI deficiency was corrected in a four-year-old boy by an enzyme replacement blood transfusion treatment. However, due to the temporary nature of the observed corrections in the biochemistry, it was concluded that a sustained reversal of the symptoms of TPI deficiency would require a continuous delivery of an active form of the TPI enzyme.

Prognosis

Individuals with TPI deficiency generally do not live past childhood. Enzyme replacement therapy and/or bone marrow transplantation may eventually prove to be effective means of treating TPI deficiency and improve survival rates for this rare genetic disorder.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

Paul A. Johnson
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Triple X syndrome

Definition

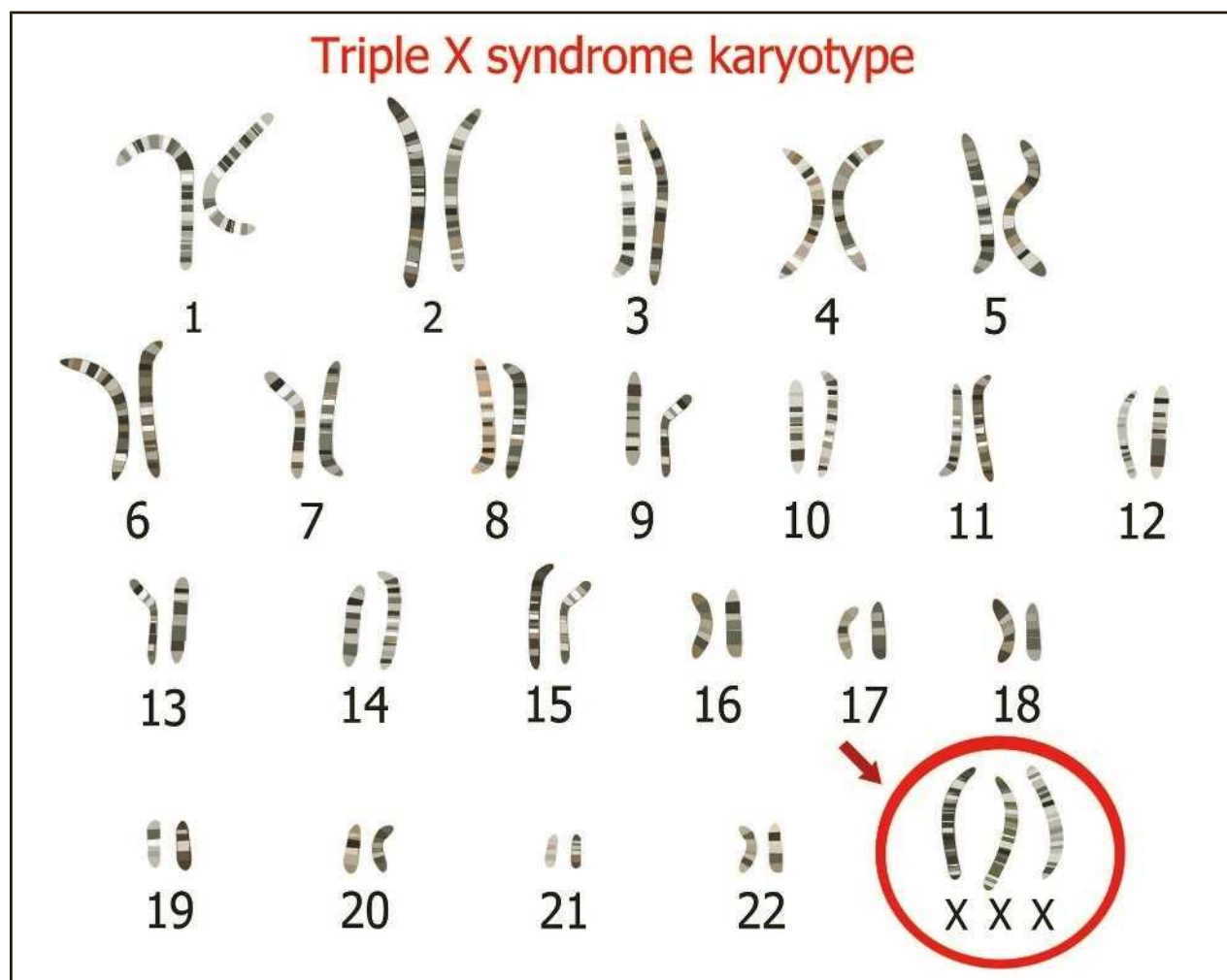
Triple X syndrome is a chromosomal disorder resulting from the presence of an extra X chromosome that can cause mild learning disabilities, tall statures, and psychiatric problems. Many women with triple X syndrome have no symptoms or complications from this condition.

Description

Triple X syndrome is also called triplo-X syndrome, trisomy X, XXX syndrome, and 47,XXX syndrome. Many women with this syndrome have no physical characteristics or intellectual differences because of it. Others have very mild differences, and a small minority of women with triple X syndrome can have more pronounced symptoms and signs of this condition.

Learning disabilities are more common in girls with triple X than in the general population. Women with triple X syndrome have an average IQ in the 85–90 range, compared to normal IQ of about 100. However, there is considerable variability in cognitive abilities, including IQs above normal for some affected girls. Many children with triple X require speech therapy in childhood, and they may reach both speech and motor milestones slightly later than their unaffected siblings. In adolescence, psychological problems such as depression or conduct disorder may be somewhat more common in girls with triple X, although this may be due to the environment in which the girls live more than the physical effects of triple X syndrome.

Triple X is not associated with abnormal physical characteristics, although girls with triple X are slightly taller (by approximately 4 inches, on average) than their siblings. Triple X is associated with normal puberty and fertility, and women with this condition are not at an increased risk to have children with chromosome



Human karyotype of Triple X syndrome. (Zuzana/Shutterstock)

abnormalities. Premature ovarian failure has been reported in some women with triple X syndrome.

Genetic profile

Triple X syndrome is caused by the presence of an extra X chromosome. Chromosomes are packages of genetic information that are present in every cell of the body. They come in pairs and humans have a total of 46 chromosomes, arranged into 23 pairs. The first 22 pairs of chromosomes are called “autosomes” and are numbered 1 to 22, from largest to smallest. The 23rd pair is called the “sex chromosomes.” Females typically have two X chromosomes (46,XX), and males have one X chromosome and one Y chromosome (46,XY). Triple X syndrome results from an extra copy of the X chromosome in each of a female’s cells. As a result of the extra X chromosome, each cell has a total of 47 chromosomes (47,XXX) instead of the usual 46. Women with triple X syndrome have three X chromosomes for a total of 47 chromosomes. Triple X syndrome occurs when there is an error in chromosome division, called nondisjunction, that occurs before conception in either the mother’s egg or the father’s sperm. This error occurs randomly; Triple X syndrome is not an inherited disorder.

Demographics

Approximately 1 in 1,000 women has triple X syndrome. This condition is underdiagnosed because of a lack of identifiable physical features. Only women are affected by triple X syndrome.

Signs and symptoms

The symptoms of this condition include the following:

- tall stature
- learning disabilities
- motor delays
- speech and language delay
- premature ovarian failure
- psychological problems

Diagnosis

Tests

Triple X syndrome is diagnosed by karyotype testing. A karyotype is a chromosome analysis that can be done on a blood sample or tissue obtained via prenatal diagnosis testing. A karyotype looks at the structure and number of a person’s chromosomes. The diagnosis of triple X syndrome is made if an extra X chromosome is present.

KEY TERMS

Chromosome—Organized package of genetic information contained in every cell of the human body. Most people have 46 chromosomes. Individuals with triple X syndrome have an extra X chromosome and 47 chromosomes total.

Karyotype—A karyotype is a picture of all the chromosomes from an individual’s cells. A karyotype also is a test used to check for chromosome abnormalities and is the diagnostic test for triple X syndrome.

Nondisjunction—An error in chromosome separation that occurs during cell division resulting in a woman receiving an extra X chromosome, leading to triple X syndrome.

Trisomy—The occurrence of an extra chromosome in a human. Women with triple X syndrome have an extra X chromosome. This is sometimes written as 47,XXX.

Most cases of triple X syndrome are diagnosed during pregnancy in mothers who have elected to have prenatal testing such as amniocentesis or chorionic villus sampling (CVS) for reasons unrelated to triple X syndrome. Prospective parents should meet with a geneticist or genetic counselor to discuss the diagnosis of triple X syndrome if this condition is diagnosed during a pregnancy. Because of its lack of physical findings and mild symptoms, triple X syndrome is underdiagnosed in the general population.

Treatment and management

Traditional

Because of the possible psychiatric issues and learning disabilities children with triple X syndrome may experience, it is important that girls with triple X syndrome be raised in a stable and supportive environment. The symptoms of this condition—especially learning disabilities and psychiatric problems—should be treated promptly.

There is no cure for triple X syndrome and treatment is based upon symptoms. The therapies for the symptoms of triple X syndrome are no different than the therapies that someone without triple X syndrome, but with the same symptoms, would receive. Individuals with symptoms due to triple X syndrome may receive speech therapy for speech delay, physical therapy for motor problems, and treatment for learning disabilities. In addition, they may receive treatment and counseling for psychiatric conditions if they develop this complication.

QUESTIONS TO ASK YOUR DOCTOR

- What are the karyotype results?
- What does this mean for my child?
- What should I do for my child?

Prognosis

The prognosis for women with triple X syndrome is very good. They live a normal lifespan and there are no physical abnormalities or intellectual disabilities associated with this condition.

Resources

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ORGANIZATIONS

- Chromosome Disorder Outreach, PO Box 724, Boca Raton, FL 33429, (561) 395-4252, info@chromodisorder.org, <http://www.chromodisorder.org>
- Unique: Understanding Chromosome Disorders, The Rare Chromosome Disorder Support Group, G1 The Stables, Station Rd. W, Oxted, Surrey, UK RH8 9EE, 144 (0)1883 723356, info@rarechromo.org, <http://www.rarechromo.org>

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Triploidy

Definition

Triploidy is a rare, lethal chromosome abnormality caused by the presence of an entire extra set of

chromosomes. A fetus with triploidy has 69 chromosomes, rather than 46. The majority of fetuses with triploidy are spontaneously miscarried during pregnancy. Those that survive until birth will have severe growth retardation and multiple birth defects.

Description

Triploidy is a condition caused by having a full extra set of chromosomes. This extra set of chromosomes causes a variety of serious birth defects, placental problems, and severe growth problems in a fetus. In fact, most pregnancies in which the fetus has triploidy end in a spontaneous miscarriage. Very few infants with triploidy survive to term. Of those that do, most are stillborn and those that are born alive usually die shortly after birth. Infants with this lethal condition are generally small due to severe intrauterine growth retardation (IUGR) and they have multiple birth defects, including facial abnormalities, such as cleft lip, heart defects, neural tube defects (spina bifida), and other serious birth defects. The exact pattern of abnormalities depends on whether the extra set of chromosomes was inherited from the mother or from the father. Unfortunately, there is nothing that can be done to treat or cure triploidy.

Genetic profile

Triploidy is a chromosomal disorder. Chromosomes are the structures that contain all of the body's genes (the basic unit of inheritance). Humans have 46 chromosomes in every cell of their body, with the exception of their sperm and egg cells, which contain only 23 chromosomes. When a sperm and an egg unite at conception, the resulting fertilized egg will have 46 chromosomes: half from the mother and half from the father. This fertilized egg will continue to develop and grow into a fetus and, eventually, into a live-born infant with 46 chromosomes in every cell of his or her body.

Of these 46 chromosomes, 22 pairs (or 44 chromosomes) are called autosomes (or nonsex chromosomes) and the twenty-third pair is the sex chromosomes. Women have two X chromosomes (46,XX) and men have an X and Y chromosomes (46,XY). Fetuses with triploidy can be 69,XXX (female), 69,XXY (male), or 69,XYY (male). Twenty-three chromosomes (or one set) are referred to as a haploid set of chromosomes, forty-six chromosomes (or two sets) are referred to as a diploid set of chromosomes, and sixty-nine chromosomes (or three sets) are referred to as a triploid set of chromosomes. A fetus with triploidy has three haploid sets of chromosomes.

Triploidy occurs in several different ways. The extra set of chromosomes can be inherited from the father

(paternal inheritance) or they can be from the mother (maternal inheritance). The most common mechanism for triploidy is the fertilization of a single egg by two sperm. This results in a triploid egg with two sets of paternal chromosomes and one set of maternal chromosomes. This accounts for about 60% of cases of triploidy. The other mechanism is an error in cell division in which an egg cell ends up with 46 chromosomes instead of 23. This egg with 46 chromosomes is fertilized by a sperm with 23 chromosomes, resulting in a fertilized egg with 69 chromosomes, which then has two sets of maternal chromosomes and one set of paternal chromosomes. This mechanism is responsible for about 40% of cases of triploidy. The physical effects of triploidy differ depending on whether the extra set of chromosomes was inherited from the mother (maternally inherited) or from the father (paternally inherited).

In pregnancies in which the extra set of chromosomes is maternally inherited, the fetuses tend to be well formed, with a small head (microcephaly). The placenta in these pregnancies is generally enlarged and cystic (filled with cysts). This type of placenta is often referred to as a hydatiform mole and the pregnancy as a whole may be referred to as a partial molar pregnancy. In pregnancies in which the extra set of chromosomes is paternally inherited, the fetuses have severe growth retardation, a large head, and a small, noncystic placenta.

The physical birth defects seen in triploidy are variable. All fetuses will have some of these birth defects, but very few will have all of them. The birth defects most commonly seen are heart defects, cleft lip, neural tube defects, kidney malformation, abnormal genitalia (males), and defects in the abdominal wall. Regardless of the presence or absence of these birth defects, triploidy is incompatible with life.

Triploidy is a sporadic (or accidental) event. It is not caused by anything that a parent may or may not have done. Unlike some other chromosome abnormalities (trisomy 21 or Down syndrome), triploidy is not associated with a mother's age. This means that there is not an increased risk for triploidy in an older woman's pregnancy. Because triploidy is an accidental event, there is no increased recurrence risk in future pregnancies. A woman who has had one triploid pregnancy is not at any increased risk to have a second one.

Demographics

Triploidy occurs in about 1%–2% of all conceptions, but most of these pregnancies end in early spontaneous miscarriage. Very few pregnancies with a triploid infant go to term. Only 1 in 10,000 infants is born with triploidy, and it is estimated that for every live-born infant

with triploidy, 1,200 have been lost as miscarriages. Most infants with triploidy are either stillborn or die shortly after birth. The longest recorded lifespan of an infant with full triploidy is 10 months, although this length of survival is extremely rare.

There is a milder form of triploidy that is the result of mosaicism, which is the presence of two separate types of cells within the same individual. Infants with mosaic triploidy have both a normal cell line (46,XX or 46,XY) and a triploid cell line (69,XXX or 69,XXY or 69,XYY). These infants can survive to be live born, but they generally have growth retardation, growth asymmetry (their limbs may be different sizes), some of the other birth defects seen in full triploidy, and severe intellectual disability. It is thought that the presence of the normal cell line aids in survival.

Signs and symptoms

Triploidy manifests itself in many different ways. It can be diagnosed both prenatally and at birth.

The diagnosis of triploidy is often made prenatally or during the course of a pregnancy. The diagnosis is often suspected because of an abnormal sonogram or because of an abnormal maternal serum screening test.

A sonogram, or ultrasound, is a common test done during pregnancy that uses sound waves to examine the fetus. There is no known risk to the fetus from an ultrasound. However, a fetus affected with triploidy will often show abnormalities that will warrant further testing to confirm the diagnosis of triploidy. Some of the most common abnormalities seen on a sonogram of a fetus with triploidy include severe growth problems or intrauterine growth retardation (IUGR), an abnormal placenta, and limb abnormalities.

Not every fetus with triploidy will have all of these findings, but most will show some signs that can be detected by sonogram. Abnormal sonogram findings include:

- severe early-onset intrauterine growth retardation (detected as early as 12 to 14 weeks)
- brain abnormalities, including isolated ventriculomegaly (enlarged ventricles), Arnold-Chiari malformation, holoprosencephaly, and agenesis of the corpus callosum
- cleft lip and possible cleft palate
- limb abnormalities, such as clubfoot or syndactyly (webbing of the fingers and toes)
- heart defects
- kidney abnormalities

- abdominal wall defects, such as an omphalocele (an opening in the abdominal wall, which causes the intestines to be located outside the body)
- neural tube defects, such as spina bifida (an opening in the spinal cord)
- oligohydramnios (a decreased amount of amniotic fluid)
- placental abnormalities, including an enlarged placenta or a cystic placenta

In addition to detection by prenatal sonogram, many fetuses with triploidy are detected by an abnormal maternal serum screening test. A maternal serum screening test is a voluntary blood test usually performed in the second trimester of pregnancy. It is not specifically designed to detect triploidy, but often does because of some of the abnormalities seen in triploidy. The blood test measures the amount of certain proteins in the mother's blood. These proteins, alpha-fetoprotein, human chorionic gonadotropin (hCG), and estriol, are all made either by the fetus or by the placenta. These proteins cross the placenta and get into the mother's blood system. By looking at the amount of these proteins present in the mother's blood system, it is possible to screen for certain genetic abnormalities. Because fetuses with triploidy often have abnormal placentas, too much or too little of these proteins are leaked into the mother's system and the blood test results are often abnormal. If a maternal serum screening test is abnormal, the patient should be offered a detailed ultrasound and amniocentesis.

Both prenatal sonograms and maternal serum tests are screening tests. They can pick out individuals with a higher risk to have a fetus with a specific disorder, but they cannot actually give a specific diagnosis. Because of this, if an individual has an abnormal screening test, further diagnostic testing is indicated.

The only way to definitively diagnose triploidy is to have a chromosome analysis (karyotype) done and actually count the number of chromosomes present. In order to do a chromosome analysis during pregnancy, it is necessary to obtain some tissue from the fetus. This is commonly done through either a chorionic villus sampling (CVS) test or through an amniocentesis. During a CVS test, a catheter is used to remove a small piece of tissue from the placenta. Since the placenta and fetus have come from the same fertilized egg, the chromosomes in the placenta are the same as the chromosomes in the fetus. A CVS test is usually done between 10 and 12 weeks of pregnancy. If a patient is further along in the pregnancy when an abnormality is suspected, an amniocentesis may be performed. This test is usually done between 16 and 18 weeks of pregnancy. It involves using a needle to remove some of the amniotic fluid from around the fetus. The amniotic fluid contains fetal skin cells, which

KEY TERMS

Diploid—Two sets of chromosomes; in humans, this is 46 chromosomes.

Haploid—One single set of chromosomes; in humans, this is 23 chromosomes.

Triploid—Three sets of chromosomes; in humans, this is 69 chromosomes.

can then be cultured (grown) and analyzed. The results from these tests can take between one and two weeks. By doing a fetal karyotype (counting the number of chromosomes the fetus has), it is possible to definitely diagnose triploidy. A newer technique, fluorescent in situ hybridization (FISH), is available in some laboratories and results may be available in as little as 24 hours. It is always wise to do a complete karyotype in addition to FISH testing.

Very few fetuses survive to be born to term with triploidy. Those infants that survive do show a very specific pattern of birth defects. Almost all of these infants will have growth retardation and characteristic facial features, including wide-set eyes (hypertelorism), low-set ears, and limb abnormalities, such as clubfoot and syndactyly (webbing of the fingers and toes). Other anomalies include heart defects, kidney malformations, and genital malformations (particularly in males). Once triploidy is suspected in an infant, a blood chromosome analysis (a karyotype) should be performed to confirm the diagnosis. Additionally, the newer technique, FISH, is advised.

Diagnosis

The diagnosis is often suspected in pregnancies due to abnormal growth parameters, abnormalities seen on a sonogram, an abnormal screening test, or an abnormal CVS or amniocentesis result.

The diagnosis in infants is made by physical examination shortly after birth. Severe growth retardation, an abnormal placenta, and physical birth defects first raise the suspicion of triploidy. This diagnosis is then confirmed through a chromosome analysis (karyotype), which is a blood test performed on the infant. A karyotype is a picture of an individual's chromosomes and in this case will show an abnormal number of chromosomes (69 instead of 46).

The diagnosis in infants with the rare mosaic form of triploidy (one normal cell line and one abnormal cell line) may be suspected shortly after birth due to the presence of growth retardation, asymmetrical growth of the limbs,

and other physical birth defects. The diagnosis is then confirmed through a chromosome analysis (karyotype), which, in this case, will show the presence of two cell lines: one normal cell line with 46 chromosomes and an abnormal cell line with 69 chromosomes.

Treatment and management

There is no cure and no treatment for triploidy. Infants that survive to term should receive palliative care, including warmth, nourishment, and comfort, until the parents have a chance to incorporate the diagnosis and make decisions about care options. Surgical correction of birth defects is not indicated given the lethal nature of this diagnosis.

If triploidy is detected during a pregnancy, patients have the option to terminate a pregnancy based upon the lethality of this condition. This is a very personal decision and should be made following complete counseling about the nature and outcome of this diagnosis. If the pregnancy continues, then the mother should be monitored for preeclampsia and hyperthyroidism. There is no need for special interventions, such as fetal monitoring or a caesarean section, based solely on the diagnosis of triploidy given the inevitability of the outcome.

Once the diagnosis has been firmly established, there is no need for heroic measures given the established lethality of the conditions. Infants should be provided with basic supportive care until the family can make decisions.

This diagnosis is devastating for families. The bleak prognosis and lack of treatment can be very shocking. Families should be reassured that there is nothing that they did or did not do that could have prevented the outcome. While grieving is inevitable and appropriate, the family needs time to incorporate the information about the diagnosis. Many families find it helpful to have reminders of their baby, including footprints, photographs, and locks of hair, and the neonatal staff can aid in collecting these materials following the birth of the infant. Parents also need to understand the genetic diagnosis and its implications for future pregnancies. It is important to make sure that they understand the sporadic nature of this diagnosis and that it is unlikely to recur in a future pregnancy.

Prognosis

The prognosis for a fetus or infant with full (non-mosaic) triploidy is very bleak. Many pregnancies end in spontaneous abortion, and those that go to term often result in a stillborn infant or one that dies shortly after birth. The longest recorded survival of an infant with

triploidy is 10 months, although this length of survival is exceedingly rare.

Infants with mosaic triploidy (two cell lines: one normal and one with triploidy) often survive pregnancy but generally have multiple birth defects, severe growth abnormalities, and severe intellectual disability. Their life expectancy is often dependent on the severity of their associated birth defects.

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ORGANIZATIONS

Compassionate Friends, PO Box 3696, Oak Brook, IL 60522, (630) 990-0010, (877) 969-0010, (630) 990-0246, <https://www.compassionatefriends.org>

Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

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Trismus-pseudocamptodactyly syndrome

Definition

Trismus-pseudocamptodactyly syndrome is a rare genetic condition characterized by the inability to completely open the mouth (trismus), difficulty chewing, short stature, and abnormally short muscle-tendon units in the fingers that cause the fingers to curve or bend when the hand is bent back at the wrist (pseudocamptodactyly).

KEY TERMS

Contracture—A tightening of muscles that prevents normal movement of the associated limb or other body part.

Pseudocamptodactyly—A condition in which the fingers curve or bend when the hand is bent back at the wrist.

Trismus—Inability to open the mouth completely.

Other names for this syndrome are Hecht syndrome and arthrogryposis, distal type 7.

Description

Trismus-pseudocamptodactyly syndrome was first described by pediatrician/geneticist Frederick Hecht and orthopedist Rodney K. Beals of the Oregon Health Sciences University in 1969 as inability-to-open-the-mouth-fully syndrome. Explaining the first descriptive name for the syndrome, individuals affected by trismus-pseudocamptodactyly syndrome cannot fully open the mouth (trismus). In addition, affected individuals are unable to bend their fingers when their wrist is extended (pseudocamptodactyly). The muscles and tendons in the forearms and/or the legs may also be abnormally short, resulting in limited movements and various deformities of the feet, including clubfoot, hammer and claw toes, and tightening of the muscles of the posterior part of the leg, producing other multiple foot abnormalities. The severity of the physical findings in trismus-pseudocamptodactyly syndrome varies from individual to individual.

Trismus-pseudocamptodactyly syndrome is also known as Dutch-Kennedy syndrome, camptodactyly-limited jaw excursion, Hecht syndrome, inability to open mouth completely and short finger-flexor, Hecht-Beals-Wilson syndrome, distal arthrogryposis, and Hecht-Beals syndrome.

Genetic profile

Trismus-pseudocamptodactyly syndrome is a rare condition inherited in an autosomal dominant pattern. In an autosomal dominant condition, only one copy of the mutated, or nonworking, gene for a particular condition is necessary for a person to experience the symptoms associated with the condition. Accordingly, most individuals with an autosomal dominant condition have one working copy and one nonworking copy of the gene for the disorder. Individuals contribute only half of their genetic

information to their children and pass on only one copy of each gene. As a result, there is a 50% chance for a person with trismus-pseudocamptodactyly syndrome to pass on the nonworking gene for that condition and have a child affected with trismus-pseudocamptodactyly syndrome. There is also a 50% chance that a person with trismus-pseudocamptodactyly syndrome will pass on the working gene and have a child unaffected by trismus-pseudocamptodactyly syndrome. Individuals in the same family who inherit the nonworking copy of the gene causing trismus-pseudocamptodactyly syndrome can be affected in different manners and with different symptoms. Symptoms of trismus-pseudocamptodactyly syndrome present in a variety of mild to severe features (variable expressivity). However, in trismus-pseudocamptodactyly syndrome, a high percentage of individuals who inherit the abnormal gene will have some sign of the disorder (high penetrance).

The cause of trismus-pseudocamptodactyly syndrome is related to mutations in the *MYH8* gene (perinatal myosin heavy-chain gene) on the short arm of chromosome 17 (17p13.1).

Demographics

Trismus-pseudocamptodactyly syndrome is a rare condition affecting both men and women equally. It was originally described in a Dutch family and believed to only occur in Dutch families or the descendants of Dutch families in West Virginia. Since the original families were identified, families of other ethnic backgrounds, including Canadians, Taiwanese, and Japanese, have been found to be affected. Accordingly, it is believed that trismus-pseudocamptodactyly syndrome can occur in any race or ethnic background.

Signs and symptoms

Individuals affected by trismus-pseudocamptodactyly syndrome classically present with two main features: limited excursion of the mandible (trismus) and flexion deformity of the fingers that occurs with wrist extension (pseudocamptodactyly). At birth, trismus-pseudocamptodactyly syndrome may be diagnosed based on the infant's clenched fists and inability to fully open its mouth. Additional features include short stature and foot malformations caused by short muscle-tendon units, which prevent normal growth and development. The forms of foot abnormalities caused by short muscle-tendons in the hamstrings, calves, and feet include malformations that occur when the foot is turned inward and downward (equinovarus or talipes equinovarus), inward bending for the front half of the foot (metatarsus varus), and angling foot at the heel with the toes pointing upward and outward (calcaneovalgus

deformity). Different family members who have inherited the same mutated, or nonworking, gene can have symptoms that range from very mild to very severe.

Diagnosis

Diagnosis of trismus-pseudocamptodactyly syndrome is made through a detailed physical exam, medical history, and family history, most often performed by a medical genetics team. Clinical genetic testing is available at this time for *MYH8* mutations.

Treatment and management

The treatment and management of trismus-pseudocamptodactyly syndrome depends on the severity of the symptoms. Most individuals are treated with a combination of physical therapy, speech therapy, occupational therapy, and surgery.

An infant's inability to fully open its mouth can cause severe difficulties with feeding, adequate calorie intake, speech development, and dental care. Speech and physical therapy are recommended to help address jaw issues. Jaw surgery may be necessary to open an infant's jaw for nourishment. The clenched fists found in many infants affected by trismus-pseudocamptodactyly syndrome can cause difficulties in learning to crawl and grasp items. Often infants will learn to crawl on their knuckles. The clenched fists involved with pseudocamptodactyly may also impair manual dexterity and cause occupational disability that requires physical and occupational therapy or surgery. Contractures due to the short muscle-tendons may result in foot abnormalities that, like clenched fists, may delay milestones. Affected infants may require surgical correction of contractures and foot abnormalities in order to walk.

Adults affected by trismus-pseudocamptodactyly syndrome continue to have issues with inability to open their mouths fully, short muscle-tendons, and foot anomalies. Although many individuals pursue surgical options, there is no consensus on the optimal treatment. In one report, endoscopic surgery to release the jaw in one patient resulted in recurrence three months postoperatively. Another technique that had some success was a passive stretching of the mouth with tongue blades. Early treatment of trismus can prevent or minimize many of the conditions. Passive motion, applied several times per day, has been shown to be more effective than static stretching for keeping short muscle-tendons supple. Recent research has shown that passive motion provides significant reduction in inflammation and pain. Ongoing physical therapy and stretching of contractures caused by short muscle-tendons may help maintain optimal muscle length over

QUESTIONS TO ASK YOUR DOCTOR

- Which medical specialists does my child need to see to help with feeding difficulties?
- When will surgery be considered for my child?
- What type of therapy will my child need?
- What are the chances of having another child affected with trismus-pseudocamptodactyly syndrome?

time, allowing improved range of motion and preventing relapse after surgery.

General anesthesia and muscle relaxants do not relieve the trismus or increase the jaw's opening. Since an open mouth is necessary to intubate in the traditional manner, general anesthesia for any surgery can be difficult and hazardous. Several reports on intubation techniques are found in the anesthesia literature that recommend techniques such as avoiding muscle relaxants and using fiberoptic-assisted nasotracheal intubation, blind nasotracheal intubation, or mask anesthesia with spontaneous ventilation to assess the delivery of anesthesia and surgery. During all surgical procedures, it is recommended that a surgeon experienced in obtaining an emergency surgical airway be available.

Prognosis

Most individuals with trismus-pseudocamptodactyly syndrome can achieve a mouth opening large enough for food and speech, and a sufficient range of motion in their affected joints to live healthy, complete lives. In many individuals, physical therapy and stretching of contractures caused by short muscle-tendons may help maintain optimal muscle length, allowing improved range of motion and quality of life. However, the severe contractures and pseudocamptodactyly that appear in some individuals affected by trismus-pseudocamptodactyly syndrome may impair manual dexterity and cause occupational disability that places physical restrictions.

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ORGANIZATIONS

About Face, 1057 Steeles Ave. W, PO Box 702, North York ON Canada M2R 3X1, (416) 597-2229, (800) 665-3223, (416) 597-8494, info@aboutface.ca, <http://www.aboutface.ca>

FACES: The National Craniofacial Association, PO Box 11082, Chattanooga, TN 37401, (423) 266-1632, (800) 332-2373, faces@faces-cranio.org, <http://www.faces-cranio.org>

National Institute of Arthritis and Musculoskeletal and Skin Diseases, 1 AMS Circle, Bethesda, MD 20892-3675, (301) 495-4484, (877) 226-4267, NIAMSinfo@mail.nih.gov, <http://www.niams.nih.gov>

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Trisomy see **Chromosomal abnormalities**

Trisomy 8 mosaicism syndrome

Definition

Trisomy 8 is defined as the presence of three full copies of chromosome 8 in all of a person's cells. Mosaic trisomy 8 describes the situation that occurs when only a portion of these cells contains three copies of chromosome 8, while others contain the usual two copies of that chromosome. For example, people with mosaic trisomy 8 may have cells in their blood and other tissues with the normal chromosome number, but they may have cells in their skin with trisomy 8.

Description

The condition is sometimes also referred to as trisomy 8 mosaicism syndrome (T8mS) and mosaic Warkany

syndrome. Common characteristics of T8mS are distinct facial features, including low-set or abnormally shaped ears and a bulbous-tipped nose; eye abnormalities like strabismus and corneal clouding; bone and tissue abnormalities; various structural heart problems; palate abnormalities; hydronephrosis; cryptorchidism; mild to moderate mental delays; and deep hand and feet creases. These characteristics tend to vary widely from person to person.

Genetic profile

The presence of three copies of a chromosome typically arises from a process called nondisjunction. This happens during the very complex process of cell division. It can occur during meiosis, the process of cell division within the sperm and eggs prior to fertilization. It can also happen during mitosis, the process of cell division in the zygote after fertilization.

A fertilized human zygote usually has 46 chromosomes in total. In mitosis, the zygote's cells divide and duplicate themselves evenly, keeping the chromosome number the same in all of the duplicated cells. If nondisjunction occurs, a pair of chromosomes does not divide evenly. This can result in too few chromosomes in some cells, which is called monosomy. It also results in too many chromosomes in other cells. If nondisjunction involves chromosome 8, it can lead to trisomy 8.

When nondisjunction happens during mitosis and causes trisomy 8, it only causes trisomy 8 in a portion of that individual's cells. A single cell then has trisomy 8, and these cells continue to duplicate themselves in certain organs and tissues. At the same time, cells with the normal number of chromosomes duplicate themselves in other organs and tissues. In the end, the affected person has a combination of cells with the normal chromosome number and those with trisomy 8, which is T8mS. This may occur in varying different tissues of that person, and the exact ones cannot be predicted. Depending on when the nondisjunction happened, the person may have few or many cells with trisomy 8.

Nondisjunction is a cell division error that occurs by chance. Thus, no parent has control over this process and cannot influence the number of chromosomes his or her child receives at, or after, conception. In turn, T8mS is considered an unpredictable event that typically carries a very low recurrence risk for that person's parents and family. Unlike other conditions involving nondisjunction, like Down syndrome, T8mS has not been strongly associated with a mother's or father's age at conception.

Most people with T8mS do not have a family history of the condition, since it usually occurs by chance.

Demographics

Full trisomy 8 occurs in about 0.7% of spontaneous miscarriages. It is estimated to occur in about 0.1% of recognized pregnancies. When seen at birth, it is almost always due to mosaic trisomy 8 as opposed to full trisomy 8. A 2009 resource reported that the annual incidence of T8mS varies between 1 in 25,000 and 1 in 50,000.

T8mS has been reported worldwide, being slightly more common in males than in females.

Signs and symptoms

Characteristics of T8mS vary. In other chromosome mosaicism conditions, more severe symptoms and a worse prognosis are associated with a larger proportion of cells with an abnormal chromosome number being present. Interestingly, that does not seem to be the case in T8mS. The percentage of cells with trisomy 8 does not appear to correlate with the types of symptoms the affected person experiences.

The creases on the palms and soles of people with T8mS are the most unique characteristic of the condition. On the palms there may be more arches than usual on the fingertips and a single crease running across the palm. The creases are often deep and vertical, with a furrowed appearance, on the soles of the feet.

People with T8mS often have distinct facial characteristics. This can include a wide upturned nose, thicker and downturned lower lip, and low-set and prominent ears that may not be shaped in the usual way. They may also have abnormalities of the palate, including a cleft (opening) or highly arched palate.

Intellectual disability can occur with the condition, and the degree of mental delays varies from mild to moderate.

Other findings in T8mS can include those of the bone and tissues. These may be narrow shoulders, absent knee caps, abnormally shaped toes, tighter joints, slender palms, extra or missing ribs, and curving of the spine.

Eye abnormalities are seen in T8mS, and the two most common findings are corneal clouding and strabismus (a turning-in of the eye). These may or may not cause significant vision problems and require treatment. Rarer eye problems can include a smaller eye size, smaller eye openings, droopy eyelids, wide-set eyes, tilted optic discs, nearsightedness, retinal abnormalities, and epicanthic folds.

Occasional other characteristics can include structural heart problems, hydronephrosis, underdeveloped genitalia, cancer, and testes that have not descended into the scrotal sacs.

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure involving removal of a small placenta sample during pregnancy to obtain fetal chromosome results.

Chromosome—A microscopic thread-like structure found within each cell of the body and consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Cryptorchidism—Failure of descent of the testis from the abdominal cavity into the scrotum.

Epicanthic fold—Fold of skin of the upper eyelid continued over the inner edge of the eye.

Hydronephrosis—Obstruction of the tube that carries urine from the kidney into the bladder causing the pelvis and kidney duct to become swollen with excess urine.

Optic disc—The circular area at the back of the eyeball where the optic nerve connects to the retina.

Strabismus—Condition in which the eyes are not properly aligned with each other.

Zygote—The sperm and egg combined to form the initial cell when a new organism is produced by means of sexual reproduction.

Diagnosis

Suspicion about T8mS are usually based on a child being born with unique characteristics, since there is typically no reason one would suspect the condition. Blood chromosome testing is widely available to diagnose chromosome abnormalities. If enough cells are carefully analyzed in the laboratory, T8mS can often be found in a blood sample.

In situations in which a child with multiple characteristics has normal blood chromosome results, other tissues like the skin can be studied for their chromosome makeup. A trained physician can do a brief procedure

QUESTIONS TO ASK YOUR DOCTOR

- What is the cause of trisomy 8 mosaicism syndrome?
- What kind of medical specialists should evaluate my child?
- Are there any treatments for trisomy 8 mosaicism syndrome?
- How can I find another family who also has a child affected with trisomy 8 mosaicism syndrome?
- What is the chance of having another child affected with trisomy 8 mosaicism syndrome?

called a skin biopsy to obtain a small skin sample. During this, the physician takes a pencil eraser-sized piece of skin from a child's arm or back. Sometimes this testing reveals the presence of trisomy 8 in skin cells, which would confirm a diagnosis of T8mS.

Many characteristics of T8mS will not be seen during a pregnancy. However, a woman may be offered a routine prenatal chromosome test for other reasons, such as her age or family history. A chorionic villus sampling (CVS) or amniocentesis procedure, done in the first two trimesters of pregnancy, can usually identify trisomy 8. Depending on the number of cells that are carefully studied, T8mS may also be identified.

In about 1%–2% of CVS procedures that are performed, chromosomal mosaicism is found. However, this is confined to the placenta and does not represent the chromosomal status of the fetus. Additionally, as reported in the literature, a few babies born with T8mS had mothers who had completely normal amniocentesis chromosome results during their pregnancies. For an unknown reason, amniocentesis may not provide the most accurate results with respect to T8mS. This makes it difficult when counseling and providing information to couples during pregnancy with respect to T8mS.

Individuals with T8mS can also be formally assessed by a medical geneticist and genetic counselor to aid in diagnosis, discussion of testing options, and interpretation of test results.

Treatment and management

There is no cure for T8mS. Therefore, treatments are based on a person's signs and symptoms.

A cleft palate can be repaired through stages with surgery, often first occurring in the first year of life. This usually requires a multidisciplinary team consisting of a plastic surgeon, pediatric dentist, pediatric anesthesiologist, nurses, dietician/feeding specialist, and social worker.

Hydronephrosis, if severe enough, can warrant surgery shortly after birth. The goal is to open the blocked area of the urinary tract and clear the obstruction into the kidney. Surgery may involve a team approach, including a pediatric urologist, pediatric nephrologist, nurses, and surgery technicians.

Congenital heart defects, if severe enough, can require surgery. Surgery varies depending on the problem and may involve a team, including a pediatric cardiologist, pediatric cardiovascular surgeon, pediatric anesthesiologist, pediatric cardiovascular radiologist, nurses, and surgery technicians.

Strabismus can often be treated with patching therapy or surgery. This may require a team involving a pediatric ophthalmologist, pediatric anesthesiologist, orthoptist, nurses, and surgery technicians. Severe corneal clouding may lead to vision problems and can sometimes be treated with surgery, laser therapy, or corneal transplants.

Undescended testicles or testes can be brought down to the proper location in the scrotal sacs by a brief surgical procedure. This can involve a team, including a pediatric urologist, pediatric anesthesiologists, and nurses.

Some characteristics of T8mS do not necessitate treatment, as they cause no medical harm. Examples of these include facial features, hand/foot creases, and some tissue and bone changes.

Mental delays and intellectual disability may be assessed by a child development team or early childhood program. Extra assistance is sometimes available through early intervention programs and special education in schools. Social workers are useful to connect families to helpful resources.

Prognosis

People with T8mS have a prognosis that is entirely dependent upon the symptoms they experience. Someone born with a severe congenital heart defect may have a poorer prognosis for survival, growth, and development based on this. The average lifespan for someone with T8mS is estimated to be near normal in the literature. Medical treatments and surgeries continue to offer hope.

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ORGANIZATIONS

Chromosome Disorder Outreach, PO Box 724, Boca Raton, FL 33429-0724, (561) 395-4252, info@chromodisorder.org, <http://www.chromodisorder.org>

Genetic Alliance, 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008-2369, (202) 966-5557, (202) 966-8553, info@geneticalliance.org, <http://www.geneticalliance.org>

Genetic Disease Foundation, 1425 Madison Ave., Box 1498, New York, NY 10029, (212) 659-6704, <http://www.geneticdiseasefoundation.org>

Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

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Trisomy 13

Definition

Trisomy 13, also called Patau syndrome, is a congenital (present at birth) disorder associated with the presence of an extra copy of chromosome 13. The extra chromosome 13 causes numerous physical and mental abnormalities, especially heart defects. Dr. Klaus Patau reported the syndrome and its association with trisomy in 1960.

Description

Children normally inherit 23 chromosomes from each parent, for a total of 46 chromosomes. A typical human being has 46 chromosomes: 22 pairs of non-sex-linked chromosomes and one pair of sex-linked



Deformed fingers and darkened skin of a patient with trisomy 13 or Patau syndrome. (Biophoto Associates/Science Source)

chromosomes that determine the child's sex. Sometimes a child may end up with more than 46 chromosomes because of problems with the father's sperm or the mother's egg, or because of mutations that occurred after the sperm and the egg fused to form the embryo (conception).

Normally, there are two copies of each of the 23 chromosomes: one from each parent. A condition called trisomy occurs when three, instead of two, copies of a chromosome are present in a developing human embryo. An extra copy of a particular chromosome can come either from the egg or sperm, or because of mutations that occur after conception.

The most well-known trisomy-related disorder is Down syndrome (trisomy 21), in which the developing embryo has an extra copy of chromosome 21. In trisomy 13, the developing embryo has three copies of chromosome 13.

An extra copy of chromosome 13 is not the only cause of trisomy 13. Other changes in the chromosome, such as mispositioning (translocation), can also result in the characteristics associated with the disorder. In these cases, an error occurs that causes a portion of chromosome 13 to be exchanged for a portion of another chromosome. There is no production of extra chromosomes, but a portion of each affected chromosome is "misplaced" (translocated) to another chromosome.

Trisomy 13 causes serious physical and mental abnormalities including heart defects; incomplete brain development; unusual facial features such as a sloping forehead, a smaller than average head (microcephaly), small or missing eyes, low-set ears, and cleft palate or hare lip; extra fingers and toes (polydactyly); abnormal genitalia; spinal abnormalities; seizures; gastrointestinal hernias, particularly at the navel (omphalocele); and

mental retardation. Due to the severity of these conditions, fewer than 20% of those affected survive beyond infancy.

Genetic profile

When an extra copy (trisomy) of a chromosome is made, it may either be a total trisomy (in which an extra copy of the entire chromosome is made), or partial trisomy (in which only one part of the chromosome is made an extra time).

In most cases of trisomy, errors in chromosome duplication occur at conception because of problems with the egg or the sperm that are coming together to produce an offspring. In these cases, every cell in the body of the offspring has an extra copy of the affected chromosome. However, errors in chromosome duplication may also occur during the rapid cell division that takes place immediately after conception. In these cases, only some cells of the body have the extra chromosome error. The condition in which only some of the cells in the body have the extra chromosome is called mosaicism.

Seventy-five to eighty percent of the cases of trisomy 13 are caused by a trisomy of chromosome 13. Some of these cases are the result of a total trisomy, while others are the result of a partial trisomy. Partial trisomy generally causes less severe physical symptoms than full trisomy. Ten percent of these cases are of the mosaic type, in which only some of the body's cells have the extra chromosome. The physical symptoms of the mosaic form of trisomy 13 depend on the number and type of cells that carry the trisomy.

Most cases of trisomy are not passed on from one generation to the next. Usually they result from a malfunction in the cell division (mitosis) that occurs after conception. At least 75% of the cases of trisomy 13 are caused by errors in chromosome replication that occur after conception. The remaining 25% are caused by the inheritance of translocations of chromosome 13 with other chromosomes within the parental chromosomes. In these cases, a portion of another chromosome switches places with a portion of chromosome 13. This leads to errors in the genes on both chromosome 13 and the chromosome from which the translocated portion originated.

Demographics

Trisomy 13 occurs in approximately 1 in 10,000 live births. In many cases, miscarriage occurs, and the fetus does not survive to term. In other cases, the affected individual is stillborn. As appears to be the case in all trisomies, the risk of trisomy 13 seems to increase with the mother's age, particularly if she is over 30 when

pregnant. Male and female children are equally affected, and the syndrome occurs in all races.

Signs and symptoms

The severity and symptoms of trisomy 13 vary with the type of chromosomal anomaly, from extremely serious conditions to nearly normal appearance and functioning. Full trisomy 13, which is present in the majority of the cases, results in the most severe and numerous internal and external abnormalities. Commonly, the forebrain fails to divide into lobes or hemispheres (holoprosencephaly) and the entire head is unusually small (microcephaly). The spinal cord may protrude through an opening in the vertebrae of the spinal column (myelomeningocele). Children who survive infancy have profound mental retardation and may experience seizures.

Incomplete development of the optic (sight) and olfactory (smell) nerves often accompany the brain abnormalities described above. The eyes may be unusually small (microphthalmia) or one eye may be absent (anophthalmia). The eyes are sometimes set close together (hypotelorism) or even fused into a single structure. Incomplete development of any structures in the eye (coloboma) or failure of the retina to develop properly (retinal dysplasia) will also produce vision problems. Individuals with trisomy 13 may be born either partially or totally deaf, and many are subject to recurring ear infections.

The facial features of many individuals with trisomy 13 appear flattened. The ears are generally malformed and low-set. Frequently, children with the disorder have a cleft lip, a cleft palate, or both. Other physical characteristics include loose folds of skin at the back of the neck, extra fingers or toes (polydactyly), permanently flexed (closed) fingers (camptodactyly), noticeably prominent heels, "rocker-bottom foot," and missing ribs. Genital malformations are common and include undescended testicles (cryptorchidism), an abnormally developed scrotum, and ambiguous genitalia in males, or an abnormally formed uterus (bicornuate uterus) in females.

In nearly all cases, affected infants have respiratory difficulties and heart defects, including atrial and ventricular septal defects (holes between chambers of the heart); malformed ducts that cause abnormal direction of blood flow (patent ductus arteriosus); holes in the valves of the lungs and the heart (pulmonary and aortic valves); and misplacement of the heart in the right, rather than the left side of the chest (dextrocardia). The kidneys and gastrointestinal system may also be affected with cysts similar to those seen in polycystic kidney disease. These abnormalities are frequently severe and life threatening.

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks of gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome—A microscopic thread-like structure found within each cell of the body consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Karyotyping—A laboratory procedure in which chromosomes are separated from cells, stained, and arranged so that their structure can be studied under a microscope.

Mosaicism—A genetic condition resulting from a mutation, crossing-over, or nondisjunction of chromosomes during cell division, causing a variation in the number of chromosomes in the cells.

Translocation—The transfer of one part of a chromosome to another chromosome during cell division. A balanced translocation occurs when pieces from two different chromosomes exchange places without loss or gain of any chromosome material. An unbalanced translocation involves the unequal loss or gain of genetic information between two chromosomes.

Trisomy—The condition of having three identical chromosomes, instead of the normal two, in a cell.

Ultrasound—An imaging technique that uses sound waves to help visualize internal structures in the body.

Partial trisomy of the distal segment of chromosome 13 generally results in less severe, but still serious, symptoms and a distinctive facial appearance including a short upturned nose, a longer than usual area between the nose and upper lip (philtrum), bushy eyebrows, and tumors

made up of blood capillaries on the forehead (frontal capillary hemangiomas). Partial trisomy of the proximal segment of chromosome 13 is much less likely to be fatal and has been associated with a variety of facial features including a large nose, a short upper lip, and a receding jaw. Both forms of partial trisomy also result in severe mental retardation.

Beyond one month of age, other symptoms include: feeding difficulties and constipation, reflux disease, slow growth rates, curvature of the spine (scoliosis), irritability, sensitivity to sunlight, low muscle tone, high blood pressure, sinus infections, urinary tract infections, and ear and eye infections.

Diagnosis

Trisomy 13 is detectable during pregnancy through the use of ultrasound imaging, amniocentesis, and chorionic villus sampling (CVS). At birth, the newborn's numerous malformations indicate a possible chromosomal abnormality. Trisomy 13 is confirmed by examining the infant's chromosomal pattern through karyotyping or another procedure. Karyotyping involves the separation and isolation of the chromosomes present in cells taken from an individual. These cells are generally extracted from cells found in a blood sample. The 22 non-sex-linked chromosomes are identified by size, from largest to smallest, as chromosomes 1 through 22. The sex-determining chromosomes are also identified. Trisomy 13 is confirmed by the presence of three, rather than the normal two, copies of chromosome 13.

Treatment and management

Some infants born with trisomy 13 have severe and incurable birth defects. However, children with better prognoses require medical treatment to correct structural abnormalities and associated complications. For feeding problems, special formulas, positions, and techniques may be used. Tube feeding or the placement of a gastric tube (gastrostomy) may be required. Structural abnormalities such as cleft lip and cleft palate can be corrected through surgery. Special diets, hearing aids, and vision aids can be used to mitigate symptoms. Physical therapy, speech therapy, and other types of developmental therapy will help the child reach his or her potential.

Since the translocation form of trisomy 13 is genetically transmitted, genetic counseling for the parents should be part of the management of the disease.

Prognosis

Approximately 45% of infants with trisomy 13 die within their first month of life; up to 70% in the first six months; and more than 70% by one year of age. Survival

to adulthood is very rare. Only one adult is known to have survived to age 33.

Most survivors have profound mental and physical disabilities; however, the capacity for learning in affected children varies from patient to patient. Older children may be able to walk with or without a walker. They may also be able to understand words and phrases, follow simple commands, use a few words or signs, and recognize and interact with others.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Support Organization for Trisomy 18, 13, and Related Disorders (SOFT), 2982 S. Union St., Rochester, NY 14624, (800) 716-7638, <http://trisomy.org>

Paul A Johnson

Tuberous sclerosis complex

Definition

Tuberous sclerosis complex (TSC) is a genetic condition that affects many organ systems, including the brain, skin, heart, kidneys, eyes, and lungs. Benign (noncancerous) growths or tumors called hamartomas form in various parts of the body, disrupting their normal functions.

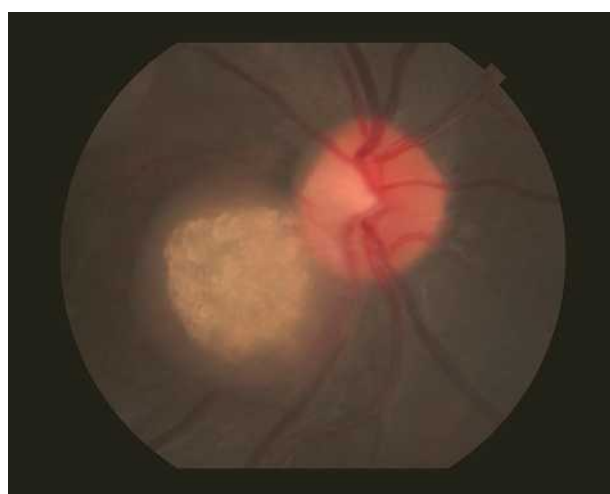
Description

The term "tuberous sclerosis" refers to the small, knoblike growths in the brain of patients with TSC that were found upon autopsy and, today, can be viewed using computed tomography (also called a CT scan). The condition is also referred to as tuberoses sclerosis or simply tuberous sclerosis. The designation tuberous sclerosis complex is used to distinguish this condition from another genetic condition called Tourette syndrome that is abbreviated TS.

Persons with TSC have a variety of symptoms ranging from very mild to severe. Affected individuals may experience no serious health problems and, in the absence of a thorough clinical examination, may go through life without knowing that they are affected. Conversely, patients with TSC may have problems with behavioral, mental, and emotional functions as well as with their kidneys, heart, and eyes. In addition, specific skin abnormalities, often medically insignificant, are among the most common symptoms of TSC.

Genetic profile

TSC is an autosomal dominant genetic disorder caused by a single change or alteration in a gene called a mutation in either the *TSC1* gene, located on chromosome 9, or the *TSC2* gene, located on chromosome 16. Approximately two-thirds (66%) of patients with TSC have it as the result of a new change in one of the TSC genes; that is, it was not inherited from one of their parents. When a new change occurs, it most commonly occurs in the *TSC2* gene. An individual must have a mutation in one of these two copies of a TSC-causing



A retinal photograph of an astrocytoma in the retina of a patient affected by tuberous sclerosis. (Paul Whitten/Science Source)

gene in order to develop the condition. In addition, a person who has been diagnosed with TSC and who, therefore, has a genetic mutation in one of the TSC genes has a 50% chance of passing on the genetic mutation to his or her offspring. Laboratory testing for changes in the TSC genes is not currently available.

TSC is a condition that can be caused by a change in either one of two separate genes. In addition, people who have the same change in the same gene may have very different medical problems and symptoms.

TSC1 is responsible for producing the protein hamartin and *TSC2*, tuberin. Both genes are known as tumor suppressor genes, meaning that their normal function is to prevent the growth of tumors. Conversely, when gene function is altered, tumor growth results. Research on how the disruption of either protein results in the clinical condition of TSC is ongoing.

It is currently believed that every person who inherits or develops a mutation in either the *TSC1* or *TSC2* gene will develop some form of TSC. However, the severity of the disease, with its wide range of symptoms and complications, cannot accurately be predicted by identifying the specific gene mutation.

Germline mosaicism can explain the rare occurrence of unaffected parents having more than one child with TSC. Germline refers to the gonadal cells (sperm in males and eggs in females) and mosaicism refers to the presence of different cell lines in any given individual. A person with germline mosaicism for either the *TSC1* or *TSC2* gene is not affected with TSC but may have an affected child. Unaffected parents of a child with TSC are quoted a 2%–3% chance of having additional affected children. Typical genetic testing methods are performed on somatic (nongermline) tissues such as blood or skin and, therefore, will not detect germline mosaicism.

Demographics

Although tuberous sclerosis complex is considered to be a rare condition, estimates of the prevalence of the disorder have increased as clinical testing methods have improved. In the United States, as many as 1 child in 6,000 born is affected with TSC and about 50,000 people are currently living in the United States with the disease. TSC is seen in all ethnic groups and populations and, worldwide, there are between one and two million cases.

Signs and symptoms

The basic underlying cause for illness and, less often, death due to tuberous sclerosis complex is the development of growths called hamartomas throughout the body. Hamartoma is a general term used to describe tumor-like

growths that are not cancerous and are composed of cells usually found in that site but poorly developed. While these growths are typically benign (i.e., not cancerous), their presence often disrupts the normal functions of a particular organ system. The various hamartomas found in TSC patients can be further distinguished and classified by their location and their histological properties—that is, their physical composition and characteristic appearance under a microscope. As each hamartoma is comprised of different cellular elements, each one has a particular name. For example, while both are hamartomas, a fibroma is comprised of connective tissue whereas a lipoma is made up of fat cells.

While the organs affected vary from person to person, most people with TSC have some type of skin irregularities called lesions. Some of the most commonly seen skin lesions are hypomelanotic macules—white or light patches sometimes in an ash-leaf shape and called Ash-leaf spots. Many people in the general population have one or two light areas of skin. However, the presence of three or more such macules in any one individual is considered a major diagnostic finding of TSC. A second major diagnostic feature of the condition is the appearance of small, red bumps called fibromas, either on the face (facial angiofibromas) or around or under the finger- or toenails (ungual fibromas). In addition, rough patches of skin termed shagreen patches are highly specific to a diagnosis of TSC. Finally, groups of small light circles called confetti spots are considered a minor feature of the disorder.

In contrast to skin lesions, brain lesions tend to be serious and are responsible for the neurological symptoms and cognitive impairment seen in severely affected individuals. There are four primary abnormalities that can be detected by magnetic resonance imaging (MRI) or computer tomography (CT) scanning, the first of which are cortical tubers—nodular growths found in the cortex of the brain—and give tuberous sclerosis (literally “hard growths”) its name. Subependymal nodules are growths found underneath the lining of the ventricles in the brain and may cause no problems for the patient unless they grow or begin to block the flow of the cerebral spinal fluid. In contrast, subependymal giant cell astrocytomas, noncancerous brain tumors comprised of star-shaped cells and found in about 5% of patients with TSC, can, if untreated, result in blindness, hydrocephalus (fluid on the brain), and even death. Finally, cerebral white matter migration lines may be seen through radiographic (x-ray) studies and are considered a minor diagnostic feature of TSC.

About 85% of affected individuals will develop epileptic seizures at some point in their lifetime, most beginning by the first year of life. Research suggests that early

control of epilepsy by medication will decrease the chance of a child developing serious mental complications. People with TSC have a range of mental abilities from normal to mild or moderate developmental delays and learning disabilities, to severe intellectual disability. Autism, attention-deficit hyperactivity disorder (ADHD), and other behavioral problems are seen in affected individuals.

Fatty kidney tumors, known as renal angiomyolipomas, are one of the most common findings in TSC patients, affecting 70%–80% of older children and adults, and often cause serious renal malfunction. In addition, the presence of multiple renal cysts (fluid-filled areas within the kidneys) is suggestive of the condition. In addition to these benign growths, malignant kidney tumors may also develop.

The most common cardiac symptom is one or more tumors (cardiac rhabdomyomas) in the heart. These tumors are almost exclusively seen in infants and young children and usually spontaneously disappear by late childhood, thereby avoiding the need for surgery. About 47%–67% of infants and children with TSC have heart tumors and some females develop the rhabdomyomas when they reach puberty.

Tuberous sclerosis complex affects the eyes in the form of retinal nodular hamartomas—multiple growths on the retina. A discoloration on the retina (retinal achromic patch) is also considered a minor feature of the condition.

In addition to the above, symptoms of TSC may include dental pits in the teeth, growths in the rectum (hamartomatous rectal polyps), bone cysts, growths on the gums (gingival fibromas), and other nonspecific growths (nonrenal hamartomas). Women with TSC may develop lymphangiomyomatosis—a serious lung disease. Furthermore, all individuals with TSC are at a higher risk over the general population for developing specific cancers, with 2% of patients developing a malignant tumor in one of the affected body tissues such as kidney or brain.

Diagnosis

When a person exhibits signs of TSC or has a family history of the condition, an evaluation by a medical geneticist, neurologist, or other qualified professional is recommended to confirm (or rule out) the diagnosis and to recommend screening and management options for the individual. In addition, speaking with a genetic counselor may help families understand the genetics behind the disorder, their recurrence risks (chances for having another affected family member), and the practical and

psychosocial implications of the disease on their personal situation.

Detection of hypomelanotic macules (light patches on the skin) can be performed quickly and easily using a special ultraviolet lamp called a Wood's lamp. This light emphasizes the lightened areas on the skin that may otherwise be difficult to see using normal light. Other skin lesions called fibromas are easily visible and identifiable due to their characteristic smooth form, red color, and their even distribution on the face and/or their protrusions among the nails on the fingers and toes. Radiographic imaging using ultrasound, MRI, or CT technology can detect growths present in the brain, kidneys, heart, and eyes.

As basic understanding of and testing methods for tuberous sclerosis complex have improved, criteria used for confirming a diagnosis of tuberous sclerosis complex have been revised. The National Institutes of Health (NIH) held a consensus conference on TSC and published the following diagnostic criteria.

Major features:

- facial angiofibromas or forehead plaque
- nontraumatic ungual or periungual fibroma
- hypomelanotic macules (more than three)
- shagreen patch
- multiple retinal hamartomas
- cortical tuber
- subependymal nodule
- subependymal giant cell astrocytoma
- cardiac rhabdomyoma (one or more)
- lymphangiomyomatosis
- renal angiomyolipoma

Minor features:

- multiple randomly distributed dental pits
- hamartomatous rectal polyps
- bone cysts
- cerebral white matter migration lines
- gingival fibromas
- nonrenal hamartoma
- retinal achromic patch
- confetti skin lesions
- multiple renal cysts

A confirmed diagnosis of TSC requires that a patient display either two major features or one major and two minor features, a suspected diagnosis of one major and one minor feature, and a possible diagnosis of one major or two minor features in any one individual.

KEY TERMS

Bone cysts—Fluid- or air-filled space within the bones.

Cardiac rhabdomyoma—Benign (noncancerous) tumor of the heart muscle.

Cerebral white matter migration lines—Pattern of defects found in the cerebral cortex of the brain probably caused by abnormal migration of neurons during brain formation.

Confetti skin lesions—Numerous light or white spots seen on the skin that resemble confetti.

Cortical tuber—Round (nodular) growth found in the cortex of the brain.

Dental pits—Small, shallow holes or crevices in the tooth enamel.

Facial angiofibromas—Benign (noncancerous) tumors of the face.

Forehead plaque—Flat, fibrous skin growth on the forehead.

Gingival fibromas—Fibrous growths found on the gums.

Hamartomatous rectal polyps—Benign (noncancerous) growths found in the rectum.

Hypomelanotic macules—Patches of skin lighter than the surrounding skin.

Lymphangioomyomatosis—Serious lung disease characterized by the overgrowth of an unusual type

of muscle cell resulting in the blockage of air, blood, and lymph vessels to and from the lungs.

Nonrenal hamartoma—Benign (noncancerous) tumor-like growths not found in the kidneys that often disrupt the normal function of a particular organ system.

Nontraumatic unguinal or periungual fibroma—Fibrous growth that appears around the fingernails and/or toenails.

Renal angiomyolipoma—Benign (noncancerous) tumors in the kidney that are made up of vascular tissue (angio), smooth muscle (myo), and fat (lipoma).

Renal cysts—Fluid or air-filled spaces within the kidneys.

Retinal achromic patch—Defect in the coloration of the retina.

Retinal hamartomas—Benign (noncancerous) tumor found on the retina.

Shagreen patch—Area of tough and dimpled skin.

Subependymal giant cell astrocytoma—Benign (noncancerous) tumor of the brain comprised of star-shaped cells (astrocytes).

Subependymal nodule—Growth found underneath the lining of the ventricles in the brain.

Treatment and management

Optimal treatment for TSC is dependent upon proper disease management. The following should be performed on all patients with TSC at the time of diagnosis to confirm a diagnosis of the disease as well as obtain baseline medical data for future evaluations:

- dermatologic (skin) examination
- fundoscopic (eye) examination
- renal (kidney) imaging study
- cardiac electrocardiogram (ECG) and echocardiogram (ECHO)
- brain magnetic resonance imaging (MRI)

Since the characteristic feature of tuberous sclerosis complex is the growth of benign tumors, treatments are often focused on appropriate surgical interventions to arrest tumor growth or remove tumors whose growth has resulted in or may lead to medical complications, especially in the kidney or brain. Regular brain MRI

studies should be performed in children and adults with previous findings as clinically indicated and every one to three years in children and, less frequently, in adults without symptoms. In addition, periodic brain electroencephalogram (EEG) studies are recommended for both children and adult patients when clinically indicated.

Children without previous kidney findings should be offered renal imaging studies using ultrasound, MRI, or CT scanning every three years until they reach adolescence and then, every one to three years as adults. Likewise, asymptomatic adults should have imaging of their kidneys done every one to three years. Both children and adults who have kidney symptoms should be monitored using imaging studies every six months to one year until the tumor growth stabilizes or decreases.

Any child with cardiac rhabdomyomas should be monitored every six months to one year until the tumor stabilizes or regresses completely. Adults with previous findings of cardiac tumors should be monitored as clinically recommended by their treating physician. While

QUESTIONS TO ASK YOUR DOCTOR

- How often should brain and MRI studies be performed?
- What are the risks and benefits of vigabatrin therapy?
- How early should we begin physical and occupational therapies?
- What developmental milestones should I look for in my child?

monitoring is important, cardiac rhabdomyomas, as well as retinal lesions and gingival fibromas, usually do not require treatment. In contrast to these benign tumors, cancerous tumors that develop in patients with TSC should be treated by an oncologist as appropriate.

Facial angiofibromas and peri- and subungual fibromas on the nails are common symptoms in TSC patients. While they are generally not medically significant, they can cause skin irritations or be a cosmetic concern to the individual. Special techniques involving dermabrasion or laser therapy can be performed by a dermatologist or plastic surgeon to remove such growths.

Patients with seizure disorders are prescribed specific medications to control seizures. The antiepileptic drug vigabatrin has been shown to be an effective medication in infants with seizures and has been shown to improve long-term outcomes in behavioral and intellectual areas. In addition to controlling seizures, early intervention programs that include special education, behavior modification, physical and occupational therapies, and speech therapy is often recommended for individuals with learning disabilities, developmental delays, intellectual disability, autism, and other mental and emotional disorders.

Neurodevelopmental testing is appropriate at the time of diagnosis for all children and should be performed every three years until adolescence and for any adult diagnosed with TSC who displays signs of impairment. Subsequent evaluations should be done on both children and adults with previous findings of developmental delays or problems.

While present in only 1% of patients with TSC, almost exclusively in females, lung complications can be serious and even fatal. Symptoms may include spontaneous pneumothorax (air in the chest cavity), dyspnea (difficult breathing), cough, hemoptysis (spitting of blood), and pulmonary failure. Therefore, a computed

tomography (CT) scan of the lungs is recommended for any TSC patient who has symptoms of lung disease or complications and for all female TSC patients at the age of 18. Clinical trials involving Tamoxifen and progesterone treatments have shown positive results in some patients with lung disease.

Prognosis

The lifespan of individuals with TSC varies with the severity of the condition in any one person. Many affected people have normal life expectancies and a high quality of life, relatively free of symptoms or complications of the disease. Conversely, severely affected or disabled individuals may experience a shortened lifespan and a high rate of illness and medical complications. Therefore, proper disease management, diagnostic monitoring, and follow-up are critical to achieving and maintaining optimal health in patients with TSC.

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ORGANIZATIONS

Tuberous Sclerosis Alliance, 801 Roeder Rd., Suite 750, Silver Spring, MD 20910, (301) 562-9890, (800) 225-6872, (301) 562-9870, info@tsalliance.org, <http://www.tsalliance.org>

Pamela E. Cohen, MS, CGC

Turcot syndrome see **Familial adenomatous polyposis**

Turner syndrome

Definition

Turner syndrome is a chromosomal disorder affecting females wherein one of the two X chromosomes is defective or completely absent.

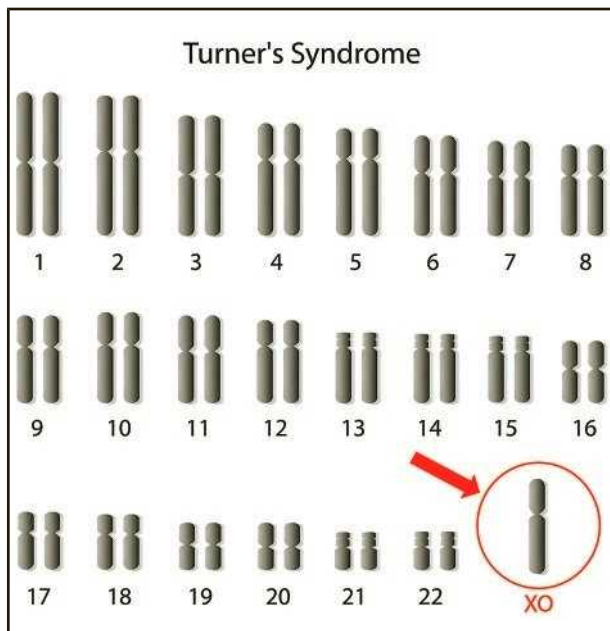
Description

Chromosomes are structures in the nucleus of every cell in the human body. Chromosomes contain the genetic information necessary to direct the growth and normal functioning of all cells and systems of the body. A normal individual has a total of 46 chromosomes in each cell, two of which are responsible for determining gender. Normally, females have two X chromosomes and males have one X and one Y chromosome.

In Turner syndrome, an error occurring very early in development results in an abnormal number and arrangement of chromosomes. Most commonly, an individual with Turner syndrome will be born with 45 chromosomes in each cell rather than 46. The missing chromosome is an X chromosome. The affected person is always female.

Genetic profile

Turner syndrome is a disorder associated with characteristic defects in the X chromosome. The most common presentation is a female with a single X chromosome and an absent X chromosome. A Greek



Human karyotype of Turner syndrome. (Alila Medical Media/Shutterstock)

KEY TERMS

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Mosaic—A term referring to a genetic situation in which an individual's cells do not have the exact same composition of chromosomes. In Down syndrome, this may mean that some of the individual's cells have a normal 46 chromosomes, while other cells have an abnormal 47 chromosomes.

Ovary—The female reproductive organ that produces the reproductive cell (ovum) and female hormones.

Zygote—The cell formed by the uniting of egg and sperm.

study from 1999 reported that the intact X chromosome was as likely to come from the mother as from the father. This means that there is no parental pattern of responsibility for the missing or defective X chromosome.

Another less common genetic pattern for Turner syndrome (35%) is a mosaic. A Danish study reported that mosaicism has an effect on malformations that are associated with Turner syndrome. Research reported in 1997 noted that the karyotype can have a significant effect on the growth of children with Turner syndrome.

The exact location of the genes on the X chromosome involved in Turner syndrome has not been determined. As of 2015, evidence indicated that there is a locus for stature on the distal portion of the short arm, there are loci for normal ovarian function on both the short and long arms, and there are loci contributing to fetal viability on the long arm of X.

Demographics

The prevalence of Turner syndrome is widely reported as being approximately 1 per 2,000 live female births, although researchers have reported prevalence rates that range from 1 in 3,125 to 1 in 5,000 live female births.

About 1%–2% of all female conceptions have a missing X chromosome. Of these, the majority (99%) spontaneously abort, usually during the first trimester of pregnancy. With ultrasound being used more frequently,

researchers have realized that some pregnancies with a missing X chromosome that progress into the second trimester are associated with nuchal cysts, severe lymphedema, or hydrops fetalis. These pregnancies are associated with a high frequency of fetal death.

Signs and symptoms

Turner syndrome is characterized by delayed growth that leads to a small stature and frequent infertility. Individuals with Turner syndrome report an increased incidence of fractures in childhood and osteoporotic fractures in adulthood. The incidence of diabetes mellitus (both insulin dependent and non-insulin-dependent varieties) has been reported to be increased in Turner syndrome. Ischemic heart disease, stroke, and hypertension are also more common.

Growth in children with Turner syndrome is characterized by a slight intrauterine growth retardation, relatively normal growth rates for the first several years of life, a progressive deceleration of growth later in childhood, and the lack of a pubertal growth spurt. Growth patterns of Chinese girls with Turner syndrome parallel those of Caucasians, although their ultimate height is still less than normal.

Contrary to earlier reports, most individuals with Turner syndrome are not intellectually disabled. They may have some learning disabilities, particularly with regard to spatial perception, visual-motor coordination, and mathematics. As a result, the nonverbal IQ in Turner syndrome tends to be lower than the verbal IQ. Cardiovascular malformations are well-recognized congenital anomalies in Turner syndrome. Dilation and dissection of the aorta are reported in approximately half of women with Turner syndrome. Because of the potential consequences of aortic dilation, some experts recommend screening all individuals with Turner syndrome. However, the specific timing for this screening remains controversial.

Juvenile arthritis, an autoimmune condition, has been recently associated with Turner syndrome. The prevalence seems to be at least six times greater than would be expected if the two conditions were only randomly associated. Women with Turner syndrome have an elevated prevalence rate of dental caries and other periodontal conditions such as gum disease and plaque.

Normal pubertal development and spontaneous menstrual periods do not occur in the majority of children with Turner syndrome. It is estimated that 3%–8% of girls with a single X chromosome and 12%–21% of females with sex chromosome mosaicism may have normal pubertal development and spontaneous menstrual periods. A few pregnancies have been reported in women with Turner syndrome.

QUESTIONS TO ASK YOUR DOCTOR

- When should screening for aortic dissection take place?
- When should we consider plastic surgery?
- Should we test for other associated problems, such as heart or kidney disorders?
- Is a hearing test recommended?

Diagnosis

Turner syndrome is diagnosed on the basis of genetic analysis of chromosomes. This can be done prior to birth. However, the predictive value of amniocentesis in diagnosing Turner syndrome varies from 21%–67%. There is no significant relation between mother's age and risk of Turner syndrome.

Treatment and management

Because it is so dangerous, experts suggest screening for aortic dissection, although the specific timing for this screening is controversial. Plastic surgery to correct webbing of the neck should be considered at an early age (before entering school) for girls with Turner syndrome.

Most individuals with Turner syndrome require female hormone therapy to promote development of secondary sexual characteristics and menstruation. The time of beginning therapy varies with individuals. Experts recommend that therapy begin when a woman expresses concern about her onset of puberty.

All women receiving long-term, exogenous female hormone therapy require periodic gynecological examinations because those with Turner syndrome have an increased risk of developing neoplasms such as gonadoblastoma and dysgerminoma, which arise from their rudimentary streak gonads.

Prognosis

Most women with Turner syndrome can live relatively normal lives. The prognosis for people with Turner syndrome is dependent on other conditions that may be present. Care must be taken to regularly monitor them for the health problems that are associated with Turner syndrome. For example, heart or kidney defects, hearing loss, or the development of inflammatory bowel disease may significantly impact the quality of life. Without these types of conditions, however, their life

expectancy is normal. Support will be necessary to help an adolescent girl cope with body image issues and to help some women accept the fact that they will never be able to have children.

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- American Academy of Pediatrics, 141 Northwest Point Blvd., Elk Grove Village, IL 60007-1098, (847) 434-4000, (800) 433-9016, (847) 434-8000, csc@aap.org, <https://www.aap.org>
- Endocrine Society, 2055 L St. NW, Suite 600, Washington, DC 20036, (202) 971-3636, (888) 363-627, (202) 736-9704, societyservices@endocrine.org, <http://www.endocrine.org>
- Human Growth Foundation, 997 Glencove Ave., Glenhead, NY 11545, (800) 451-6434, (516) 671-4055, hgf1@hgfound.org, <http://hgfound.org>
- MAGIC Foundation, 6645 W. North Ave., Oak Park, IL 60302, (708) 383-0808, (800) 362-4423, ContactUs@magicfoundation.org, <http://www.magicfoundation.org>
- Turner Syndrome Society of Canada, 30 Cleary Ave., Room 9, Ottawa ON Canada K2A 4A1, (800) 465-6744, info@turnersyndrome.ca, <http://www.turnersyndrome.ca>
- Turner Syndrome Society of the United States, 11250 West Rd., Suite G, Houston, TX 77065, (800) 365-9944, (832) 912-6006, <http://www.turnersyndrome.org>

L Fleming Fallon, Jr., MD, PhD, Dr.PH

Twin reversed arterial perfusion (TRAP) sequence

Definition

Twin reversed arterial perfusion (TRAP) sequence, also called acardia, is a very rare and serious condition that occurs exclusively in monochorionic pregnancies (identical twins that share a placenta). The condition occurs when one twin, the "acardiac" twin, lacks a functioning heart and receives blood circulated by the normally developing "pump" twin. The pump twin is at risk for cardiac failure because of the heavy demand placed on its heart.

Description

TRAP sequence is a pregnancy complication in which twins abnormally share blood flow from the umbilical artery of one twin to the umbilical vein of the other. This abnormal connection can cause serious complications including loss of the pregnancy. In TRAP sequence pregnancies, there may be a fused placenta or abnormal connection between the twins in the placenta. The placenta is the important interface of blood vessels between a mother and baby through which babies receive nutrients and oxygen. This abnormal connection forces the twin with stronger blood flow to pump blood for both. This strains the heart of the pump twin. This abnormal connection causes the malformed twin to receive blood directly from the pump twin before this blood gathers new oxygen. The poorly oxygenated blood from the pump twin may be the cause of the other malformations in the acardiac twin. The abnormal blood flow between twins is the most likely cause for the variety of malformations and complications of this condition.

The acardiac twin

The acardiac twin is severely malformed and may be incorrectly referred to as a tumor. In 1902, a physician named Das established four categories of acardiac twins based on their physical appearance. There is controversy surrounding the use of these traditional four categories because some cases are complex and do not fit neatly into one of Das's four categories. These four traditional categories include acardius acephalus, amorphus, aniceps, and acornus:

- Acardius acephalus is the most common type of acardiac twin, being found in 60%–75% of cases. These twins do not develop a head, but may have an underdeveloped skull base. They have legs, but do not have arms. On autopsy, they are generally found to lack chest and upper abdominal organs.

- **Acardius amorphus** occurs in 20% of cases and appears as a disorganized mass of tissues containing skin, bone, cartilage, muscle, fat, and blood vessels. This type of acardiac twin is not recognizable as a human fetus and contains no recognizable human organs.
- **Acardius aniceps** is the most developed form of acardiac twin. This form has arms, legs, and a partially developed head with brain tissues and facial structures. This type of acardiac twin is associated with a high risk for complications in the normal twin.
- **Acardius acornus** is the rarest type of acardiac twin. This type of acardiac twin presents as an isolated head with no body development.

Thus, the acardiac twin can have various and numerous malformations.

The pump twin

The pump twin can develop complications as a result of the increased work of providing blood flow to the acardiac twin. The pump twin may develop cardiac failure or overload, leading to fetal death. About 10% of pump twins also have a malformation.

Pregnancy complications

Polyhydramnios, or extra amniotic fluid, is a frequent complication of this condition. The extra fluid can cause early rupture of the amniotic membranes and premature delivery. It is also possible to have a miscarriage of the whole pregnancy, either due to polyhydramnios and premature delivery, or due to complications from *in utero* fetal demise of the acardiac twin. This latter condition can lead to the demise of the pump twin due to the abnormal blood flow between the two.

Genetic profile

There is no single known genetic cause for TRAP sequence and the condition does not appear to run in families. There have been a number of types of chromosomal conditions reported in both the acardiac and the pump twin. However, the chromosome abnormality is not believed to be the underlying cause of the condition, but rather the abnormal blood flow between the twins. About 9% of pump twins have a chromosomal abnormality. In most cases, the pump twin is genetically identical to the acardiac twin and they both have normal chromosomes. Specific rates for recurrence are unknown. However, a mother who has had a pregnancy complicated by TRAP sequence is very unlikely to have another pregnancy with the same complication.

KEY TERMS

Dizygotic—From two zygotes, as in nonidentical, or fraternal, twins. The zygote is the first cell formed by the union of sperm and egg.

Fetal echocardiogram—A detailed ultrasound of the fetal heart usually performed between 18 and 24 weeks of gestation.

Fetoscope—A tubular instrument that can be inserted into the abdomen and uterus and used to visualize a fetus during pregnancy.

Fetus—The term used to describe a developing human infant from approximately the third month of pregnancy until delivery. The term “embryo” is used prior to the third month.

Monozygotic—From one zygote, as in identical twins. The zygote is the first cell formed by the union of sperm and egg.

Placenta—An organ in the uterus during pregnancy that allows nutrients and oxygenated blood to flow between mother and fetus.

Polyhydramnios—An overabundance of amniotic fluid present in the amniotic sac surrounding a fetus that can lead to early labor and delivery.

Demographics

TRAP sequence is a rare complication of twinning, occurring only once in about every 35,000 identical twin births. TRAP sequence is believed to complicate 1% of monozygotic twin pregnancies. Risks in triplet, quadruplet, and other higher-order pregnancies are even higher. However, it is believed the condition is underreported because some women miscarry before the condition is identified. Some studies have suggested a slightly higher number of female fetuses with the condition, but other studies have not borne this out. This condition has been documented for more than five centuries and it occurs in many countries and among different races. This condition does not appear to be associated with maternal or paternal age. Chronic illnesses like seizures or lifestyle choices like smoking in the mother do not seem to be contributing factors.

Diagnosis

A mother carrying an acardiac twin pregnancy is not likely to have any unusual symptoms. TRAP sequence is most often found incidentally on prenatal ultrasound. No two cases of acardiac twins are formed exactly alike, so

they may present differently. During ultrasound, an acardiac twin may appear as tissue mass or it may appear to be a twin who has died in the womb. TRAP sequence is always suspected when, on ultrasound, a twin once considered to be dead shows signs of life. The acardiac twin may begin to move or grow or there may be visible blood flow through that twin's umbilical cord. In 50% of cases the acardiac twin has only two, instead of the normal three, vessels in the umbilical cord. A two-vessel umbilical cord may also be found in some normal pregnancies.

Ultrasound diagnostic criteria for the acardiac twin usually include:

- absence of fetal activity
- no heartbeat
- continued growth
- increasing soft tissue mass
- undergrowth of the upper torso
- normal growth of the lower trunk

TRAP sequence may also be missed on prenatal ultrasound. A 1991 report describes an acardiac twin who was missed on ultrasound and only detected at delivery. In rare cases, a diagnosis of acardia is not possible until autopsy.

Treatment and management

There is no consensus on which therapy is best for pregnancies complicated by TRAP sequence. No treatment can save the acardiac twin, so the goal of prenatal therapy is to help the pump twin. The pump twin is not always saved by prenatal treatment.

Cutting off blood circulation to the acardiac twin has been attempted and accomplished through a variety of techniques. The most common techniques are cauterization, which uses heat to seal off the blood-vessel connections between the twins, and radio-frequency ablation (RFA), which accomplishes the same thing but with a smaller instrument and a lower risk of complications. These are both outpatient procedures that can be performed by inserting small hollow needles called trochars through the mother's abdomen into the amniotic sac. Instruments such as a fetoscope (to visualize the fetuses) and coagulation devices are inserted through the trochars. Medications like digoxin may be used to treat congestive heart failure in the pump twin.

Fetal echocardiography is recommended to assist with early detection of heart failure in the pump twin. Chromosome studies are recommended for both fetuses in all pregnancies complicated by TRAP sequence. If an

QUESTIONS TO ASK YOUR DOCTOR

- What type of therapy can lower the risk for heart failure and premature birth of the normal pump twin?
- How often are prenatal ultrasounds recommended?
- What are the risks to the pump twin associated with interrupting the blood flow to the acardiac twin?
- What are my chances of this occurring in future pregnancies?

early delivery of the pump twin is likely, then treatment of the fetus with steroids is recommended to mature the fetal lungs. Delivery at a major medical center with a neonatologist present for the delivery is also recommended. The neonatologist can be prepared to treat the surviving infant for any complications.

Prognosis

The acardiac or parasitic twin never survives, given the severe malformation and lack of a functioning heart. Complications associated with having an acardiac twin cause 50%–75% of pump twins to die. The risk to the pump twin increases with the weight of the acardiac twin. If the acardiac twin outweighs the pump twin by 50%, there is a 65% mortality rate for the pump twin. If the acardiac twin outweighs the pump twin by 75%, then the pump twin dies in 95% of cases. The pump twin is at risk for heart failure and complications associated with premature birth. Heart failure in the pump twin is common. The pump twin of an acardiac twin pregnancy has about a 10% risk for malformations. However, treatment with cord coagulation or radio frequency ablation increases survival in the normal twin up to 90%. A risk with these procedures is premature delivery, although the average gestational age at delivery is 36 to 38 weeks. There is uncertainty about when to treat the pregnancy and when to watch and wait. Some researchers suggest that treatment should occur only if heart failure in the pump twin is imminent. Others recommend earlier treatment. The argument follows that because prognostic indicators for the pump twin are lacking, assistance for the pump twin should begin as soon as possible. There is no long-term data available on the outcomes of surviving pump twins.

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Twin to Twin Transfusion Foundation, 411 Longbeach Pkwy., Bay Village, OH 44140, (800) 815-9211, <http://www.tttsfoundation.org>

Society for Maternal-Fetal Medicine (SMFM), 409 12th St. SW, Washington, DC 20024, (202) 863-2476, (202) 554-1132, smfm@smfm.org, <https://www.smfm.org>

Sonja E. Higgins, MS

Twinner-Kieser syndrome see **Nail-patella syndrome**



Urea cycle disorders

Definition

Urea cycle disorders are inborn errors in metabolism that can lead to brain damage and death. They involve a deficiency in one of the enzymes required by the urea cycle, which removes ammonia from the blood.

Description

Ammonia accumulates in toxic levels if the urea cycle does not convert nitrogen from protein metabolism into urea for excretion into the urine. A series of biochemical reactions are necessary to complete the urea cycle. The urea cycle takes place in liver cells. When an enzyme is missing or deficient, the cycle is interrupted and nitrogen accumulates in the form of ammonia. It cannot be excreted from the body and enters the bloodstream, damaging nervous tissues, including the brain.

Seizures, poor muscle tone, respiratory distress, and coma follow if an affected infant is not treated. Acute neonatal symptoms are most frequently seen in boys with ornithine transcarbamylase (OTC) deficiency. Intellectual disability and even death may follow. People with partial deficiencies may not discover the problem until childhood or adulthood. Children may avoid meat or other protein foods. As ammonia levels rise in the body, individuals begin to show lethargy and delirium. Left untreated, they may suffer a coma or death.

Sometimes young people with urea cycle disorders who go undiagnosed begin to show behavioral and eating problems. Those with partial enzyme deficiencies may experience episodes of high ammonia levels in the blood. This can occur after suffering from viral illnesses, including chicken pox; after eating high-protein meals; or even after significant physical exertion.

The incidence of adults with urea cycle disorders is increasing. Recent evidence has indicated that some people have survived undiagnosed into adulthood. They can

KEY TERMS

Encephalopathy—The medical term for any global dysfunction of the brain. It is not a single disease but rather a syndrome that has many different causes and prognoses.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Urea cycle—A series of complex biochemical reactions that remove nitrogen from the blood so ammonia does not accumulate.

suffer stroke-like symptoms, lethargy, and delirium. Without proper diagnosis and treatment, adults are at risk for permanent brain damage, coma, and death. Symptoms can appear after giving birth or after contracting a virus, and some adults have shown deficiencies after using the medication valproic acid (an antiepileptic drug). Adult onset is more common in women with OTC deficiency.

Different enzymes may be lacking in the various forms of urea cycle disorders. The six major disorders of the urea cycle include the following:

- CPS—Carbamoyl phosphate synthetase
- NAGS—N-acetylglutamate synthetase
- OTC—Ornithine transcarbamylase
- ASD—Argininosuccinic acid synthetase (citrullinemia)
- ALD—Argininosuccinase acid lyase (argininosuccinic aciduria)
- AG—Arginase

Genetic profile

Urea cycle disorders, except for OTC deficiency, are inherited as autosomal recessive traits. OTC deficiency is inherited as an X-linked trait from the mother.

The six major disorders of the urea cycle are caused by mutations of different genes.

- CPS is due to a mutation in the *CPS1* gene located on the long arm of chromosome 2 and responsible for coding the enzyme carbamoyl phosphate synthetase I, which is necessary for many steps in the urea cycle.
- NAGS is due to a mutation in the *NAGS* gene located on the long arm of chromosome 17 and responsible for the enzyme N-acetylglutamate synthase utilized in the urea cycle.
- ASD, also known as citrullinemia, is due to a mutation in genes *ASS1* and *SLC25A13*.
- ALD is due to a mutation in the *ASL* gene located on the long arm of chromosome 7 and responsible for coding the enzyme argininosuccinic aciduria, which is necessary to start reactions within the urea cycle.
- AG is due to a mutation in the *ARG1* gene located on the long arm of chromosome 6 and responsible for the enzyme arginase, which controls the last step of the urea cycle.

If any of these genes are mutated, the urea cycle will be disrupted, and a urea cycle disorder will result.

Demographics

It is estimated that the incidence of urea cycle disorders is about 1 in 30,000 births. These disorders affect males and females equally, except for OTC deficiency, which is more prevalent in males because it is an X-linked disorder.

Signs and symptoms

In severe urea cycle disorders, rising ammonia levels cause irritability, vomiting, and lethargy within the first 24–72 hours of life. Seizures, poor muscle tone, respiratory distress, and coma follow if the infant is not treated. Acute neonatal symptoms are most frequently seen in boys with ornithine transcarbamylase or OTC deficiency. However, patients with mild or moderate urea cycle enzyme deficiencies may not show symptoms until early childhood. In childhood, early symptoms include failure to thrive, inconsolable crying, agitated and/or hyperactive behavior, and refusal to eat. Later symptoms include vomiting, lethargy, delirium, coma, and eventually death if left untreated. Specifically for a deficiency in arginase, childhood symptoms are progressive, usually between the ages of one and four, and include failure to thrive, spastic tetraplegia, seizures, and abnormal movements.

QUESTIONS TO ASK YOUR DOCTOR

- What specific dietary recommendations do you have?
- Can you recommend a dietitian?
- How often should blood tests be performed?
- What symptoms should I report immediately?

Diagnosis

Early detection through blood testing is essential to prevent irreversible brain damage in severe cases of urea cycle disorders. An increase in blood ammonium levels is the primary indicator of a urea cycle disorder, followed by central nervous system manifestation such as irritability progressing to lethargy, decrease in body temperature, seizures, altered muscle tone, and encephalopathy.

Treatment and management

Therapy consists of eating a diet that provides enough protein so the body gets the essential amino acids needed for growth, but not so much that toxic levels of ammonia are formed. Treatment may entail a protein-restricted diet together with medications that provide alternative pathways for the removal of ammonia from the blood. These medications tend to be unpalatable and may be given by way of tube feedings. Blood tests are needed to monitor levels of ammonia, and hospitalizations may become necessary if levels rise too high. Liver transplant may also be a potential treatment protocol, and studies have shown that it has had success in some cases.

Prognosis

With early detection and proper diet restrictions, individuals can lead relatively normal lives. However, irreversible brain damage can develop quickly in severe cases that go undetected.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

National Urea Cycle Disorders Foundation, 75 S. Grand Ave., Pasadena, CA 91105, (626) 578-0833, info@nucdf.org, <http://www.nucdf.org>

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Urogenital adysplasia syndrome

Definition

Urogenital adysplasia syndrome describes a rare disorder characterized by anomalies of the kidneys, urinary tract, and/or reproductive system.

Description

The identification of urogenital adysplasia syndrome resulted from the combined work of multiple physicians examining several families. The first report of siblings born with both kidneys missing (bilateral renal agenesis) was made by H. Madisson in 1934. However, the term “hereditary renal adysplasia” was not coined until 1973 when R. M. Buchta combined the terms “aplasia,” the complete absence of one or both kidneys, and “dysplasia,” developmental anomalies of the kidneys, to form the term “adysplasia” to apply to familial, bilateral kidney anomalies. In 1980, R. N. Schimke and C. R. King suggested that the developmental defects in certain families’ reproductive and urinary tracts (mesonephric and müllerian ducts) may have a common genetic basis and that the designation “hereditary urogenital adysplasia” should be used as a descriptive syndrome name.

Urogenital adysplasia syndrome is an autosomal dominant inherited condition. The symptoms of urogenital adysplasia syndrome are variable. Affected individuals within families may have features of the disease that include one or two missing kidneys (renal agenesis), one or two malformed kidneys (renal dysplasia), bladder anomalies, ureter abnormalities, hypertension, vaginal anomalies, uterine anomalies, fallopian tube anomalies,

lack of a menstrual period (amenorrhea), and cysts of the seminal vesicle. Fetuses that have two missing or very abnormal kidneys are often born with a condition called Potter’s sequence, or syndrome. Potter’s sequence occurs when the fetal kidneys cannot produce enough amniotic fluid to surround the fetus as it develops. Features of Potter’s sequence include wide-set eyes, squashed nose, small and receding chin, low-set ears, deformities of the hands and feet, and incompletely formed lungs (lung hypoplasia).

Urogenital adysplasia syndrome is also referred to as renal hypodysplasia/aplasia 1 (RHDA1), renal agenesis, and renal hypoplasia, isolated. The age of diagnosis for affected individuals often is determined by the symptoms they exhibit. Individuals affected by urogenital adysplasia syndrome may be diagnosed prenatally based on two (bilateral) missing kidneys, at birth based on the features of Potter’s syndrome, or not until adulthood with the findings of reproductive problems or one missing kidney.

Genetic profile

The genetic causes of urogenital adysplasia syndrome are complex and related to mutations in three or more different genes. As of 2015, renal hypodysplasia/aplasia 1 was thought to be caused by mutations in the *ITGA8* gene found on chromosome 10p13. Renal agenesis is believed to be caused by mutations in the *RET* gene found on chromosome 10q11.21, and renal hypoplasia, isolated, is believed to be caused by mutations in the *PAX2* gene found on chromosome 10q24.31.

All three types of urogenital adysplasia are inherited in an autosomal recessive manner. In an autosomal recessive disorder, the individual affected with the condition inherits a mutation from both parents. The parents are carriers of the disease but are not affected. Parents who carry a mutation for the same disease have a 25%, or 1 in 4, chance to have an affected child with each pregnancy.

There is also a form of urogenital adysplasia syndrome known as Mayer-Rokitansky-Küster-Hauser syndrome, which is inherited in an autosomal dominant manner. In an autosomal dominant condition, only one mutated copy of a gene is necessary for a person to experience symptoms of the condition. If a parent has an autosomal dominant condition, there is a 50% chance for each of his or her children to have the same or a similar condition. The genetic cause for this condition was not known as of 2015.

Demographics

Urogenital adysplasia syndrome is a genetic condition that has been found in individuals descended from a

KEY TERMS

Adysplasia—A term referring to the combination of renal agenesis (complete absence of one or both kidneys) and renal dysplasia (developmental anomaly of the kidney).

Amniotic fluid—Fluid contained in a sac within the uterus that surrounds and protects the fetus during its development.

Mesonephric duct—Embryonic structure that in the male becomes the vas deferens, and in both sexes gives rise to the ureters leading to the kidney.

Müllerian ducts—Two embryo structures that in the female develop into vagina, uterus, and oviducts, and in the male disappear except for the vestigial vagina masculina and the appendix testis.

Oligohydramnios—Reduced amount of amniotic fluid. Causes include nonfunctioning kidneys and premature rupture of membranes. Without amniotic fluid to breathe, a baby will have underdeveloped and immature lungs.

Renal agenesis—Complete absence of one or both kidneys.

Renal dysplasia—A developmental anomaly of the kidney.

variety of ethnic backgrounds. Although the exact frequency of urogenital adysplasia syndrome is unknown, it can be estimated based on past family studies. Family studies also indicate that disease symptoms are more severe in males than in females. Between 1 in 3,000 and 1 in 10,000 newborns are born with two severely malformed or missing kidneys (bilateral renal agenesis or dysplasia). It is suggested that urogenital adysplasia syndrome is currently underdiagnosed due to its variability of symptoms within families.

Signs and symptoms

The signs and symptoms of urogenital adysplasia syndrome vary from individual to individual (variable expressivity). Most people diagnosed with urogenital adysplasia syndrome have anomalies in their urinary and reproductive tract. The most common findings include missing kidneys and uterine abnormalities. Specific features may include any of the following:

- one or two missing kidneys (renal agenesis)
- one or two malformed kidneys (dysplastic kidneys)
- bladder anomalies

- hypertension
- vaginal anomalies
- uterine anomalies
- fallopian tube anomalies
- lack of a menstrual period (amenorrhea)
- cysts of the seminal vesicle
- heart anomalies
- small, underdeveloped chin
- intestinal abnormalities
- other facial abnormalities

Additionally, since Potter's sequence occurs when the fetal kidneys cannot produce enough amniotic fluid to cushion the fetus as it develops, the features of Potter's sequence can suggest a diagnosis of urogenital adysplasia syndrome in a baby with wide-set eyes, squashed nose, small and receding chin, low-set ears, deformities of the hand and feet, and incompletely formed lungs (lung hypoplasia).

Diagnosis

Diagnosis of urogenital adysplasia syndrome is usually made by physical examination by a medical geneticist or other physician, an ultrasound of the kidneys and the urinary and reproductive tracts, and a detailed medical family history.

Prenatal diagnosis of severe cases can sometimes be made using targeted ultrasound imaging during pregnancy to provide pictures of the fetal kidneys, bladder, and amniotic fluid levels. Ultrasound results that may indicate urogenital adysplasia syndrome include low amniotic fluid levels (oligohydramnios) combined with missing or abnormally formed kidneys (renal agenesis or adysplasia). Ultrasonographic screening for parents and siblings of infants born with agenesis or adysplasia of the kidneys is recommended, since the diagnosis of urogenital adysplasia syndrome can have implications for their health and medical care.

Treatment and management

Urogenital adysplasia syndrome is a genetic condition that has no specific treatment that can remove, cure, or fix its underlying genetic error. Treatment for urogenital adysplasia syndrome is limited to the management of specific symptoms. Individuals with only one kidney should be followed by a nephrologist who can evaluate their need for antihypertensive agents and/or a kidney transplant. Individuals affected by urinary tract anomalies should be followed by an urologist. Individuals with reproductive anomalies can consult an obstetrician/gynecologist who specializes in pelvic reproductive reconstructive surgery for infertility, endometriosis, pelvic pain, and congenital anomalies. Medical geneticists and

QUESTIONS TO ASK YOUR DOCTOR

- What form of urogenital adysplasia syndrome does my child have?
- Is genetic testing available for this condition?
- What are the chances of having another child affected with urogenital adysplasia syndrome?
- Which medical specialist does my child need to see?
- Can you recommend any literature or websites to learn more about this condition?

genetic counselors are available to discuss inheritance patterns of the syndrome and reproductive options with affected individuals. Pregnant women whose fetuses are at risk for urogenital adysplasia syndrome should be evaluated by a perinatologist or maternal fetal medicine specialist. Other specialists and/or surgeons may be added to an individual's medical team to address specific individual concerns.

Prognosis

Since urogenital adysplasia syndrome results in a variety of different physical symptoms, the prognosis for each affected individual is very different.

Individuals who have one normal kidney and one malformed kidney have an excellent prognosis, and most live normal lives. Individuals who have only one functional kidney may have issues with hypertension and proteinuria.

Individuals with reproductive anomalies may be infertile or have fertility issues. An obstetrician/gynecologist who specializes in pelvic reproductive reconstructive surgery for infertility, endometriosis, pelvic pain, and congenital anomalies may be able, in some cases, to correct some anomalies and restore fertility.

On the most severe end of the spectrum, babies found prenatally to have low amniotic fluid (oligohydramnios) and two missing kidneys (bilateral agenesis or adysplasia) might be miscarried, stillborn, or die after birth due to combined health implications of incompletely formed lungs and missing kidneys.

Resources

BOOKS

Jones, Kenneth Lyons, et al., eds. *Smith's Recognizable Patterns of Human Malformation*. 8th ed. Philadelphia: Elsevier, 2021.

Yu, Alan S. L., et al., eds. *Brenner and Rector's The Kidney*. 11th ed. Philadelphia: Elsevier, 2020.

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Jacquinet, Adeline, et al. "GREB11 Variants in Familial and Sporadic Hereditary Urogenital Adysplasia and Mayer-Rokitansky-Kuster-Hauser Syndrome." *Clinical Genetics* 98, no. 2 (August 2020): 126–137. DOI:10.1111/cge.13769.

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"Urogenital adysplasia." NORD. <https://rarediseases.org/gard-rare-disease/urogenital-adysplasia/> (accessed June 24, 2021).

ORGANIZATIONS

American Association of Kidney Patients, 2710 N. Rocky Point Dr., Suite 150, Tampa, FL 33607, (813) 636-8100 or (800) 749-AAKP, (813) 636-8122, info@aakp.org, <http://www.aakp.org>

Kidney and Urology Foundation of America, 104 W. 40th St., Suite 500, New York, NY 10018, (800) 633-6628, <http://www.kidneyurology.org>

National Kidney Foundation, 30 E. 33rd St., New York, NY 10016, (800) 622-9010, (212) 689-9261, info@kidney.org, <http://www.kidney.org>

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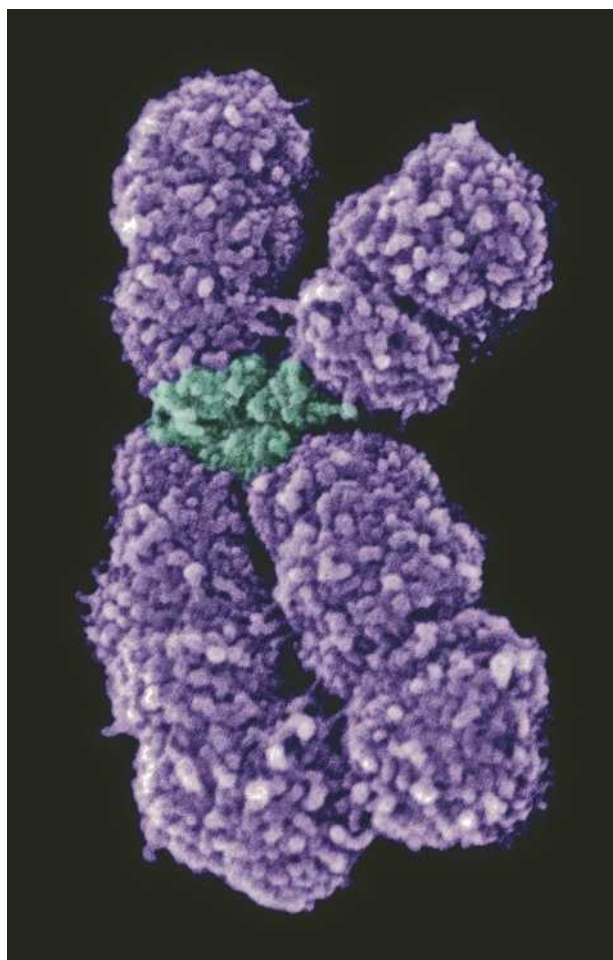
Usher syndrome

Definition

Usher syndrome is an inherited condition that causes hearing loss and a form of vision loss called retinitis pigmentosa (RP), which worsens over time. Some people with Usher syndrome also have difficulties with balance and/or psychological problems. Although the symptoms of Usher syndrome were first described in 1858 by an ophthalmologist named Albrecht von Graefe, it was not until 1914 that it was well documented and recognized to be a genetic condition by another ophthalmologist, Charles Usher. There are three forms of Usher syndrome: type I, II, and III. Genetic research has shown there are many genes located on different chromosomes, all of which can lead to one of the types of Usher syndrome if they are altered.

Description

Usher syndrome is sometimes called hereditary deafness—retinitis pigmentosa, or retinitis pigmentosa and congenital deafness. Usher syndrome causes a specific type of hearing impairment called sensorineural



Colored scanning electron micrograph of human chromosome 10. Gene defects on this chromosome are related to diseases such as Usher syndrome, nonsyndromic deafness, and a form of porphyria. (SPL/Science Source)

hearing loss (SNHL). In order to understand how SNHL occurs, it is important to first understand how normal hearing works. The ear can be divided into three main parts: the outer ear, the middle ear, and the inner ear. The parts of the outer ear include the pinna (the visible portion of the ear), the ear canal, and eardrum. The pinna directs sound waves from the environment through the ear canal and toward the eardrum. The eardrum vibrates and causes tiny bones called ossicles located in the middle ear to move. This movement causes pressure changes in fluids surrounding the parts that make up the inner ear. The main structures of the inner ear are the cochlea and the vestibular system. These structures send information regarding hearing and balance to the brain. The cochlea is shaped like a snail shell and it contains specialized sensory cells (hair cells) that change the sound waves into electrical messages. These messages are then sent to the brain through the auditory nerve that allows the brain to

“hear” sounds from the environment. The vestibular system is a specialized organ that helps people maintain their balance. The vestibular system contains three structures called semicircular canals, which send electrical messages to the brain about movement and body position. This allows people to maintain their balance when moving by sensing changes in their direction and speed.

Sensorineural hearing loss occurs when parts of the inner ear (including the cochlea and/or auditory nerve) do not work correctly. The amount or degree of hearing loss can be described by measuring the hearing threshold (the sound level that a person can just barely hear) in decibels (dB). The greater a person’s dB hearing level, the louder the sound must be to just barely be heard. Hearing loss is often defined as mild, moderate, severe, or profound. For people with mild hearing loss (26–45 dB), understanding conversations in a noisy environment, at a distance, or with a soft-spoken person is difficult. Moderate hearing loss (46–65 dB) causes people to have difficulty understanding conversations, even if the environment is quiet. People with severe hearing loss (66–85 dB) have difficulty hearing conversation unless the speaker is nearby or is talking loudly. Profound hearing loss (85 dB) may prevent people from hearing sounds from their environment or even loud conversation. People with Usher syndrome generally have moderate, severe, or profound SNHL, depending upon the type with which they are diagnosed.

Usher syndrome also causes a specific type of vision loss called retinitis pigmentosa (RP). The eye is made up of many different types of cells and tissues that all work together to send images from the environment to the brain, similar to the way a camera records images. When light enters the eye it passes through the lens and lands on the retina, a very thin tissue lining the inside of the eye. The retina is actually made up of ten different layers of specialized cells, which allow the retina to function similarly to film in a camera, by recording images. There is a small, yellow-pigmented area called the macula, located in the back of the eye in the center of the retina. The retina contains many specialized cells called photoreceptors, which sense light coming into the eye and convert it into electrical messages that are then sent to the brain through the optic nerve. This allows the brain to “see” the environment.

The retina contains two types of photoreceptor cells: rod cells and cone cells. Rod cells are located primarily outside of the macula and they allow for peripheral (side) and night vision. Most of the photoreceptor cells inside of the macula are the cone cells, which are responsible for perceiving color and for viewing objects directly in front of the eye (central vision). In RP, the rod and cone cells degenerate (breakdown) and die over time, resulting in

night blindness and decreased peripheral vision (also called “tunnel vision”). People with Usher syndrome develop RP at different ages depending upon the type (I, II, or III) diagnosed. Although most people with Usher syndrome have fairly good vision before they reach their 30s, it worsens slowly over time and approximately 75% of people in their 70s are blind.

Usher syndrome type I

People with Usher syndrome type I are born with profound SNHL that occurs in both ears. As a result, they do not learn to speak and typically learn to use sign language to communicate with others. Hearing aids usually are not very helpful, due to the amount of hearing loss present. However, some individuals benefit from a procedure called cochlear implantation, in which a small electronic device is surgically placed underneath the skin behind the ear and is attached to a wire that stimulates the inner ear, allowing people to hear useful sounds.

Usher syndrome type I also causes vestibular areflexia; this means affected individuals have balance problems because they cannot sense changes in direction or speed when they are moving. This causes children to more slowly develop certain skills that are required for movement and thus be clumsier and have a hard time with activities that require good balance, such as riding a bicycle. As affected people age, they tend to have an ataxic gait, which means they tend to stumble and shuffle their feet when walking.

The visual problems caused by RP usually develop during childhood among people with this type of Usher syndrome, and they gradually worsen over time. Usually the rod cells in the peripheral retina are affected first, causing night blindness and tunnel vision during childhood. Cone cells may eventually be affected causing blind spots to develop. Eventually, vision loss worsens and affected people can have vision problems during the day. Cataracts (cloudiness in the lens of the eye) may also develop and cause decreased central vision. Although most people with this type of Usher syndrome do not become completely blind, worsening vision may make communication via sign language and lip reading difficult.

Intellectual disability and psychiatric problems (such as depression, bipolar disorder, and psychosis) have been diagnosed in a number of people with Usher syndrome type I as well. Although some specialists believe that the stress of losing both hearing and vision may lead to psychological problems, at least one study has suggested that these problems may be due to an overall smaller brain size that has been measured in some affected individuals.



Hearing aids are medical devices that amplify sound for individuals experiencing hearing loss. (Paul Matthew Photography/Shutterstock)

Usher syndrome type II

People with Usher syndrome type II are born with mild to severe SNHL for low frequency sound that occurs in both ears. The SNHL is profound for higher frequency sounds. The amount of hearing loss is different between affected individuals, even those within the same family, although the ability to hear low frequency sound is often maintained. While hearing problems may worsen very slowly over time, speech therapy and the use of hearing aids are often helpful. Unlike people with type I, the vestibular system is not affected in people with Usher syndrome type II. Thus, they learn to walk in their first year as children and do not have problems with clumsiness. Although the symptoms of RP do occur among individuals with type II, they generally occur later in life during adolescence and adulthood. Symptoms also include night blindness, tunnel vision, blind spots, cataracts, and generally decreased vision. In addition, intellectual disability, psychiatric problems, and decreased brain size have been seen in some people with Usher syndrome type II.

Usher syndrome type III

People with Usher syndrome type III may be born with normal hearing or mild hearing loss, but their hearing loss is progressive, which means that it tends to worsen over time. The vestibular system causes mild balance problems that worsen over time. Older affected people may have balance problems similar to those seen in type I. There is a broad age range when the symptoms of RP occur among people with type III, although usually they happen later in life during the late teens to early adult years. Vision problems also worsen over time. In addition, intellectual disability and psychiatric problems also have been seen in some people with Usher syndrome type III.

People with Usher syndrome and their families often experience emotional and psychological distress.

Depression, anger, and grief are common among affected teenagers and adults. The vision and hearing problems create ongoing challenges for people in terms of their ability to receive information from the world and to effectively communicate with others. Affected people have to continually learn new skills, such as Braille or tactile sign language (i.e. using their hands to physically feel the signs), to adapt to their gradually worsening vision.

Genetic profile

Usher syndrome is inherited in an autosomal recessive manner. “Autosomal” means that males and females are equally likely to be affected. “Recessive” refers to a specific type of inheritance in which both copies of a person’s gene pair (i.e. both alleles) need to have a change or “mutation” in order for the disease to develop. In this situation, an affected individual receives a mutated copy of the same gene from each parent. If the parents are not affected, they each have one working copy of the gene and one nonworking (mutated) copy, and are only “carriers” for Usher syndrome. The chance that two carrier parents will have a child affected with Usher syndrome is 25% for each pregnancy. They also have a 50% chance to have an unaffected child who is simply a carrier, and a 25% chance to have an unaffected child who is not a carrier, with each pregnancy. In the United States, as many as 1 in every 70 people may be a carrier of a mutation that can lead to Usher syndrome.

Although there are three recognizable types of Usher syndrome, genetic research has shown that there are numerous genes located on different chromosomes that can all lead to Usher syndrome. This indicates that there is genetic heterogeneity among different families with Usher syndrome, meaning that different genes can lead to the same or similar disease among different families. As of 2006, researchers had identified six different subtypes of Usher syndrome type I (*USH1B*, *USH1C*, *USH1D*, *USH1E*, *USH1F*, and *USH1G*), four subtypes of Usher syndrome type II (*USH2A*, *USH2B*, *USH2C*, and *USH2D*), and one type of Usher syndrome type III (*USH3*). Although specific genes have been identified for only four of the eleven subtypes, the other seven have been linked to specific chromosomal regions. Two genes initially associated with the syndrome, *USH1A* and *USH2B*, have been removed from the list; *USH1A* was found to be incorrectly determined, and *USH1B* has yet to be verified as an Usher syndrome gene.

Genetic classification of Usher syndrome:

- *USH1B*—Located on chromosome 11q13.5. Specific gene called *myosin VIIA*.
- *USH1C*—Located on chromosome 11p15.1. Specific gene called *harmonin*.
- *USH1D*—Located on chromosome 10q21-22. Specific gene called *CDH23*.

- *USH1E*—Located on chromosome 21q21. Specific gene unknown.
- *USH1F*—Located on chromosome 10q11.2-q21. Specific gene called *protocadherin 15*.
- *USH1G*—Located on chromosome 17q24-q25. Specific gene called *SANS*.
- *USH2A*—Located on chromosome 1q41. Specific gene called *usherin*.
- *USH2C*—Located on chromosome 5q14.3-21.3. Specific gene called *VLGR1b*.
- *USH2D*—Chromosome location unknown. Specific gene called *whirlin*.
- *USH3*—Located on chromosome 3q21-25. Specific gene called *clarin-1*.

Although specific genes have been identified for some of the Usher syndrome subtypes, not all mutations in these genes lead specifically to Usher syndrome. For example, although mutations in *CDH23* can lead to Usher syndrome type 1D, some people who have certain types of mutations in both of their *CDH23* gene copies have a form of autosomal recessive deafness called DFNB12, in which affected individuals have profound SNHL at birth but do not have balance or vision changes that are typically seen in Usher syndrome.

Demographics

It is estimated that 2.5–4.5 per 100,000 people are affected with Usher syndrome in various countries including the United States, Denmark, Sweden, Norway, Finland, and Colombia, although it has been diagnosed in other parts of the world as well. There are some areas where Usher syndrome seems to be more common, including communities in northern Sweden and among the French Acadians in Louisiana. Certain types of Usher syndrome are more common in particular areas of the world as well. For example, among affected people in Finland, approximately 40% have type III. However, in the United States, types I and II are most common and occur with nearly equal frequency, while type III is very rare.

Signs and symptoms

Symptoms of Usher syndrome type I:

- Profound hearing loss at birth, causing lack of speech
- Lack of vestibular function at birth, leading to delayed ability to walk and increased clumsiness
- Retinitis pigmentosa in childhood, causing night blindness, tunnel vision, and decreased vision over time
- Intellectual disability or psychiatric problems in some people

Symptoms of Usher syndrome type II:

- Mild to severe hearing loss for low-frequency sound and profound hearing loss for high-frequency sound at birth
- Normal vestibular function, resulting in normal ability to maintain balance
- Retinitis pigmentosa in teens or early adult years, causing night blindness, tunnel vision, and decreased vision over time
- Intellectual disability or psychiatric problems in some people

Symptoms of Usher syndrome type III:

- Normal hearing or mild hearing loss at birth that worsens over time
- Abnormal vestibular function, causing mild balance problems that worsen over time
- Retinitis pigmentosa by teenage or early adult years, causing night blindness, tunnel vision, and decreased vision over time
- Intellectual disability or psychiatric problems in some people

Diagnosis

Although nine genes that cause Usher syndrome have been identified, genetic testing is not widely used to confirm a diagnosis. Some families do participate in genetic research studies by providing blood samples with the hope that useful information may be learned about their genetic mutations, as well as Usher syndrome in general.

The diagnosis of Usher syndrome is based on the results from a variety of tests that measure hearing, vision, and balance. Sometimes the diagnosis is not made until a person with SNHL reaches adolescence and develops vision problems. A follow-up eye examination may allow an eye care specialist to detect changes seen in RP, thus confirming the diagnosis of Usher syndrome. Specialized testing of an affected person's vestibular system can be done to help determine the type of Usher syndrome as well.

Treatment and management

There is currently no cure for Usher syndrome. Treatment regimens are palliative, addressing symptoms of the syndrome to improve the quality of life for patients.

Treatment and management of SNHL

Regular hearing exams are important to check for changes in hearing ability, especially for people with type II or type III Usher syndrome. Among people with milder

KEY TERMS

Central vision—The ability to see objects located directly in front of the eye. Central vision is necessary for reading and other activities that require people to focus on objects directly in front of them.

Cochlea—A bony structure shaped like a snail shell located in the inner ear. It is responsible for changing sound waves from the environment into electrical messages that the brain can understand, so people can hear.

Genetic heterogeneity—The occurrence of the same or similar disease, caused by different genes among different families.

Peripheral vision—The ability to see objects that are not located directly in front of the eye. Peripheral vision allows people to see objects located on the side or edge of their field of vision.

Photoreceptors—Specialized cells lining the innermost layer of the eye that convert light into electrical messages so that the brain can perceive the environment. There are two types of photoreceptor cells: rod cells and cone cells. The rod cells allow for peripheral and night vision. Cone cells are responsible for perceiving color and for central vision.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Retinitis pigmentosa—Progressive deterioration of the retina, often leading to vision loss and blindness.

Sensorineural hearing loss (SNHL)—Hearing loss that occurs when parts of the inner ear, such as the cochlea and/or auditory nerve, do not work correctly. It is often defined as mild, moderate, severe, or profound, depending upon how much sound can be heard by the affected individual.

Vestibular system—A complex organ located inside the inner ear that sends messages to the brain about movement and body position. It allows people to maintain their balance when moving by sensing changes in their direction and speed.

forms of hearing loss, hearing aids and speech therapy are often useful. Sign language training for people with profound SNHL and their families provides a method of communication, although these skills need to be modified into tactile sign language as vision decreases. Some people with severe to profound forms of hearing loss may have cochlear implants placed in an effort to improve their perception of sound.

QUESTIONS TO ASK YOUR DOCTOR

- When should hearing evaluations begin, and how often should they be repeated?
- Do you recommend vitamin A?
- What are the signs of vitamin A toxicity?
- What measures or resources do you recommend to improve quality of life?
- How likely is it that my children will be affected by my diagnosis?

Treatment and management of RP

People with night blindness, tunnel vision, and decreasing vision may benefit from a variety of techniques that help them cope with their ever-changing vision. The use of walking canes, guide dogs, magnifying lenses, flashlights, and Braille may be helpful. Specialized filtering lenses may decrease glare and make the eye more comfortable. Some people also find it useful to meet with low-vision specialists who can help them adapt to new lifestyle changes that help with daily living. Regular eye exams are important and allow early detection of cataracts, which may be treated with surgery.

Although there is no way to completely halt the symptoms of RP, studies published in the 1990s found that 15,000 IU of vitamin A palmitate can slow the course of the retinal changes among people with Usher syndrome type II. This therapy has not been recommended for people under 18 years of age; women who may become pregnant need to discuss with their doctor the potential harms that vitamin A can cause for a developing baby. People who want to take the vitamin should speak with their doctor first and have regular blood tests to check vitamin levels as well as to rule out liver problems caused by the supplement.

There are a number of support groups available that provide education, support, and helpful advice to help people cope with the symptoms of Usher syndrome.

Prognosis

Usher syndrome generally does not cause a shortened lifespan for affected individuals. Although people live for many years with Usher syndrome, the physical symptoms and emotional side effects change over time. The vision problems usually worsen slowly over the years, forcing people to adapt their lifestyles, modify their habits, and sometimes change professions. Regular eye exams can help diagnose cataracts that may be removed in an effort to maintain the

best vision possible. Regular monitoring of hearing may be helpful for people with mild, moderate, and/or severe hearing loss so that they can receive appropriate hearing aids. As vision problems (and sometimes hearing and/or balance problems) worsen, people are more likely to suffer emotionally due to decreasing quality of life and loss of independence. Many low-vision devices, lifestyle modifications, and various support groups often provide much-needed assistance to help maintain and/or improve quality of life for affected individuals.

Resources

BOOKS

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Jones, Kenneth Lyons, et al., eds. *Smith's Recognizable Patterns of Human Malformation*. 8th ed. Philadelphia: Elsevier, 2021.

Nelson, Leonard B., et al., eds. *Pediatric Ophthalmology*. 2nd ed. Philadelphia: Wolters Kluwer, 2019.

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Bahena, Paulina, et al. "Unraveling the Genetic Complexities of Combined Retinal Dystrophy and Hearing Impairment." *Human Genetics* (June 20, 2021). DOI: 10.1007/S00439-021-02303-1.

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"Usher Syndrome." NORD. <https://rarediseases.org/rare-diseases/usher-syndrome/#:~:text=Usher%20syndrome%20is%20a%20rare,and%20causes%20progressive%20loss%20of> (accessed June 25, 2021).

ORGANIZATIONS

American Council of the Blind, 2200 Wilson Blvd., Suite 650, Arlington, VA 22201-3354, (202) 467-5081 or (800) 424-8666, (703) 465-5085, info@acb.org, <http://www.acb.org>

Foundation Fighting Blindness, 7168 Columbia Gateway Dr., Suite 100, Columbia, MD 21046, (410) 423-0600 or (800) 683-5555, info@FightBlindness.org, <http://www.blindness.org>

Helen Keller Services for the Blind, 141 Middle Neck Rd., Sands Point, NY 11050, (516) 944-8900, (516) 944-7302, info@helenkeller.org, <https://www.helenkeller.org>

Usher Syndrome Coalition, 2 Clock Tower Place, Suite 418, Maynard, MA 01754, (978) 637-2625, <http://www.usher-syndrome.org>

Vestibular Disorders Association, 5018 NE 15th Ave., Portland, OR 97211, (612) 724-6982, (503) 229-8064, info@vestibular.org, <http://www.vestibular.org>

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VACTERL see **VATER association**

Van der Woude syndrome

Definition

Van der Woude syndrome (VWS) is a condition affecting the lips, palate, and teeth. Depressions or pits typically are present on the lower lip at birth and cleft lip and/or cleft palate may also be present. Less commonly, certain teeth may not develop. VWS has previously been known as the lip pit syndrome.

Description

Van der Woude syndrome primarily involves pits developing on the lower lip, clefting of the lip and/or palate, and the absence of certain teeth. More than 80% (more than eight out of ten) individuals with VWS will develop pits near the center of the lower lip and about 60%–70% (six to seven people out of ten) will have a cleft lip and/or palate at birth. About one-half to two-thirds of the individuals will have both lower lip pits and a cleft of the lip and/or palate. In some cases, a cleft palate is present but is not immediately noticeable; this is called a submucosal cleft palate. The least common feature in VWS, missing teeth, is seen in about 10%–20% (one to two people out of ten) of individuals with VWS. The teeth most commonly affected are the second incisors and the second molars.

Van der Woude syndrome is related to another condition called popliteal pterygium syndrome (PPS). PPS is similar to VWS in that both conditions cause lip pits and cleft lip and/or palate to develop. PPS differs from VWS in that popliteal pterygium webs are present at birth. Pterygium means webbed skin. Popliteal refers to the back of the legs. Popliteal pterygium means that there is webbed skin on the back of the legs,

usually on the back of the knees. Individuals with PPS may also have underdevelopment of the genitals, webbing between the fingers, adhesion of the lower and upper eyelids, and fibrous bands attaching the lower and upper jaws.

Some families have features consistent with both VWS and PPS. In other words, within a family, some family members have features that are entirely consistent with VWS and other family members have features consistent with PPS.

Genetic profile

Mutations in the interferon regulatory factor 6 (*IRF6*) gene cause van der Woude syndrome. This gene, located on chromosome 1 at position 1q32.3–q41, provides instructions for making a protein that plays an important role in early development, particularly in cells associated with the growth of tissues in the head and face. A shortage of the IRF6 protein impairs the maturation of these tissues, resulting in the symptoms of van der Woude syndrome. The syndrome follows autosomal dominant inheritance, indicating that every individual affected by VWS has a 50% (1 in 2) chance of passing on the condition to each of his/her children. Every individual inheriting the VWS gene will develop at least one feature of VWS. However, family members may develop different features, and some may develop very minor features whereas another family member may have more severe problems. In some cases, a family member's features may be so mild that he or she is initially thought to be unaffected. Apparently unaffected parents of a newborn with VWS should undergo a thorough examination since it is possible that one of the parents is very mildly affected. If such a parent is determined to be affected, all of his or her children will have a 50% chance of inheriting VWS.

Mutations in the *IRF6* gene are also responsible for PPS, a congenital disorder that affects the face, skin, and genitals. Individuals with abnormalities of the *IRF6* gene

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Cleft—An elongated opening or slit in an organ.

Genetic test—Testing of chromosomes and genes from an individual or unborn baby for a genetic condition. Genetic testing can only be done if the gene is known.

Palate—The roof of the mouth.

Transcription factor—Proteins that activate or deactivate individual genes within the genome.

Ultrasound examination—Visualizing the unborn baby while it is still inside the uterus.

are also at a greater risk of being born with the isolated cleft lip, cleft palate, or both. These malformations are caused because of a deficiency of one of several proteins that are transcription factors, meaning that they help turn genes off and on during development. When these genes are not activated or when the wrong genes are activated, the facial features and other symptoms of VWS are created.

Demographics

According to the Office of Rare Diseases (ORD), van der Woude syndrome is a rare condition, meaning that it affects fewer than 200,000 people in the United States. Prevalence in the general European population is estimated at around 1 in 60,000.

Signs and symptoms

The primary symptom associated with VWS is the development of pits near the center of the lower lip (present in more than 80% of cases). In addition, 60%–70% of individuals with VWS also have cleft lip and/or cleft palate. A few individuals (about 10%–20%) with VWS are missing teeth; most commonly the second incisors and the second molars.

Diagnosis

As of 2009, diagnosis of VWS relied solely upon physical examination and whether or not the characteristic features of VWS are present or absent. The family history may also have an important role in determining the diagnosis. For example, if lower lip pits and a cleft palate are present in a newborn and no popliteal webs or other

feature of PPS is present, then the child has VWS. If a newborn is born with a cleft palate only but has a family history of VWS, then the child most likely has inherited VWS.

As cleft lip and/or palate occurs in other genetic conditions as well as by itself, a newborn with this birth defect needs to be fully evaluated to ensure that the reason for the cleft is correctly determined. Likewise, lower lip pits may be seen in VWS, in PPS, and rarely, in a third genetic condition called orofaciogigital syndrome, type 1; consequently, a baby born with lower lip pits needs to be fully evaluated.

Prenatal diagnosis for VWS can be attempted through ultrasound examination of unborn babies at risk for the condition. Cleft lip and very rarely cleft palate can be identified on ultrasound examination. However, as some clefts are small and some individuals with VWS do not have clefts at all, a normal ultrasound examination cannot completely rule out the chance the baby has inherited VWS. An ultrasound examination with high resolution, or a level 2 ultrasound, and an experienced technician may increase the chance of seeing cleft lips or palate. Lip pits cannot be seen on ultrasound examination, even with a higher resolution ultrasound.

Treatment and management

An individual with VWS will be treated and followed according to the features he or she has developed. The lip pits seen in VWS rarely cause problems. Occasionally, saliva may ooze from the pits and if so, a fistula may have developed. A fistula is an abnormal passage-way or opening, and in VWS, a fistula may develop between a salivary gland located under the lip and the lip surface. The pits and fistulas may be surgically removed.

If a cleft lip and/or palate is present, surgery will be necessary to correct this problem. The treatment and management of cleft lips and palates in individuals with VWS is no different from cleft lips and palates occurring in other genetic conditions or by themselves. The child will need to be followed closely for ear and sinus infections and hearing problems. The child may need speech therapy and should be followed by a dentist and orthodontist. Counseling may be needed as the child grows up to address any concerns about speech and/or appearance.

Prognosis

Overall, individuals with VWS do well. If a cleft lip and/or palate is present at birth, there may be some feeding difficulties in the newborn period and in the following

QUESTIONS TO ASK YOUR DOCTOR

- How is van der Woude syndrome diagnosed in a newborn child?
- What procedures are typically used for the treatment of this disorder?
- Does van der Woude syndrome result in serious mental or physical abnormalities later in life?
- How common is van der Woude syndrome in the United States?

three to six months, until the cleft is corrected. However, once surgery repairing the cleft is completed, the child typically does well. Van der Woude syndrome is not associated with a shorter lifespan.

Resources

BOOKS

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ORGANIZATIONS

- Cleft Palate Association, 1504 E. Franklin St., Suite 102, Chapel Hill, NC 27514-2820, (919) 933-9044 or (800) 242-5338, (919) 933-9604, <http://www.cleftline.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

Cindy L. Hunter, CGC
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VATER association

Definition

VATER association describes a pattern of related birth defects in the same infant involving three or more of the following: vertebrae (spine), anus and rectum, heart, trachea (windpipe), esophagus, radius (bone of the arm), and kidneys. Infants can have any combination of features, and there is a wide range of severity. Survival and medical complications depend on the extent and severity of features in each case.

Description

Doctors Linda Quan and David Smith first developed the term "VATER association" in 1973 to describe a similar pattern of birth defects in more than one infant. The problems at birth did not represent a certain syndrome but appeared to be associated since they were present in several babies. VATER is an acronym or abbreviation representing the first letter of each feature in the association: Vertebral (spine) abnormalities, Anal atresia (partial absence of the anus or unusual connection between anus and rectum), Tracheo-Esophageal fistula (connection between the windpipe and the tube carrying food from mouth to stomach), and Radial (bone of the forearm) or Renal (kidney) differences.

In the 1970s, some researchers expanded the VATER abbreviation to VACTERL. It was expanded to include cardiac (heart) abnormalities, and limb differences in general (differences in the arms and hands). In the expanded VACTERL, "L" includes radial differences and "R" represents kidney differences only. Both VATER and VACTERL are used to describe the same association of birth defects.

The exact cause of VATER is unknown. This is because VATER is rare and because the features vary from patient to patient. Many researchers agree that the cause of VATER occurs very early in the development of the embryo in order to affect so many organ systems. It is unknown whether VATER has a single cause or multiple causes during this early development process.

In the first couple of weeks after conception, a human embryo is a clump of cells that are unspecialized and full of potential. In the third week of pregnancy the embryo undergoes a process called gastrulation. This is when the cells of the embryo begin to group together in different areas. The different cell groups begin to specialize and prepare to form different organs and body parts. The mesoderm is the group of cells that organizes and eventually forms the baby's bones, muscles, heart, blood, kidneys, and reproductive organs. In the third week of

pregnancy, the notochord also develops. The notochord is the future spinal cord and gives the early embryo a center and stability. It may also have a role in organizing other cell groups. The primitive gut also organizes in the fourth week. The primitive gut undergoes more specialization and division into zones called the foregut, midgut, and hindgut. The esophagus (tube from mouth to stomach) and trachea (windpipe) develop from the foregut. The anus and rectum develop from the hindgut. The constant cell movement, grouping, and specialization is a precise process. Any interruption or damage in this early stage can affect multiple organs and body structures.

Some researchers believe the cause of VATER is a problem with gastrulation. Other researchers believe the error occurs when mesoderm cells begin to move to areas to begin specialization. Another theory is that the mesoderm receives abnormal signals and becomes disorganized. Other researchers believe more than one error occurs in more than one area of the early embryo to produce VATER. Some also believe an abnormality of the notochord is involved in the development of VATER.

One group of researchers has discovered that pregnant rats that are given a toxic drug called Adriamycin have offspring with birth defects very similar to those seen in humans with VATER. This has allowed the researchers to study normal and abnormal development of the early embryo. The study of rats showed abnormal notochord development in offspring with connections of the trachea and esophagus. In those offspring, the notochord was thickened and connected unusually to the foregut. More research of this animal model will answer many questions about the development and cause of the features of VATER.

Genetic profile

The exact genetic cause of VATER association is unknown. Most cases are sporadic and do not occur more than once in the same family. This was determined by studies of families with an affected individual. Since cases are rare and most are isolated in a family, studies to find a genetic cause have been unsuccessful. Parents of a child with VATER association have a 1% or less chance of having another baby with the same condition. There have been a few reports of affected individuals with a parent or sibling showing a single feature of the VATER spectrum. There has only been one reported case of a parent and child both affected with multiple VATER features.

Most individuals with VATER association have a normal chromosome pattern. However, a few cases of chromosome differences have been reported in individuals with VATER. One child with VATER had a deletion (missing piece) on the long arm of chromosome 6.

Another male infant had a deletion on the long arm of chromosome 13. There have been other children reported with a chromosome 13 deletion and VATER-like features. This infant was the first reported with the deletion to have all of the VACTERL main features. He was also the first with this chromosome deletion to have a connection between his trachea and esophagus. Another child with VATER association had an extra marker chromosome. This is a fragment of chromosomal material present in the cell in addition to the usual 46 chromosomes. This child's marker was found to contain material from chromosome 12. These cases have not led to the discovery of a gene involved in VATER.

There has only been one VATER case reported in which a genetic change was identified. That female infant died one month after birth because of kidney failure. Her mother and sister later were diagnosed with a mitochondrial disease. Mitochondria are the structures in the cell that create energy by chemical reactions. The mitochondria have their own set of DNA, and a person inherits mitochondrial DNA from the mother only. Stored kidney tissue from the deceased infant was analyzed and she was found to have the same genetic change in her mitochondrial DNA, as her mother and sister. The researchers could not prove that the gene change caused the infant's features of VATER.

There are two subtypes of VACTERL that seem to be inherited. Both types have the typical VACTERL features in addition to hydrocephaly (excess water in the brain). They are abbreviated VACTERL-H. The first subtype was described in 1975 by David and O'Callaghan and is called the David-O'Callaghan subtype. It appears to be an autosomal recessive condition. Parents of an affected child are carriers of a normal gene and a gene that causes VACTERL-H. When both parents are carriers, there is a 25% chance for an affected child with each pregnancy. The second subtype is called Hunter-MacMurray and appears to be an X-linked recessive condition. In X-linked conditions, the disease-causing gene is located on the X chromosome, one of the sex-determining chromosomes. Females have two X chromosomes and males have an X chromosome and a Y chromosome. A female who carries a disease-causing gene on one of her X chromosomes shows no symptoms. If a male inherits the gene he will show symptoms of the condition. A woman who carries the VACTERL-H X-linked gene has a 25% chance of having an affected son with each pregnancy. Both of these subtypes are rare and account for a small number of VACTERL cases.

Demographics

VATER is rare, but has been reported worldwide. Exact incidence can be difficult to determine because of

different criteria for diagnosis. Some studies consider two or more VATER features enough to make the diagnosis. Other studies require at least three features to diagnose VATER. Also, infants with features of VATER may have other genetic syndromes such as trisomy 13, trisomy 18, Holt-Oram syndrome, TAR syndrome, and Fanconi anemia. VATER does appear to be more frequent in babies of diabetic mothers. It is also more frequent in babies of mothers taking certain medications during pregnancy, including estroprogestins, methimazole, and doxorubicin.

Signs and symptoms

VATER has six defining symptoms. “V” represents vertebral abnormalities. Approximately 70% of individuals with VATER have some type of spine difference such as scoliosis (curvature of the spine), hemivertebrae (unusually aligned, extra, or crowded spinal bones), and sacral absence (absence of spinal bones in the pelvic area). Vertebral differences are usually in the lumbosacral area (the part of the spine in the small of the back and pelvis). “A” represents anal atresia which is present in about 80% of individuals with VATER. This is an unusual arrangement or connection of the anus and rectum. Imperforate anus is also common, in which the anal opening does not form or is covered. Babies with this problem cannot pass bowel movements out of the body. “TE” stands for tracheo-esophageal fistula. About 70% of babies with VATER have this problem. This is a connection between the two tubes of the throat: the esophagus (carries food from mouth to stomach) and the trachea (windpipe). This connection is dangerous because it causes breathing problems. These babies can also get food into their windpipe and choke. Lung infections are also common with this connection. Some infants may be missing part of their esophagus, causing problems with choking and feeding. These babies spit up their food because the food cannot get to the stomach.

In the original VATER association, “R” stood for radial differences and renal (kidney) problems. The radius is the forearm bone that connects to the hand on the side of the thumb. Radial differences can include an absent or underdeveloped radius. This often results in a twisted, unusual position of the arm and hand. The thumb can also be small, misplaced, or absent. Kidney problems are present in about half of individuals with VATER. These can include missing kidneys, kidney cysts, or fluid buildup in the kidneys. Some individuals also have an abnormal position of the urethra (the tube that carries urine out of the body).

The expanded VACTERL includes “C” for cardiac (heart) problems and “L” for limb differences. The heart problems are usually holes or other structural abnormalities. Limb differences usually involve the arms rather

KEY TERMS

Anus—The opening at the end of the intestine that carries waste out of the body.

Fistula—An abnormal passage or communication between two different organs or surfaces.

than the legs. The term includes more general differences such as extra fingers, shortened or missing fingers, and underdeveloped humerus (the bone of the upper arm). These differences often cause unusual arm or hand positions (bent or twisted) and fingers that are short, absent, or misplaced.

Many people have proposed an expanded VACTERL pattern to include differences of the reproductive system and absent sacrum. Small or ambiguous (not clearly male or female) genitalia, or misplaced reproductive parts are common in VACTERL. They tend to occur more frequently in infants with anal and kidney abnormalities. They are seen less often with esophagus and arm features. Absence of the bones of the sacrum (spine in the pelvis area) is also commonly seen in VACTERL.

Individuals with VATER have an average of seven to eight features or differences at birth. About two-thirds of features involve the lower body (intestines, genitals, urinary system, pelvis, and lower spine). One-third of features involve the upper body (arms, hands, heart, esophagus, and trachea). In addition to the typical VATER features, infants may have problems with the intestines or excess water in the brain. Intestinal problems (such as missing sections of intestine) are more common in individuals with anal or esophagus features.

Shortly after birth, infants with VATER often have failure to thrive. This involves feeding problems and difficulty gaining weight. Their development is often slow. Infants with visible signs of VATER should immediately be checked for internal signs. Quick detection of problems with the trachea, esophagus, heart, and kidneys can lead to earlier treatment and prevention of major illness. Most individuals with VATER have normal mental development and mental retardation is rare.

Diagnosis

Some features of VATER can be seen on prenatal ultrasound so that the diagnosis may be suspected at birth. Ultrasound can see differences of the vertebrae, heart, limbs, limb positions, kidneys, and some reproductive parts. Other problems that are associated with VATER on ultrasound are poor fetal growth, excessive

QUESTIONS TO ASK YOUR DOCTOR

- What are the risks and benefits for the surgical procedures?
- When should my baby be tested to see whether internal disorders are present?
- Do you recommend orthopedic devices?
- Which family members should undergo genetic testing?

fluid in the womb, absent or collapsed stomach, and one artery in the umbilical cord instead of the usual two. VATER features that cannot be seen on ultrasound are differences of the anus, esophagus, and trachea.

Even if VATER is suspected before birth, an infant must be examined after birth to determine the extent of features. The entire pattern of internal and external differences will determine if the infant has VATER association, another multiple birth defect syndrome, or a genetic syndrome (such as Holt-Oram syndrome, TAR syndrome, or Fanconi anemia). Since VATER overlaps with some genetic syndromes, some infants may fit the VATER pattern and still have another diagnosis. VATER only describes the pattern of related birth defects. Since the genetic causes of VATER are unknown, genetic testing is not available. A family history focusing on VATER features can help to determine if an infant has a sporadic case or a rare inherited case.

Treatment and management

Treatment for VATER involves surgery for each separate feature. Holes in the heart can be closed by surgery. Structural problems of the heart can also often be repaired. Prognosis is best for infants with small or simple heart problems. Some vertebral problems may also need surgery. If the vertebral differences cause a problem for the individual's posture, braces or other support devices may be needed.

Problems with the trachea and esophagus can also be repaired with surgery. Before surgery the infant usually needs a feeding tube for eating. This will stop the choking and spitting up. The infant may also need oxygen to help with breathing. If the trachea and esophagus are connected, the connection is separated first. Once separated, the two trachea ends and esophagus ends can be sealed together. When part of the esophagus is missing, the two loose ends are connected. If the gap between the loose ends is too big, surgery may be delayed until the

esophagus grows. Some infants still have problems after surgery. They may have a difficult time swallowing or food may get stuck in their throat. They may also have asthma and frequent respiratory infections.

Surgery can also repair problems of the anus and rectum. Before surgery, a temporary opening is made from the small intestine to the abdomen. This allows the infant to have bowel movements and pass stool material. An anal opening is created with surgery. The intestines and rectum are adjusted to fit with the new anal opening. The temporary opening on the abdomen may be closed immediately after surgery or it may be closed weeks or months later. Surgeons must be very careful not to damage the nerves and muscles around the anus. If they are damaged, the individual may lose control of their bowel movements.

Differences of the hands and arms can also be improved with surgery. Infants with underdeveloped or absent radius may have a stiff elbow, stiff wrist, or twisted arm. Surgery can loosen the elbow and wrist to allow for movement. The arm can also be straightened. If needed, muscles from other parts of the body can be put into the arm. This may also improve movement. Even after surgery, individuals may not have completely normal function of the muscles and tendons of the arms and hands.

Prognosis

Prognosis for individuals with VATER association depends on the severity of features. Infants with complex heart problems or severe abnormalities of the anus, trachea, or esophagus have a poorer prognosis. Infants with several features that require surgery have a higher death rate than infants that need minor surgery or no surgery. Survival also depends on how quickly internal problems are discovered. The sooner problems with the heart, anus, trachea, and esophagus are found and repaired, the better the outlook for the infant. One study estimated that infants with VATER have a death rate 25 times higher than healthy infants. Another study estimated that up to 30% of individuals with VATER die in the newborn period.

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Ventriculomegaly see **Hydrocephalus**

Viral variant

Definition

A viral variant contains a specific variation (mutation) in its genetic material that makes it different from the virus it originated from. Variants result from errors when the virus replicates, or makes copies of itself. Recombination is another important element in viral variation. Recombination involves mutations occurring in multiple variants that combine during replication to create a newer and sometimes more durable variant or strain of the virus.

Description

In order to replicate, a virus must duplicate its genetic material. The genetic material of SARS-CoV-2, the virus that causes COVID-19 is ribonucleic acid (RNA). It is called an RNA virus. Some viruses, called DNA viruses, have deoxyribonucleic acid (DNA) as their genetic material. Humans have both RNA and DNA.

Viral RNA and DNA contain genes that are the instructions for the creation of proteins. Proteins guide the development and functioning of a virus. The simplest viruses have only enough DNA or RNA to create four

KEY TERMS

DNA—The genetic material that contains the instructions for creating proteins.

DNA virus—A virus whose genetic material is deoxyribonucleic acid (DNA). The instructions from DNA are transcribed into RNA.

Gene—A gene is the unit of information on DNA that contains the instructions for making one protein.

Host—The body that A virus has infected.

Mutation rate.—How often a virus makes errors when copying itself.

Protein—Proteins are the building blocks for life. They guide the development and functioning of a virus.

Replication—The process by which a virus makes copies of itself.

RNA—The genetic material that is involved in creating proteins.

RNA virus—A virus whose genetic material is ribonucleic acid (RNA).

proteins, while more complex viruses have instructions for hundreds of proteins. The DNA holds the instructions for developing proteins but does not create the proteins. In DNA viruses, some of the information from the DNA is transcribed into a molecule called RNA. The pieces of DNA that are transcribed into RNA are called genes. For RNA viruses, the genes are already present in the RNA. In either case, the RNA instructions are converted into proteins.

Because viruses are not much more than genetic material wrapped in a protein shell and sometimes an envelope, they possess genes that allow them to hijack the host's cellular machinery. Viruses use this machinery to help with replication.

Errors can sometimes happen during replication, resulting in a change in the genetic material and a new variant. In some cases, the change is so minor that it doesn't change the virus significantly. If the change is significant and changes the way the virus acts, then it is sometimes called a variant of concern or significance. For example, a variant of concern can be more infectious or more deadly than the original virus. Variants that are more infectious or are more resistant to vaccines often become dominant, since they can outcompete other variants. For example, during the COVID-19 pandemic,

QUESTIONS TO ASK YOUR DOCTOR

- Are there any new treatments for my viral infection?
- How often will I need to be vaccinated?
- What side effects should I watch out for with this vaccine?

variants like the Alpha variant (UK) and the Delta variant (India) spread more quickly than the original virus, since they were 50 to 60 percent better at moving from person to person (transmission). Scientists at the Los Alamos Laboratory in New Mexico documented at least one recombination event involving the SARS-CoV-2 virus in early 2021, a combination derived from the Alpha variant from the U.K. and the Beta variant from California. The resulting variant did not become dominant or circulate widely. Researchers have also presented evidence that the evolution of SARS-CoV-2 and spillover to humans could have been the result of recombination of coronaviruses hosted by pangolins and bats.

The more people who are infected with a virus, the more likely there will be new variants. This is because every time a virus replicates, there is a chance that a new variant will result. New variants may be more likely to occur in patients who are ill for a long period of time or who undergo treatment that forces the virus to mutate in an attempt to evade destruction.

A new strain of a virus is a variant that has very different characteristics. For example, the original SARS-CoV-2 virus is a new strain of the coronavirus. Most coronaviruses cause mild to moderate respiratory conditions like the cold. SARS-CoV-2, on the other hand, causes COVID-19, which is a more deadly infection that affects many different systems in the body.

Vaccines and variants

How easy it is to create a vaccine, and how often you need to be vaccinated depend, in part, on how quickly a virus makes variants. This is called the mutation rate. DNA viruses have lower mutation rates than RNA viruses, since they tend to create variants less often than RNA viruses do. DNA viruses, like smallpox, have a lower mutation rate, since they make a protein called polymerase, which fixes many of the errors that happen during replication. RNA viruses, on the other hand, tend to have higher mutation rates. The mutation rate of RNA

viruses can be a million times higher than the that of human DNA.

The higher the mutation rate, the more difficult it can be to create a lasting vaccine against a virus. Usually the vaccine also needs to be changed frequently to fight viruses that have high mutation rates. Influenza, an RNA virus, has a high mutation rate and requires yearly vaccinations. Vaccine manufacturers have to adjust their vaccine to fight the influenza variant(s) that they think will be dominant in a particular year. Smallpox only required one vaccination, on the other hand, because it has a low mutation rate. That is also one of the reasons why we were able to eradicate smallpox completely, and we no longer require vaccinations against this disease.

SARS-CoV-2 is a coronavirus. Coronaviruses have a slightly lower mutation rate than some other RNA viruses, because they are able to fix some of the errors that happen during replication. They appear to have a higher mutation rate than smallpox. The exact mutation rate of SARS-CoV-2 is unknown, and scientists are unsure of how often the COVID-19 vaccines will need to be modified and how often we will need booster shots.

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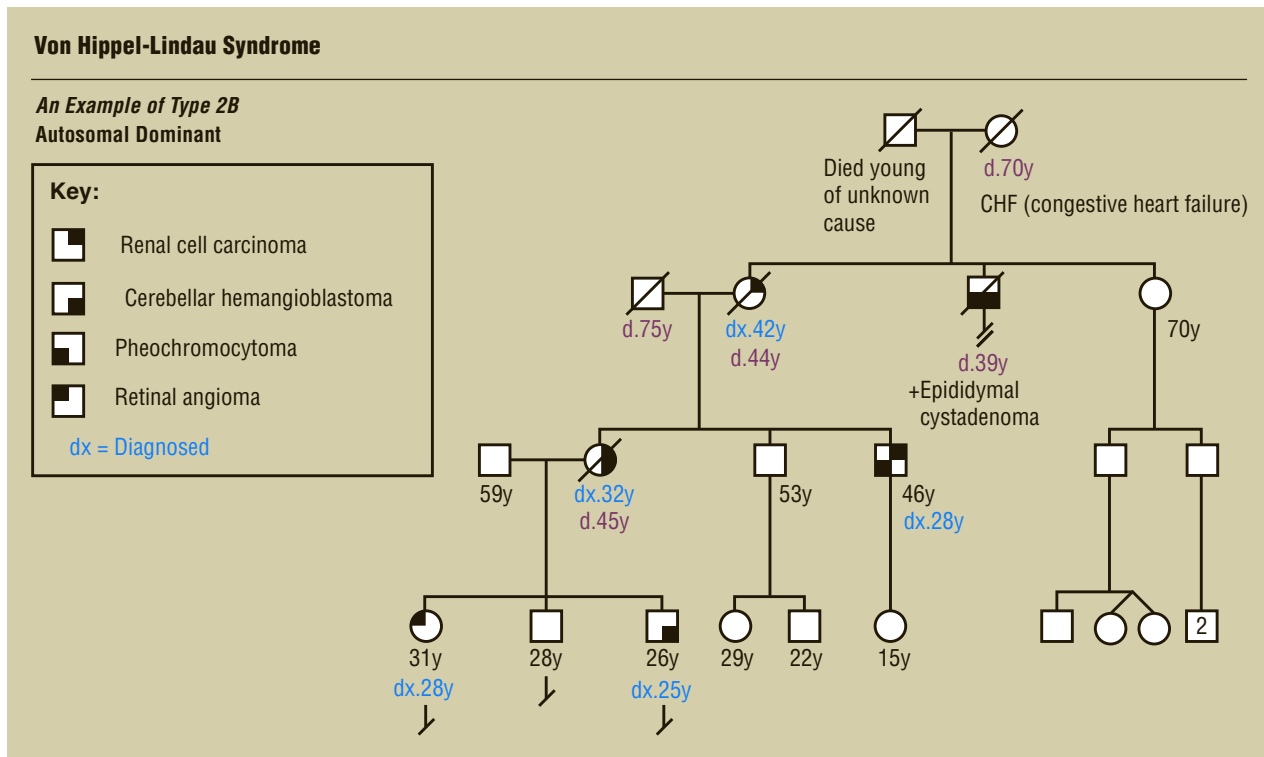
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Von Hippel-Lindau syndrome

Definition

Von Hippel-Lindau (VHL) syndrome is an inherited condition characterized by tumors that arise in multiple locations in the body. Some of these tumors cause cancer and some do not. Many of the tumors seen in VHL are



(Gale)

vascular, meaning that they have a rich supply of blood vessels.

Description

In the mid-1800s, ophthalmologists described vascular tumors in the retina, the light-sensitive layer that lines the interior of the eye. These tumors, called angiomas, were not cancerous but were associated with vision loss. In 1904, a German ophthalmologist named Eugen von Hippel noted that these retinal angiomas seemed to run in families. Twenty-three years later, Arvid Lindau, a Swedish pathologist, reported a connection between these retinal angiomas and similar tumors in the brain, called hemangioblastomas. Like angiomas, hemangioblastomas are vascular tumors. After Lindau noted this association, there were many more reports describing families in which there was an association of retinal angiomas and central nervous system (CNS) hemangioblastomas. Other findings were found to be common in these families as well. These findings included cysts and/or tumors in the kidney, pancreas, adrenal gland, and various other organs. In 1964, Melmon and Rosen wrote a review of the current knowledge of this condition and named the disorder von Hippel-Lindau disease. More recently, the tumors in the retina were determined to be identical to

those in the CNS. They are now referred to as hemangioblastomas, rather than angiomas.

There are four distinct types of VHL, based on the manifestations of the disorder. Type 1 is characterized by all VHL-related tumors except those in the adrenal gland. Type 2 includes tumors of the adrenal gland and is subdivided into type 2A (without kidney tumors or cysts in the pancreas), type 2B (with kidney tumors and cysts in the pancreas), and type 2C (adrenal gland tumors only).

Genetic profile

VHL is inherited in an autosomal dominant manner. This means that an affected person has a 50% chance of passing the disease on to each of his or her children. Nearly everyone who carries the mutation in the *VHL* gene will show signs of the disorder, the average of about 26 years of age and most by 65 years of age.

VHL is caused by a change or mutation in the *VHL* gene. This gene is located on chromosome 3 and produces the VHL protein. The VHL protein is a tumor suppressor, meaning that it controls cell growth. When the *VHL* gene is changed, the VHL protein does not function correctly and allows cells to grow out of control. This

KEY TERMS

Adrenal gland—A triangle-shaped endocrine gland, located above each kidney, that synthesizes aldosterone, cortisol, and testosterone from cholesterol. The adrenal glands are responsible for salt and water levels in the body, as well as for protein, fat, and carbohydrate metabolism.

Angioma—A benign tumor composed of blood vessels or lymph vessels.

Benign—A non-cancerous tumor that does not spread and is not life-threatening.

Bilateral—Relating to or affecting both sides of the body or both of a pair of organs.

Broad ligament—The ligament connecting the ovaries to the uterus.

Computed tomography (CT) scan—An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

Cyst—An abnormal sac or closed cavity filled with liquid or semisolid matter.

Epididymis—Coiled tubules that are the site of sperm storage and maturation for motility and fertility. The epididymis connects the testis to the vas deferens.

Hemangioblastoma—A tumor of the brain or spinal cord arising in the blood vessels of the meninges or brain.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

Magnetic resonance imaging (MRI)—A technique that employs magnetic fields and radio waves to create detailed images of internal body structures and organs, including the brain.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Pancreatic islet cell—Cells located in the pancreas that serve to make certain types of hormones.

Pheochromocytoma—A small vascular tumor of the inner region of the adrenal gland. The tumor causes uncontrolled and irregular secretion of certain hormones.

Renal cell carcinoma—A cancerous tumor made from kidney cells.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

uncontrolled cell growth forms tumors, and these tumors may lead to cancer.

People without VHL have two working copies of the *VHL* gene, one on each chromosome 3. Each of these copies produces the VHL protein. People affected with VHL inherit one working copy and one non-working copy of the gene. Thus, one gene does not make the VHL protein but the corresponding gene on the other chromosome continues to make the functional protein. In this case, cell growth will still be controlled because the VHL protein is available. However, as this person lives, another mutation may occur in the working gene. If this happens, the VHL protein can no longer be made. Cell growth cannot be controlled and tumors develop. Mutations like this occur in various organs at various times, leading to multiple tumors forming in distinct parts of the body over a period of time.

The majority of patients with VHL syndrome inherited the mutation from one of their parents. In approximately 20% of cases, there is no family history of the disorder and VHL occurs because of a new mutation in

the affected individual, termed a *de novo* mutation. If a person appears to be an isolated case, it is important that the parents have genetic testing. It is possible that a parent could carry the mutation in the *VHL* gene but have tumors that do not cause any noticeable symptoms. If a parent is affected, each of his or her future children would have a 50% of being affected with VHL. If both parents test negative for the *VHL* gene mutation, each future child has a 5% risk of inheriting VHL. This small risk is to account for the rare possibility that one parent carries the mutation in his or her sex cells (egg or sperm) but does not express the disorder in any of the other cells of the body.

Demographics

VHL occurs in approximately 1 in 36,000 live births. It is seen in all ethnic groups and both sexes are affected equally.

Signs and symptoms

There are several characteristic features of VHL but no single, unique finding. Thus, it is necessary that many

different specialties be involved in the diagnosis and management of the disease. This approach will ensure proper, thorough care for these patients.

VHL is characterized by hemangioblastomas, tumors that arise in the blood vessel. These tumors are found in the central nervous system, or the brain and spinal cord. They most commonly present between the ages of 25 and 40 years and are the first symptom of VHL in 40% of cases. It is common to see multiple tumors. They may appear at the same time or at different times. These tumors generally grow slowly but, in some cases, may enlarge more rapidly. Hemangioblastomas seen in VHL are benign (non-cancerous) but may produce symptoms depending on their size, site, and number. Hemangioblastomas in the brain may lead to headache, vomiting, slurred speech, or unsteady and uncoordinated movements. These symptoms are usually due to the tumors disrupting brain function or causing increased pressure in the brain. Hemangioblastomas of the spine are usually accompanied by pain, and can lead to loss of sensation and motor skills. Some of these tumors may fail to cause any observable symptoms.

In patients with VHL, hemangioblastomas also appear in the retina, the light-sensitive layer that lines the interior of the eye. These tumors occur in approximately half the cases of VHL and may be the first sign that a person is affected. It is common to see numerous retinal hemangioblastomas develop throughout a person's lifetime. They often can be found in both eyes. These tumors have been detected as early as the age of four years but are more typically found between the ages of 21 and 28 years. They often occur without symptoms, but can be detected on a routine eye exam. If untreated or undetected, they may cause the retina to detach from the eye. This condition is accompanied by bleeding and leads to vision loss and possibly blindness.

Approximately 50%–70% of individuals with VHL also have numerous cysts on their kidneys. Cysts are sacs or closed cavities filled with liquid. In VHL, these cysts are vascular and frequently occur in both kidneys; however, they rarely result in noticeable symptoms. In some cases, these cysts may develop into renal cell carcinomas. These are cancerous tumors that are composed of kidney cells. Seventy percent of people affected with VHL will develop this type of kidney tumor during their lifetime. This type of cancer is generally diagnosed between the ages of 41 and 45 years. By the time this condition produces symptoms, it is likely that the cancer has already spread to other parts of the body. If this is the case, the tumors will respond poorly to chemotherapy and radiation, two common cancer treatments.

VHL can also cause multiple cysts in the pancreas. These occur at the average age of 41 years and are vascular in nature. Pancreatic cysts rarely cause problems and tend to grow fairly slowly. Pancreatic islet cell tumors can occur as well but are unrelated to the cysts. Islet cells in the pancreas produce hormones. Hormones are substances that are produced in one organ and then carried through the bloodstream to another organ where they perform a variety of functions. When tumors occur in the islet cells of the pancreas, these cells secrete too many hormones. This increase in hormones rarely leads to recognizable symptoms. Pancreatic islet cell tumors grow slowly and are non-cancerous.

Additionally, tumors in the adrenal gland, called pheochromocytomas, are common in VHL. The adrenal glands are located on top of each kidney. They secrete various hormones into the bloodstream. Pheochromocytomas are made of cells from the inner region of the adrenal gland. These tumors are benign, but can be numerous and are often located in both adrenal glands. They can be confined to the inside of the adrenal gland, or they can travel and appear outside of it. Some do not cause any observable symptoms. Others can lead to high blood pressure, sweating, and headaches.

In approximately 10% of cases, tumors can also be found in the inner ear. Most often, these tumors occur in both ears. They may lead to hearing loss of varying severity. This hearing loss may be one of the first signs that an individual is affected with VHL. Less commonly, a person may complain of dizziness or a ringing in the ear due to these inner ear tumors.

Men with VHL commonly have tumors in the epididymis. The epididymis is a structure that lies on top of the testis and serves as the site for sperm storage and maturation for motility and fertility. If these tumors occur bilaterally, they can lead to infertility. However, as a general rule, they do not result in any health problems. The equivalent tumor in females is one that occurs in the broad ligament. This ligament connects the ovaries to the uterus. These tumors, however, are much less common than those in the epididymis.

It is important to note that wide variation exists among all individuals affected with VHL in regard to the age of onset of the symptoms, the organ systems involved, and the severity of disease.

Diagnosis

VHL can be diagnosed clinically, with or without genetic testing. If a person has no family history of the disorder, a diagnosis of VHL can be made if one of the following criteria are met:

- the patient has two or more hemangioblastomas of the retina or CNS
- the patient has a single hemangioblastoma along with one of the other tumors or cysts that are commonly associated with the disorder.

A diagnosis of VHL can also be established in a person who has a positive family history of the disorder if they show one or more of the following before the age of 60:

- retinal hemangioblastoma
- CNS hemangioblastoma
- pheochromocytoma
- multiple pancreatic cysts
- tumor of the epididymis
- multiple renal cysts
- renal cell carcinoma
- endolymphatic sac tumors

Several tests are available that can assist in the diagnosis of VHL. They can also determine the extent of symptoms if the diagnosis has already been made. A computed tomography (CT) scan or magnetic resonance imaging (MRI) is often utilized for these purposes. These procedures serve to produce images of various soft tissues in the body, such as the brain and abdominal area. In someone with VHL, they are used to assess for the presence of CNS hemangioblastomas and other tumors associated with the disorder, such as pheochromocytomas and inner ear tumors. Pheochromocytomas may also cause abnormal substances to be released into the urine. A urinalysis can detect these substances and, therefore, suggest the existence of these tumors. Additionally, ultrasound examination can assist in evaluating the epididymis, broad ligament, and kidneys. Ultrasound examination involves the use of high frequency sound waves. These sound waves are directed into the body and the echoes of reflected sound are used to form an electronic image of various internal structures.

VHL can also be diagnosed via examination of the *VHL* gene on the molecular level. This type of testing detects approximately 90%–100% of people who are affected with the disorder and is indicated for confirmation of the diagnosis in cases of suspected or known VHL. Molecular genetic testing examines the *VHL* gene and detects any mutations, or changes in the gene. Most often, in this disorder, the gene change involves a deletion of a part of the gene or a change in one of the bases that makes up the genetic code.

Since molecular testing is so accurate, it is recommended even in cases where the clinical criteria for diagnosis are not met. It is possible that the tumors associated

QUESTIONS TO ASK YOUR DOCTOR

- How frequently should we evaluate for the presence of tumors?
- What tests do you recommend?
- When should gene testing be performed?
- When should renal testing be performed, and how often should it be repeated?

with VHL are present but are not causing any observable symptoms. Thus, even if a person does not meet the diagnostic criteria mentioned above, molecular testing can be used as a means of “ruling out” VHL with a high degree of certainty. For patients with numerous, bilateral pheochromocytomas, or for those who have a family history of these tumors, molecular testing is strongly suggested since these tumors may be the only signs of the disorder in those with VHL type 2C.

VHL can be diagnosed at various ages, ranging from infancy to the seventh decade of life or later. The age of diagnosis depends on the expression of the condition within the family, and whether or not asymptomatic lesions are detected.

Treatment and management

There is no treatment for VHL because the genetic defect cannot be fixed. Management focuses on routine surveillance of at-risk and affected individuals for early detection and treatment of tumors.

For at-risk relatives of individuals diagnosed with VHL, molecular genetic testing is recommended as part of the standard management. If a person tests negative for the mutation, costly screening procedures can be avoided. If an at-risk relative has not been tested for the mutation, surveillance is essential for the early detection of signs of VHL.

The following groups of people should be routinely monitored by a physician familiar with VHL:

- individuals diagnosed with VHL
- individuals who are asymptomatic but who have tested positive for a mutation in the *VHL* gene
- individuals who are at-risk due to a family history of the disorder but have not undergone molecular testing

For these groups of people, annual physical examinations are recommended, along with neurologic evaluation for signs of brain or spinal cord tumors. Additionally, blood pressure screening and an eye exam

should be completed annually, beginning around one year of age. These exams can detect retinal hemangioblastomas, which often produce no clinical symptoms until serious damage occurs. Beginning at the age of five, in addition to the screenings started at age one, urinary screening for fractionated metanephrines should be performed yearly, and auditory screening should be performed every two to three years, particularly in those with recurrent inner ear infections. When a person reaches the age of 16, an abdominal ultrasound should be completed annually as well. Any suspicious findings should be followed up with a CT scan or MRI. If pheochromocytomas are in the family history, blood pressure should be monitored annually. Although the majority of tumors associated with VHL are benign in nature, they all have a small possibility of becoming cancerous. For this reason, surveillance and early detection is very important to the health of those affected with VHL.

If any tumors are identified by the above surveillance, close monitoring is necessary and surgical intervention may be recommended. Hemangioblastomas of the brain or spine may be removed before they cause symptoms. They may also be followed with yearly imaging studies and removed only after they begin to cause problems. Most of these tumors require surgical removal at some point and results are generally good. Retinal hemangioblastomas can be treated with various techniques that serve to decrease the size and number of these tumors.

Early surgery is recommended for renal cell carcinoma (RCC). Extreme cases may require removal of one or both kidneys, followed by a transplant. Additionally, studies have proposed further trials should be done for the treatment of RCC in patients with VHL via oral drugs such as Sunitinib, which is a multitargeted receptor tyrosine kinase inhibitor with antiangiogenic and antitumor activity. This drug has shown success in patients with RCC and may be effective in patients with RCC due to VHL. Additionally, pheochromocytomas should be surgically removed if they are causing symptoms. Inner ear tumors, however, generally are slow-growing. The benefit of removing one of these tumors must be carefully compared to the risk of deafness, which may result from the surgery. Epididymal and broad ligament tumors generally do not require surgery.

Prognosis

The average life expectancy of an individual with VHL is 49 years. Renal cell carcinoma is the leading cause of death for affected individuals. If an affected person is diagnosed with renal cell carcinoma, their average life expectancy decreases to 44.5 years. CNS hemangioblastomas are responsible for a significant proportion of

deaths in affected individuals as well, due to the effects of the tumor on the brain.

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- VHL Family Alliance, 2001 Beacon St., Suite 208, Boston, MA 02135-7787, (800) 767-4845, info@vhl.org, <http://www.vhl.org>

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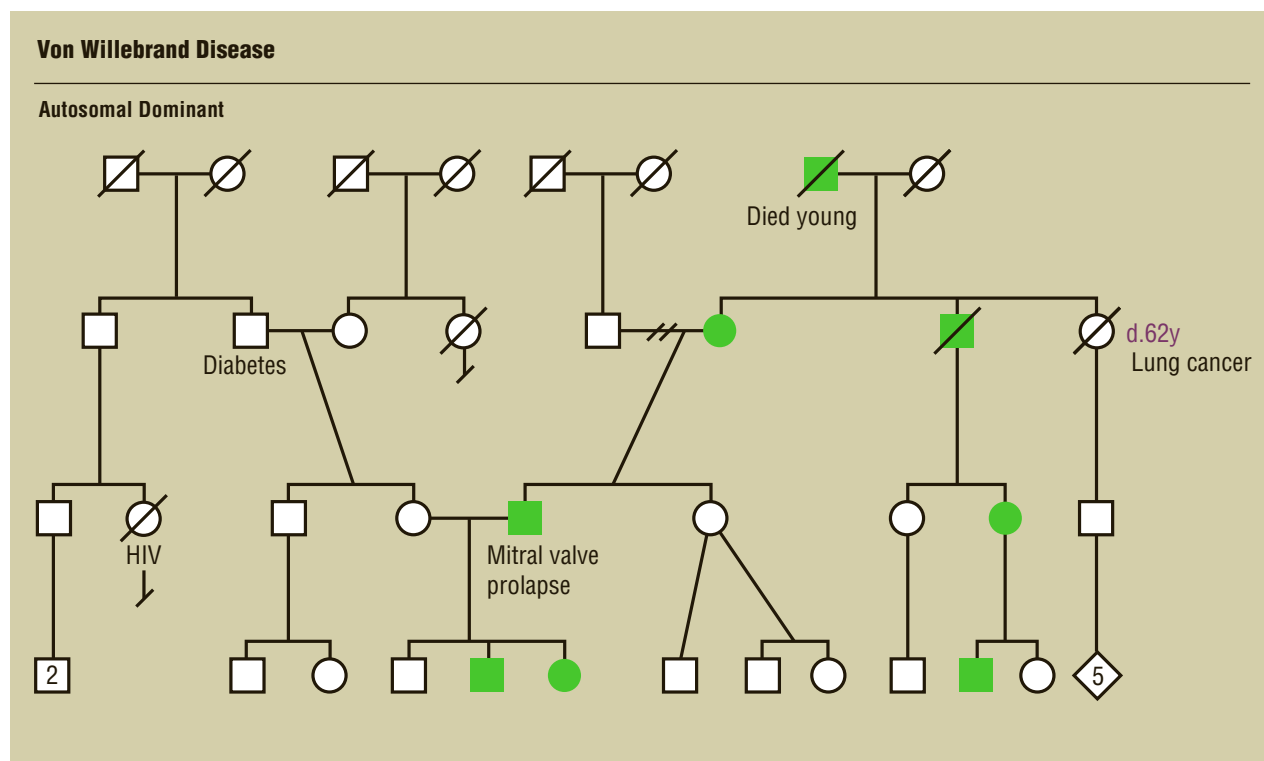
von Willebrand disease

Definition

Von Willebrand disease is caused by a deficiency or an abnormality in a protein called von Willebrand factor (VWF) and is characterized by prolonged bleeding.

Description

The Finnish physician Erik von Willebrand was the first to describe von Willebrand disease (VWD). In 1926 Dr. von Willebrand noticed that many male and female members of a large family from the Åland Islands had increased bruising (bleeding into the skin) and prolonged episodes of bleeding. The severity of the bleeding varied between family members, ranged from mild to severe, and typically involved the mouth, nose, genital and urinary tracts, and occasionally the intestinal tract. Excessive bleeding during the menstrual period was also experienced by some of the women in this family. What



von Willebrand Disease: pedigree analysis chart (Gale)

differentiated this bleeding disorder from classical hemophilia was that it appeared not to be associated with muscle and joint bleeding and affected women and men rather than just men. Dr. von Willebrand named this disorder hereditary pseudohemophilia.

Pseudohemophilia, or von Willebrand disease (VWD) as it is now called, is caused when the body does not produce enough of a protein called von Willebrand factor (VWF) or produces abnormal VWF. VWF is involved in the process of blood clotting (coagulation). Blood clotting is necessary to heal an injury to a blood vessel. When a blood vessel is injured, VWF enables blood cells called platelets to bind to the injured area and form a temporary plug to seal the hole and stop the bleeding. VWF is secreted by platelets and by the cells that line the inner wall of the blood vessels (endothelial cells). The platelets release other chemicals, called factors, in response to a blood vessel injury, which are involved in forming a strong permanent clot. VWF binds to and stabilizes factor VIII, one of the factors involved in forming the permanent clot.

A deficiency or abnormality in VWF can interfere with the formation of the temporary platelet plug and also affect the normal survival of factor VIII, which can indirectly interfere with the production of the permanent clot. Individuals with VWD, therefore, have difficulty in

forming blood clots and, as a result, they may bleed for longer periods of time. In most cases the bleeding is due to an obvious injury, although it can sometimes occur spontaneously.

VWD is classified into three basic types: type 1, 2, and 3, based on the amount and type of VWF that is produced. Type 1 is the most common and mildest form, and results when the body produces slightly decreased amounts of typically normal VWF. Type 2 can be classified into four subtypes (A, B, M, N) and results when the body produces an abnormal type of VWF. Type 3 is the rarest and most severe form, and results when the body does not produce any detectable VWF.

Genetic profile

The genetics of VWD are complex and involve a gene that produces VWF and is found on chromosome 12. Since individuals inherit two of each type of chromosome, they inherit two *VWF* genes. There are different types of changes in the *VWF* gene that can affect its production. Some types of changes can cause the *VWF* gene to produce decreased amounts of normal VWF, while other changes can cause the gene to produce abnormal VWF. Most of the gene changes are significant enough that a change in only one *VWF* gene is sufficient to cause VWD. Some gene changes only cause VWD if both

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Biochemical testing—Measuring the amount or activity of a particular enzyme or protein in a sample of blood, urine, or other tissue from the body.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Desmopressin (DDAVP)—A drug used in the treatment of von Willebrand's disease.

Diagnostic testing—Testing performed to determine if someone is affected with a particular disease.

DNA testing—Analysis of DNA (the genetic component of cells) in order to determine changes in genes that may indicate a specific disorder.

Endothelial cells—The cells lining the inner walls of the blood vessels.

Factor VIII—A protein involved in blood clotting that requires VWF for stability and long-term survival in the bloodstream.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

Platelets—Small disc-shaped structures that circulate in the bloodstream and participate in blood clotting.

Prenatal testing—Testing for a disease such as a genetic condition in an unborn baby.

Protein—Important building blocks of the body, composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

Skin hematoma—Blood from a broken blood vessel that has accumulated under the skin.

von Willebrand factor (VWF)—A protein found in the blood that is involved in the process of blood clotting.

genes are changed, which often leads to more severe symptoms. Type 1 VWD is called an autosomal dominant condition since it is caused by a change in only one *VWF* gene. Since type 1 VWD results in only a slight decrease in the amount of VWF produced, the symptoms are often mild and even nonexistent in some patients. Most cases of Type 2 VWD are autosomal dominant since they are caused by a change in only one *VWF* gene that results in the production of an abnormal protein. An autosomal dominant form of VWD can be inherited from either

parent or can occur spontaneously in the embryo that is formed when the egg and sperm cells come together during fertilization.

Some cases of type 2 VWD and all cases of type 3 VWD are autosomal recessive since they are caused by changes in both *VWF* genes. A person with an autosomal recessive form of VWD has inherited a changed gene from his or her mother and a changed gene from his or her father. Parents who have a child with an autosomal recessive form of VWD are called carriers, since they

each possess one changed *VWF* gene and one unchanged *VWF* gene. Many carriers for the autosomal recessive forms of type 2 VWD and type 3 VWD do not have any symptoms, although some people with type 3 VWD are born to parents who have type 1 VWD and may have symptoms. Each child born to parents who are both carriers for VWD has a 25% chance of having VWD, a 50% chance of being a carrier, and a 25% chance of being neither a carrier nor affected with VWD disease. A person with an autosomal dominant form of VWD has a 50% chance of passing the changed gene on to his or her children, who may or may not have symptoms.

Demographics

Approximately 1 out of 100 to 1 out of 10,000 people are affected with VWD, making it the most common inherited bleeding disorder (hemophilia). VWD affects people of all ethnic backgrounds. Approximately 70%–80% of people with VWD have type 1 and close to 20%–30% have type 2. Type 3 is very rare and occurs in less than one percent of people with VWD.

Signs and symptoms

VWD is usually a relatively mild disorder characterized by easy bruising, recurrent nosebleeds, heavy menstrual periods, and extended bleeding after surgeries and invasive dental work. There is a great deal of variability in the severity of symptoms, which can range from clinically insignificant to life threatening. Even people within the same family who are affected with the same type of VWD may exhibit different symptoms. An individual with VWD may exhibit a range of symptoms over the course of his or her lifetime and may experience an improvement in symptoms with age. The severity of the disease is partially related to the amount and type of VWF that the body produces, but is also influenced by other genetic and nongenetic factors.

Type 1

Type 1, the mildest form of VWD, is usually associated with easy bruising, recurrent nosebleeds, heavy menstrual periods, and prolonged bleeding after surgeries and invasive work. Many people with type 1 VWD do not have any noticeable symptoms or only have prolonged bleeding after surgery or significant trauma. The amount of VWF produced by the body increases during pregnancy, so prolonged bleeding during delivery is uncommon in people with type 1 VWD.

Type 2

People with type 2 VWD usually have symptoms from early childhood and symptoms may even be present

at birth. They usually experience prolonged bleeding from cuts, easy bruising, nosebleeds, skin hematomas, and prolonged bleeding from the gums following teeth extraction and minor trauma. More than 50% of women with type 2 VWD experience heavy periods that may require a blood transfusion. Gastrointestinal bleeding is rare but can be life-threatening. Some women with type 2 VWD exhibit prolonged bleeding during delivery.

Type 3

Type 3 VWD can be quite severe and is associated with bruising and bleeding from the mouth, nose, intestinal, and genital and urinary tracts. Type 3 is also associated with spontaneous bleeding into the muscles and joints, which can result in joint deformities. Some women with type 3 VWD experience prolonged bleeding during delivery.

Diagnosis

Diagnostic testing

Many people with VWD have mild symptoms or symptoms that can be confused with other bleeding disorders making it difficult to diagnose it on the basis of clinical symptoms. VWD should be suspected in any person with a normal number of platelets in their blood and bleeding from the mucous membranes such as the nose, gums, and gastrointestinal tract. Testing for an individual with suspected VWD often includes the measurement of:

- how long it takes for the bleeding to stop after a tiny cut is made in the skin (the bleeding time)
- the amount of VWF (VWF antigen measurement)
- the activity of VWF (ristocetin co-factor activity)
- the amount of factor VIII (factor VIII antigen measurement)
- activity of factor VIII

People with type 1 VWD usually have an increased bleeding time but they may have an intermittently normal bleeding time. They also have a decreased amount of VWF, decreased VWF activity, and usually have slightly decreased factor VIII levels and activity. People with type 2 VWD have a prolonged bleeding time, decreased activity of VWF, and may have decreased amounts of VWF and factor VIII, and decreased factor VIII activity. Type 3 individuals have undetectable amounts of VWF, negligible VWF activity, factor VIII levels of less than 5%–10%, and significantly reduced factor VIII activity. The activity of VWF is reduced for all types of VWD, making it the most sensitive means of identifying all three types of VWD. Patients with borderline results should be tested two to three times over a three-month period.

Once a patient is diagnosed with VWD, further testing such as VWF multimer analysis and ristocetin-

QUESTIONS TO ASK YOUR DOCTOR

- What are the risks and benefits of DDAVP therapy?
- In DDAVP therapy, do you recommend the intravenous or nasal inhaler mode of treatment?
- How can nasal and mouth bleeding be managed?
- In addition to aspirin, should other drugs be avoided?

induced platelet aggregation (RIPA) may need to be performed to determine the subtype. Multimer analysis evaluates the structure of the VWF, and RIPA measures how much ristocetin is required to cause the clumping of platelets in a blood sample. The VWF multimer analysis is able to differentiate people with a structurally normal VWF (type 1) from people with a structurally abnormal VWF (type 2), and is often able to identify the subtype of patients with type 2 VWD. People with type 1 VWD usually have normal to decreased RIPA concentrations. Depending on the subtype, patients with type 2 VWD either have increased or decreased RIPA. In people with type 3 VWD, RIPA is usually absent and the multimer analysis shows undetectable VWF.

In some cases DNA testing can be a valuable adjunct to biochemical testing. The detection of gene alteration(s) can confirm a diagnosis and can determine the type and subtype of VWD. It can also help to facilitate prenatal testing and testing of other family members. Unfortunately, many people with VWD possess DNA changes that are not detectable through DNA testing. A person who has a mother, father, or sibling diagnosed with VWD should undergo biochemical testing for VWD. If the relative with VWD possesses a detectable gene change, then DNA testing should also be considered.

Prenatal testing

If one parent has been diagnosed with an autosomal dominant form of VWD, or both parents are carriers for an autosomal recessive form of VWD, then prenatal testing can be considered. If the parent with an autosomal dominant form of VWD possesses a detectable gene change, or both parents who are carriers for an autosomal recessive form of VWD possess detectable mutations, then DNA testing of their fetus would be available. DNA testing can be performed through amniocentesis or chorionic villus sampling. If the DNA change in the

parent(s) is unknown then prenatal testing can sometimes be performed through biochemical testing of blood obtained from the fetal umbilical cord, which is less accurate and is associated with a higher risk of pregnancy loss.

Treatment and management

VWD is most commonly treated by replacement of VWF through the administration of blood products that contain VWF or through treatment with desmopressin (DDAVP, 1-deamino-8-D-arginine vasopressin). DDAVP functions by increasing the amount of factor VIII and VWF in the bloodstream. Treatment with blood products or DDAVP may be started in response to uncontrollable bleeding or may be administered prior to procedures such as surgeries or dental work. The type of treatment chosen depends on the type of VWD and a patient's response to a preliminary treatment trial.

Treatment with desmopressin

DDAVP is the most common treatment for people with type 1 VWD. About 80% of people with type 1 VWD respond to DDAVP therapy. Treatment with DDAVP can also be used to treat some people with type 2 VWD. Patients with Type 2B VWD should not be treated with this medication since DDAVP can induce dangerous platelet clumping. Type 3 VWD should not be treated with DDAVP since this medication does not increase the level of VWF in type 3 patients. DDAVP should only be used in people who have been shown to be responsive through a pre-treatment trial transfusion with this medication.

DDAVP can be administered intravenously or through a nasal inhaler. DDAVP has relatively few side effects, although some people may experience facial flushing, tingling sensations, and headaches after treatment with this medication. Often treatment with this medication is only required prior to invasive surgeries or dental procedures.

Treatment with blood products

Patients who are unable to tolerate or are unresponsive to drug-based treatments are treated with concentrated factor VIII obtained from blood products. Not all factor VIII concentrates can be used since some do not contain enough VWF. The concentrate is treated to kill most viruses, although caution should be used since not all types of viruses are destroyed. If the factor VIII concentrates are unable to manage a severe bleeding episode, then blood products called cryoprecipitates, which contain concentrated amounts of VWF, or platelet concentrates should be considered. Caution should be

used when treating with these blood products since they are not treated to kill viruses.

Recombinant VWF

As of 2013, patients who did not respond to treatments with desmopressin or other therapy methods could be treated using Recombinant VWF. Recombinant VWF is a protein replacement therapy and in clinical trials has shown very high efficacy in the treatment and management of musculoskeletal and mucosal bleeding.

Other treatments and precautions

Medications called fibrinolytic inhibitors can be helpful in the control of intestinal, mouth, and nose bleeding. Estrogens such as are found in oral contraceptives increase the synthesis of VWF and can sometimes be used in the long-term treatment of women with mild to moderate VWD. Estrogens are also sometimes used prior to surgery in women with type 1 VWD. Some topical agents are available to treat nose and mouth bleeds. Patients with VWD should avoid taking aspirin, which can increase their susceptibility to bleeding, and people with severe forms of VWD should avoid activities that increase their risk of injury such as contact sports.

Prognosis

The prognosis for VWD disease is generally fairly good and most individuals have a normal lifespan. The prognosis can depend, however, on accurate and early diagnosis and appropriate medical treatment.

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ORGANIZATIONS

- Canadian Hemophilia Society, 301–666 Sherbrooke St. W, MontrealQuebecCanada H3A 1E72, (514) 848-0503, (514) 848-9661, chs@hemophilia.ca, <http://www.hemophilia.ca/english/index.html>
- National Hemophilia Foundation, 7 Penn Plaza, Suite 1204, New York, NY 10001, (800) 424-2634, handi@hemophilia.org, <http://www.hemophilia.org>

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Vrolik type of osteogenesis imperfecta see
Osteogenesis imperfecta



Waardenburg syndrome

Definition

Waardenburg syndrome (WS) encompasses several different hereditary disorders, the main features of which variably include abnormal pigmentation, hearing loss, and a subtle difference in facial features. Certain other physical anomalies occur less frequently in WS.

Description

In 1951, Dr. Petrus Waardenburg reported a syndrome of dystopia canthorum, heterochromia of the irides, and hearing loss. Dystopia canthorum (also called telecanthus) describes a subtle, unusual facial feature in which the inner corners of the eyes (canthi) are spaced farther apart than normal, yet the eyes (pupils) themselves are normally spaced, resulting in eyes that appear to be widely spaced, even though they are not. Heterochromia means different-colored, and irides is the plural form of iris—the colored portion of the eye. Thus, someone with heterochromia of the irides has different colored eyes, often one brown and one blue. Another feature not originally noted by Dr. Waardenburg, but now considered a major sign of WS, is a white forelock (white patch of hair extending back from the front of the scalp). In fact, disturbances in pigmentation (coloring) of various parts of the body are consistent features of WS. Uncommon but serious physical anomalies associated with WS include Hirschsprung disease (intestinal malformation), spina bifida, cleft lip/palate, and musculoskeletal abnormalities of the arms.

Five types of WS have been defined based on clinical symptoms or genetic linkage. Six different genes are associated with WS. Most families show autosomal dominant inheritance, but autosomal recessive inheritance and sporadic (single) cases are also seen. People with WS are not at increased risk for intellectual disability and vision loss is not more common. For the majority of those with

WS, hearing loss is the only major medical problem they will have.

WS1 is the “classic” form of WS, and if someone uses just the name Waardenburg syndrome with no modifying number, they are most likely referring to the group of disorders as a whole or just WS1. WS2 may occasionally be referred to as WS without dystopia canthorum. WS3 is also known as Klein-Waardenburg syndrome, as well as WS with upper limb anomalies. Alternate names for WS4 include Waardenburg-Hirschsprung disease, Waardenburg-Shah syndrome, Shah-Waardenburg syndrome, and Hirschsprung disease with pigmentary anomaly.

Genetic profile

Since Dr. Waardenburg’s original description of his patients in 1951, many more families with the same or similar symptoms have been reported. By 1971, it became clear that a proportion of families have WS without dystopia canthorum. At that time, Waardenburg syndrome was divided into two distinct types: WS1 and WS2. In addition, a few individuals with typical signs of WS1 were found to also have musculoskeletal symptoms. This form of the disorder was named Klein-Waardenburg syndrome, now also known as WS3. Further, some researchers noted yet a different pattern of anomalies involving pigmentation defects and Hirschsprung disease, which eventually became known as WS4. Finally, genetic testing of WS2 families has shown at least two subtypes—those that show genetic linkage are designated as WS2A and WS2B.

The four major types of WS have all been studied through DNA (genetic) analysis. There is some agreement between the clinical subtypes of WS and mutations in different genes, but genetic analysis has also served to confuse the naming scheme somewhat.

WS1

A number of different mutations in a single copy of the *PAX3* gene on chromosome 2 are responsible for all

Waardenburg Syndrome					
Type	Inheritance	Gene	Chromosome	Demographics	Symptoms
WS 1	AD	PAX3	2	1 in 40,000 for all types; WS 3 and WS 4 are less common than WS 1 and WS 2	Dystopia canthorum (99%); Medial flare of eyebrow or joining of eyebrows in the middle (70%); Hypopigmentation of skin, hair, and/or irides; Heterochromia of irides (30%); Hearing loss (60%)
WS 2A	AD	MITF	3		Same symptoms as WS 1, but without dystopia canthorum; Incidence of symptoms varies from WS 1, e.g. hearing loss (80%), heterochromia of irides (50%), joining of eyebrows (5%)
WS 2B	AD	"WS2B"	1		See WS 2A
WS 3	AD or sporadic	Deletions including PAX3	2		Similar symptoms to WS 1 but also features abnormalities of arm muscles and bones
WS 4	AR AR AD	EDNRB EDN3 SOX10	13 20 22		Usually dystopia canthorum is absent and incidence of hearing loss is reduced; Hirschsprung disease

(Gale)

cases of WS1, meaning it is always inherited as an autosomal dominant trait. The *PAX3* gene plays a role in regulating other genes that have some function in producing melanocytes, which are pigment-producing cells. *PAX3* was formerly known as the *HUP2* gene.

WS2A

People that have typical signs of WS2 are designated as having WS2A only if genetic testing shows them to have a mutation in the *MITF* gene on chromosome 3. As with WS1, all cases of WS2A appear to be autosomal dominant. There is evidence that *MITF* is one of the genes regulated by *PAX3*.

WS2B

Some individuals with typical WS2 have had normal *MITF* gene analysis. A search for a different WS2 gene showed that some cases are linked to a gene on chromosome 1. This gene has been tentatively designated WS2B until its exact chromosomal location and protein product are identified. WS2B displays autosomal dominant inheritance.

WS3

Several people with a severe form of WS1 have been shown by genetic analysis to have a deletion of a small section of chromosome 2. Several genes are located in this section, including the *PAX3* gene. Not all patients with WS3 have had the exact same genetic anomaly on chromosome 2, which may explain the variation in symptoms that have been reported. Some families with WS3 have displayed autosomal dominant inheritance,

while other individuals with the condition have been sporadic cases.

WS4

Mutations in three different genes—*EDNRB*, *EDN3*, and *SOX10* on chromosomes 13, 20, and 22, respectively—have been linked to WS4. Those cases of WS4 associated with *EDNRB* and *EDN3* show autosomal recessive inheritance, while the *SOX10*-associated cases are dominantly inherited.

Individuals with one of the autosomal dominant types of WS have a 50% risk of passing on the gene each time they have a child. A couple that has a child with WS4 linked to *EDNRB* or *EDN3* faces a 25% risk for recurrence in each subsequent child. WS is quite variable, even within families. For instance, a parent with minimal pigment disturbance, mild facial features, and no hearing loss may have a child with pronounced physical features and deafness, and vice versa. There may be some correlation between specific gene mutations and the incidence of certain symptoms, but precise predictions are not possible.

The six genes listed are those known to be associated with WS. It is expected, however, that more genes will be identified, especially since only a minority of WS2 cases have shown linkage to the *MITF* and WS2B genes.

Demographics

The prevalence of WS is estimated at 1 in 40,000. About 3% of all children with congenital deafness have WS. WS1 and WS2 occur with approximately the same frequency. WS3 and WS4 are much less common than

KEY TERMS

Dystopia canthorum—A wide spacing between the inner corners of the eyes, with the eyes themselves having normal spacing. Also called telecanthus.

Heterochromia irides—A medical term for individuals with different-colored eyes.

Hirschsprung disease—A deformation in which the colon becomes enlarged (megacolon) due to abnormal nerve control of that portion of the large intestine.

Hypopigmentation—Decreased or absent color (pigment) in a tissue.

Neural crest cells—A group of cells in the early embryo, located on either side of the area that will eventually develop into the spinal cord. The cells migrate (move) away from the area and give rise to various body structures, including melanocytes (pigment producing cells), certain structures of the face and head, and parts of the nervous system.

Neurocristopathy—A disorder that results from abnormal development and/or migration of the neural crest cells in the embryo.

Sensorineural—Type of hearing loss due to a defect in the inner ear (sensing organ) and/or the acoustic nerve.

Synophrys—A feature in which the eyebrows join in the middle. Also called blepharophimosis.

the other types. The majority of people with WS are Caucasian, but members of other ethnic groups may be affected as well.

Signs and symptoms

WS1

Dystopia canthorum is seen in 99% of people with WS1. Other facial features may include decreased length of the nasal bone, a broad/high nasal root (top of the nose), and increased length of the lower face. Seventy percent of people with WS1 have either a medial flare of the eyebrows or synophrys.

Some type of pigmentary disturbance is nearly always present and involves hypopigmentation of the skin, hair, and/or irides. Unlike the more common forms of albinism that often involve a generalized lack of pigment in the body, WS is characterized by patches of hypopigmentation—often termed “partial albinism.” A white forelock or premature graying is seen in about

70% of people with WS1. The eyelashes and patches of body hair may also be hypopigmented. Heterochromia of the irides may be complete (25% of patients) or partial (5% of patients). In complete heterochromia, each eye is a different color. In partial heterochromia, an individual iris in one or both eyes is composed of two colors. Those people with WS1 who do not have iris heterochromia often have brilliant blue coloring of both eyes.

Although estimates vary, hearing loss of some type is present in about 60% of individuals with WS1. The true prevalence is difficult to determine because of the variable nature of the condition. About 80% of those with hearing loss are affected in both ears (bilateral). Profound hearing loss occurs in some 25% of all people diagnosed with WS1.

Spina bifida is seen in a very small percentage of newborns with WS1, as is cleft lip/palate. Hirschsprung disease, a deformation in which the colon becomes enlarged, is a somewhat more frequent anomaly. Sprengel anomaly (elevated shoulder blade) can also be seen. Overall, about 10% of children with WS1 have one of these anomalies.

WS2

The major clinical distinction between WS1 and WS2 is the absence of dystopia canthorum in WS2. Otherwise the conditions mostly differ by incidences of the various symptoms. The incidence of hearing loss in WS2 is 80%, with about 30% having a profound loss. Heterochromia of the irides occurs in 50% of patients. White forelock, premature graying, and hypopigmented skin patches are each found in about 15%–20% of people with WS2. Synophrys occurs in only 5% of patients.

WS3

WS3 could be considered a subtype of WS1 since both are associated with the *PAX3* gene. The distinction is clinical, with the added feature in WS3 being abnormalities of the muscles and bones of the arms. Some cases of WS3 have been sporadic; several individuals diagnosed with WS3 have been in families where other members have typical signs of WS1. Thus, in some cases, WS3 can be considered a severe form of *PAX3*-associated WS and is a dramatic example of the variability that can occur within families.

WS4

Individuals with WS4 usually do not have dystopia canthorum, and often do not have hearing loss. Hirschsprung disease is the major distinguishing feature of WS4. In fact, individuals who carry a single abnormal *EDNRB* or *EDN3* gene, as opposed to two abnormal copies of

either gene in WS4 have only Hirschsprung disease. A small proportion of people with WS4 have been found to have an abnormal *SOX10* gene.

Diagnosis

In the early 1990s, a group of researchers known as the Waardenburg Consortium established criteria for diagnosing someone with WS1. They considered the major criteria of WS1 to be:

- congenital sensorineural hearing loss not due to some other obvious cause
- pigmentary disturbance of the iris
- hair hypopigmentation of some type
- dystopia canthorum
- an affected first-degree relative (parent, sibling, or child)

Minor criteria established by the Waardenburg consortium include:

- several areas of hypopigmented skin
- synophrys or medial flare of the eyebrows
- broad and high nasal root
- hypoplastic alae nasi (cartilage and skin around the nostrils)
- premature graying of hair

In order to be diagnosed with WS1, a person must have two major criteria, or one major plus two minor criteria. A modification of the list for WS2 includes removing dystopia canthorum, and including premature graying as a major criterion. With those modifications, a person with no family history of the condition should have two major criteria to be considered for WS2, and someone with an affected family member need only have one major criterion. Diagnosing WS2 can be more difficult than diagnosing WS1 because of the lack of dystopia canthorum. In addition, some people with a white forelock or premature graying may color their hair, and thus conceal an important sign.

As indicated, the distinction between WS1 and WS3 is clinical, with musculoskeletal anomalies added to the list of criteria for WS1. The criteria for diagnosing WS4 would be similar to those for WS2, with the inclusion of Hirschsprung disease as a major criterion, and the probable exclusion of dystopia canthorum, broad nasal root, and severe hearing loss. In addition, by definition WS4 is not linked to *PAX3*, *MITF*, or *WS2B*, and is linked to one of the established WS4 genes (assuming genetic testing is available and informative).

QUESTIONS TO ASK YOUR DOCTOR

- At what point should my baby be evaluated for hearing loss?
- Which family members should undergo genetic testing?
- If I have WS, when should my child be screened for Hirschsprung disease?
- Do you recommend any orthopedic treatments?

Treatment and management

The primary medical consideration for people with WS is hearing loss. The most effective intervention is hearing aids. It is widely accepted that infants at risk for hearing loss, such as those who may inherit WS from a parent, can benefit from screening in the newborn period. An undiagnosed hearing deficit can result in delays in speech and learning. Children with profound hearing loss are eligible for special accommodations in their education, and the entire family can benefit by starting to use sign language very early.

Although spina bifida in WS is uncommon, the potential complications are serious. Infants with spina bifida usually have damage to the spinal cord at the level of the open spine and consequently have either partial or total paralysis below that point. The opening in the spine can be repaired, but the neurological damage to the spinal cord is permanent. Cleft lip/palate is also uncommon in WS and can be a serious birth defect. Children with cleft lip/palate usually require several surgeries, but the outcome of the repair is generally very good. It would be prudent to screen any infant of a parent with WS for Hirschsprung disease. Surgical removal or repair of the affected segment of colon is often necessary. Depending on the severity of the musculoskeletal anomalies, a child with WS3 might require some sort of orthopedic intervention, such as casting, bracing, or surgery. A few children with WS3 have had only minor joint contractures of the arms and hands.

Genetic counseling is beneficial for any family with WS. Prenatal diagnosis might be an option if genetic testing in the family is informative, but many couples may not choose invasive testing if they would not terminate a pregnancy for WS.

Prognosis

The majority of people with WS lead productive lives. In the absence of severe hearing loss, many people

with WS would not be noticed as having a condition by anyone in the general population. If hearing loss is present, it usually does not get worse and is often amenable to treatment. There is little hope for any preventive measures for WS since all of the features of the syndrome occur early in embryonic development and are present at birth.

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- "Waardenburg Syndrome." NORD. <https://rarediseases.org/rare-diseases/waardenburg-syndrome/> (accessed June 25, 2021).

ORGANIZATIONS

- Alexander Graham Bell Association for the Deaf, 3417 Volta Place NW, Washington, DC 20007-2778, (800) 432-7543, <http://www.agbell.org>
- FACES: The National Craniofacial Association, PO Box 11082, Chattanooga, TN 37401, (423) 266-1632 or (800) 332-2373, faces@faces-cranio.org, <http://www.faces-cranio.org>
- National Association of the Deaf, 814 Thayer, Suite 250, Silver Spring, MD 20910-4500, (301) 587-1788, nadinfo@nad.org, <http://www.nad.org>
- National Organization for Albinism and Hypopigmentation, 1530 Locust St., No. 29, Philadelphia, PA 19102-4415, (215) 545-2322 or (800) 473-2310, <http://www.albinism.org>

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Walker-Warburg syndrome

Definition

Walker-Warburg syndrome (WWS) is a congenital disorder of the central nervous system involving fatal neurological lesions. There are multiple malformations of the brain,

KEY TERMS

Agyri—A lack of convolutions or normal folds in the brain tissue.

Encephalocele—A gap in the skull through which membranes and brain tissue may protrude.

Hydrocephalus—The excess accumulation of cerebrospinal fluid around the brain, often causing enlargement of the head.

Retina—The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

Retinal dysplasia—Improper development of the retina that can lead to detachment of the retina.

eyes, and muscle tissue that distinguish WWS from similar malformation syndromes. It is also known by the acronym HARD +/- E syndrome (hydrocephalus, agyri, retinal dysplasia, plus or minus "e" for encephalocele).

Description

Individuals affected by WWS typically show a combination of severe brain, eye, and muscle defects. Multiple malformations of the brain include type II lissencephaly, a condition in which the brain lacks normal convolutions and is unusually smooth without folds. Eighty-four percent of the infants with WWS have macrocephaly (an enlarged head). In half of these cases the macrocephaly is apparent at birth, and in a quarter of the cases it develops postnatally. Hydrocephalus, or excessive accumulation of cerebrospinal fluid around the brain, occurs in 95% of infants with WWS. This fluid fills abnormally large ventricles or spaces in the brain. Fifty percent of affected infants have an encephalocele, or gap in the skull that does not seal. The meninges or membranes that cover the brain may protrude through this gap. The formation of an encephalocele may be associated with the failure of the neural tube to close during development of the fetus. A malformed cerebellum characterizes the syndrome as well as distinct muscle abnormalities, including congenital muscular dystrophy.

Ocular defects occur in 100% of infants with WWS. The most common are abnormally small eyes and retinal abnormalities, which arise from the improper development of the light sensitive area at the back of the eye. Cataracts may also be present, and more than three quarters of the infants born with WWS have a defect in the anterior chamber of the eye. WWS syndrome leads to severely delayed mental development and is often lethal in infancy.

QUESTIONS TO ASK YOUR DOCTOR

- What supportive measures do you recommend for children born with WWS?
- At what point should seizures be controlled medically?
- What are the risks and benefits of shunting?
- Which family members should undergo genetic testing?
- If WWS runs in my family, what are the chances that I will have a child affected by WWS?

Genetic profile

WWS is inherited in an autosomal recessive pattern. Offspring of parents who have had one affected infant have a 25% chance of having another child with WWS. The locations of the causative genes remain unknown.

Demographics

WWS is extremely rare. Cases described in the literature cite siblings with WWS born to consanguineous (closely related) parents as well as cases in families not known to be at risk.

Signs and symptoms

Clinical signs include a malformed head, small eyes, cataracts, retinal abnormalities, and muscle weakness. An encephalocele may be present as well. Microscopic examination reveals that the cells and tissues of the brain develop in a highly disorganized fashion. Seizures may occur in affected individuals.

Diagnosis

Prenatal ultrasound can reveal some of the brain anomalies associated with WWS; most commonly, hydrocephalus and encephalocele. Lissencephaly cannot be diagnosed prenatally as normal fetal brains appear smooth. After birth, diagnosis is made on the basis of physical features and ultrasound exams. MRI may be used to confirm the smooth brain feature or type II lissencephaly typical of WWS. Genetic analysis can also help distinguish WWS from Fukuyama-type congenital muscular dystrophy (FCMD), which has several similar features. WWS can be differentiated from other syndromes that display hydrocephalus or encephalocele by the presence of eye abnormalities including retinal defects, cataracts, and anterior

chamber defects. Genetic testing for Fukuyama-type congenital muscular dystrophy distinguishes these symptoms from WWS.

Treatment and management

The severe malformations of the brain are untreatable and many infants with WWS die within the first year of life. Supportive care is required to provide comfort and nursing needs. Seizures may be controlled with medication and shunting may be required to control the swelling effects of hydrocephalus. A shunt or short plastic tube can be placed to divert the excess cerebral spinal fluid to another area of the body where it can ultimately be absorbed.

Genetic counseling is recommended for families at risk.

Prognosis

Patients have a very limited life expectancy and the syndrome is generally considered lethal. Most patients die before the age of two.

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- "Walker Warburg Syndrome." NORD. <https://rarediseases.org/rare-diseases/walker-warburg-syndrome/> (accessed June 25, 2021).

ORGANIZATIONS

- National Hydrocephalus Foundation, 12413 Centralia, Lakewood, CA 90715-1623, (562) 402-3523 or (888) 260-1789, hydrobrat@earthlink.net, <http://www.nhfonline.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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Ward-Romano syndrome see **Long QT syndrome**

Weaver-Williams syndrome see **Weaver syndrome**

Weaver syndrome

Definition

Weaver syndrome is a congenital genetic syndrome associated with rapid growth beginning in the prenatal period, as well as with a specific facial appearance and certain skeletal features. It has also been referred to as Weaver-Williams syndrome.

Description

Weaver syndrome was first described by Dr. David Weaver in 1974. A number of different symptoms occur in Weaver syndrome. However, it primarily results in rapid growth beginning in the prenatal period and continuing through the toddler years and into the elementary school years. It is also strongly associated with the bones developing and maturing more quickly (advanced bone age), a distinctive appearing face, and developmental delay. Babies often have a hoarse, low-pitched cry.

Genetic profile

Weaver syndrome is caused by mutation in the *EZH2* gene and, in rare cases, the *NSD1* gene. The *EZH2* gene provides instructions for making a type of enzyme called histone methyltransferase that modifies proteins (histones) that help DNA give chromosomes their shape. The *EZH2* enzyme is part of a protein group called the polycomb repressive complex-2. This complex turns off individual genes involved in the process of cell differentiation (the process that determines the type of cell an immature cell will become). Mutations in the *EZH2* enzyme may disrupt a process called methylation (an essential process by which genes are activated and deactivated) and affect many organs and tissues, resulting in the symptoms of Weaver syndrome.

The *NSD1* gene is involved in production of a protein that is not fully understood. Researchers suspect that this protein is involved in the genetic component of normal growth and development. Abnormalities in this

protein may cause growth to accelerate. Individuals with mutations in the *NSD1* gene have been diagnosed with Weaver syndrome, but researchers believe they should be diagnosed with Sotos syndrome (which is also characterized by rapid and accelerated growth) instead, since it is caused by mutations of this gene.

Weaver syndrome is, for the most part, a sporadic condition, which means that a child affected by it did not inherit it from a parent. In a very few families, autosomal dominant inheritance has been reported, which means that both a parent and his/her child is affected by Weaver syndrome. The exact cause of Weaver syndrome is not fully understood. Symptoms of Weaver syndrome are sometimes confused with Sotos syndrome.

Demographics

Weaver syndrome is rare; only about 30 to 50 cases have been published in the medical literature. It occurs in both males and females.



Seventeen-year-old Rumeysa Gelgi has Weaver syndrome, which has led to her 2.13-meter height (about 6 feet, 11 inches). (Ibrahim Yozoglu/Anadolu Agency/Getty Images)

Signs and symptoms

Children with Weaver syndrome tend to have large heads. The faces of children with Weaver syndrome are usually very similar to each other, more so than to other family members, and include a round face, small chin, long philtrum (groove in the midline of the upper lip), large ears, and eyes that are farther apart from each other than usual. Other common symptoms include hypertonia (increased muscle tone, tight muscles) as well as hypotonia (decreased muscle tone, “floppy” muscles) and a hoarse, low-pitched cry in babies.

The excessive prenatal growth often results in the newborn being large with respect to weight, length, and head circumference. The rapid growth continues through the toddler and youth years with the child’s length and height often being above the 97th percentile, meaning that out of 100 children of the same age, the child is longer/taller than 97 of the children. There is very limited information on the rate of growth through adolescence and on final height, as most of the patients diagnosed with Weaver syndrome who have been reported in the medical literature have been children. In addition, given that the condition was first described 25 years ago, long-term clinical information is just becoming available.

There are a number of other features that have been associated with Weaver syndrome. The child may have difficulty extending elbows and knees completely, fingers and/or toes may be permanently flexed (camptodactyly) or have other problems such as overlapping fingers/toes or clubfoot, and the skin may appear loose. The child may have normal or delayed development; severe intellectual impairment is rarely seen. Speech may be delayed, and when present, may be slurred. A child with Weaver syndrome may also have behavioral problems such as poor concentration; temper tantrums, which may be related to frustrations arising from communication problems; and obsessive and repetitive patterns of play.

Diagnosis

Diagnosis of Weaver syndrome is based solely upon clinical examination, medical history, and x-ray data. There are no laboratory tests that can provide a diagnosis. The clinical criteria that are considered to be diagnostic for Weaver syndrome are excessive growth beginning in the prenatal and infancy period, a characteristic facial appearance, advanced bone age with the bones in the wrist being more advanced than other skeletal bones, metaphyseal flaring in the leg bones (the ends of the bone are wider than normal), and developmental delay.

There are many conditions and genetic syndromes that cause excessive growth; consequently, a baby and/or child who has accelerated growth needs to be

KEY TERMS

Advanced bone age—The bones, on x-ray, appear to be those of an older individual.

Congenital—Refers to a disorder that is present at birth.

Developmental milestones—Infants and toddlers develop skills at certain ages. For example, by nine months, a child should be able to grasp and toss a bottle.

Karyotype—A standard arrangement of photographic or computer-generated images of chromosome pairs from a cell in ascending numerical order, from largest to smallest.

Metaphyseal flaring—A characteristic found only by x-rays. If present, it means that the ends of the bone are wider than normal.

thoroughly examined by a physician knowledgeable in overgrowth and genetic syndromes. The evaluation includes asking about health problems in the family as well as asking about the growth patterns of the parents and their final height. In some families, growth patterns are different and thus may account for the child’s excessive growth. The child will also undergo a complete physical examination. The child will also be examined in terms of his/her facial appearance, with special attention paid to the shape of his/her head, width of the face at the level of the eyes, and appearance of the chin and forehead. Besides measurement of the head circumference, arm length, leg length, and wing span will also be measured. Laboratory testing may also be done. A chromosome analysis (karyotype) may be performed as well as testing for another genetic syndrome called fragile-X syndrome. The patient’s bone age should also be assessed. Bone age is determined by x-rays of the hand. It is known that a child’s age can be predicted by the appearance of the wrist bones. In some cases the bones may develop or mature more quickly than normal, or in other words, the child’s wrist bones appear to be those of an older child. This is referred to as advanced bone age. Advanced bone age is present in nearly every child with Weaver syndrome. It does not appear to result in other health problems. If the child begins to lose developmental milestones or appears to stop developing, metabolic testing may be done to evaluate for a metabolic condition called Sanfilippo syndrome. Developmental milestones refer to the skills infants and toddlers acquire as they get older, such as smiling, cooing, grasping toys, rolling over, walking, and talking.

QUESTIONS TO ASK YOUR DOCTOR

- What are the risks and benefits of surgery?
- Do you recommend physical, occupational, or speech therapy?
- Is a behavioral assessment recommended?
- What developmental milestones should I look for in my baby?

Treatment and management

There is no cure for Weaver syndrome. However, the symptoms that cause problems can be treated and managed. Surgery may be used to correct any skeletal problems such as clubfoot or finger or toe problems. Physical and occupational therapy may help with muscle tone. Speech therapy may help with speech, and behavioral assessments and treatments may help with behavioral problems.

Prognosis

With appropriate treatment and management, children with Weaver syndrome appear to do well. Intellectually, most individuals with Weaver syndrome are normal. Weaver syndrome is not associated with a shortened lifespan.

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ORGANIZATIONS

MAGIC Foundation, 6645 W. North Ave., Oak Park, IL 60302, (708) 383-0808 or (800) 362-4423, ContactUs@magicfoundation.org, <http://www.magicfoundation.org>

Sotos Syndrome Support Group, PO Box 4626, Wheaton, IL 60187, (888) 246-7772, info@sotossyndrome.org, <http://sotossyndrome.org>

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Weissenbacher-Zweymuller syndrome

Definition

Weissenbacher-Zweymuller syndrome (WZS) is a genetic form of dwarfism in which affected individuals are born with small, underdeveloped jaws (micrognathia), cleft palate, short arms and legs (rhizomelia), dumbbell-shaped arm and leg bones, protruding wide-spaced eyes (hypertelorism), and incompletely formed back bones (vertebral coronal clefts). Unlike most other forms of dwarfism, individuals affected by Weissenbacher-Zweymuller start out being affected by dwarfism and then have a period of gradual growth and bone change that leads to normal physical development by five or six years of age.

Description

Weissenbacher-Zweymuller syndrome refers to a rare disorder of small underdeveloped jaws (micrognathia), delayed bone growth, and unusual bone formation first described in 1964 by Weissenbacher and Zweymuller. The formation of bones is delayed because an important structural component of bone called cartilage does not form correctly. Since bone development is delayed, early milestones like walking and physical growth are delayed. Due to cleft palate, many individuals affected by WZS have speech and language delays. In most cases, physical, motor, mental, and academic development is normal by five or six years of age. Alternate names sometimes used for WZS include Pierre Robin syndrome with fetal chondrodysplasia and heterozygous otospondylomegaepiphyseal dysplasia (OSMED).

Genetic profile

Weissenbacher-Zweymuller syndrome appears to be caused by a single change or mutation in a gene called *COL11A2* located on the short arm of chromosome 6. The mutation in *COL11A2* leads to the incorrect formation of collagen. Since collagen is an important structural part of cartilage and bone, a mutation in *COL11A2* leads to the signs and symptoms of WZS. The specific mutation that leads to WZS is inherited in an autosomal

recessive pattern. An autosomal recessive condition is caused by the inheritance of two abnormal copies of a gene.

In the 1970s and 1980s, there was some confusion among geneticists who were uncertain if WZS is a separate syndrome or part of another genetic syndrome. Although this confusion is not completely resolved, in 1993 an important study compared WZS to other related genetic syndromes and concluded that WZS is a separate genetic disorder that should not be “lumped” into the category of other genetic syndromes like Stickler syndrome. Since that study, a 1998 genetic study found that WZS and another syndrome called otospondylomegaepiphyseal dysplasia (OSMED) appear to be caused by different mutations in the same gene. This finding led the authors to suggest that the term “OSMED” be used to encompass a broad category that includes WZS as “heterozygous” OSMED while the other syndrome now called OSMED should be called “homozygous” OSMED. Because it has been found that WZS results from both heterozygous and homozygous mutations, researchers have suggested that this disorder follows both autosomal dominant and autosomal recessive inheritance patterns.

Demographics

WZS is a very rare disorder. The ethnic origin of individuals affected by WZS is varied and is not specific to any one country or ethnic population.

Signs and symptoms

Signs and symptoms of Weissenbacher-Zweymuller syndrome include: short arms and legs (rhizomelia), short stature at birth, an underdeveloped jaw (micrognathia), cleft palate, widely spaced eyes (hypertelorism), protruding eyes, a “snub” nose (depressed nasal bridge), dumb-bell shaped long leg and arm bones (widening of the metaphyses of long bones), and incompletely formed back bones (coronal cleft of the lumbar vertebrae). The most unique sign of WZS is the gradual improvement of these changes.

Diagnosis

Diagnosis of Weissenbacher-Zweymuller syndrome is usually made from physical examination by a medical geneticist and x-rays of the legs, arms, and back. Careful charts of growth and development over time also help with diagnosis. Most characteristic of WZS is the gradual improvement in bone size, growth, and shape.

Prenatal diagnosis of WZS is difficult, but can sometimes be made through a level II ultrasound examination of bone growth in the late second to third trimester of pregnancy. Genetic testing may be available through an

KEY TERMS

Autosomal dominant—A pattern of genetic inheritance where only one abnormal gene is needed to display the trait or disease.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Micrognathia—A term used to describe a small, underdeveloped lower jaw and chin.

Rhizomelia—A term used to describe the physical growth difference of short arms and legs.

Syndrome—A group of signs and symptoms that collectively characterize a disease or disorder.

amniocentesis procedure if the exact mutations running in the family are known. Genetic testing is done on a research basis in most cases.

One of the most important aspects in the diagnosis of WZS is ruling out other diagnoses. Conditions can be eliminated based on features that are not seen in WZS or are missing in other syndromes. For example, other conditions that look like WZS usually have progressively worsening symptoms instead of WZS’s characteristic catch-up growth. Additionally, most conditions resembling WZS are inherited in an autosomal dominant pattern through the family. In an autosomal dominant condition, only one copy of the gene for a particular condition is necessary for a person to experience symptoms of the condition. If a parent has an autosomal dominant condition, there is a 50/50 chance for each child to have the same or similar condition.

Conditions to rule out in differential diagnosis include:

- Stickler syndrome, in which affected individuals have eye problems and do not have short arms and legs at birth.
- Kniest dysplasia, in which affected individuals do not have an underdeveloped jaw, but they do have eye abnormalities.
- Marshall syndrome, in which affected individuals have hearing and eye abnormalities, but do not have short limbs at birth.
- Isolated Pierre-Robin sequence, in which individuals have an underdeveloped jaw and cleft palate alone without short arms and legs.
- Diastrophic dwarfism, in which affected individuals often have club feet, joint contractures, hypermobile thumbs, and non-bulbous bones.

QUESTIONS TO ASK YOUR DOCTOR

- How often should my baby have hearing, vision, and growth monitored?
 - Do you recommend physical, occupational, or speech therapy?
 - What developmental milestones should I watch for in my child?
 - Is there anything we can do during the preschool years in order to monitor intellectual development?
- Metatropic dwarfism, which is characterized by visible changes of the trunk and short limbs as the spine flattens and the bones become progressively deformed.
 - Traditional oto-spondylo-megaepiphyseal dysplasia (OSMED), which includes individuals affected by deafness and abnormal growth and development of the spine and growth plates at the end of the long bones (spondyloepiphyseal dysplasia) with large growth plates at the end of the long bones (epiphyses).

In conclusion, it is important to do a thorough and long-term physical examination, a family history, and a test for growth, hearing, and eyesight before making a diagnosis of WZS.

Treatment and management

The symptoms of WZS can be treated through follow-up and careful evaluation by a pediatric medical geneticist during the first years of life. Especially important to check are eyesight, hearing, and growth. Specific craniofacial clinics can help individuals affected by cleft palate with surgery, speech, and other related issues. Physical, occupational, speech, and language therapy may be suggested to help reduce “catch-up” time and developmental delays. As with any other disorder that includes developmental delays, specialists providing physical and language therapy can assist in the decision on whether special classes may help an individual child develop academically.

Prognosis

The chance for an individual affected by WZS to have normal physical, motor, mental, and school development by age six or seven is very good. To help in this development, early intervention with physical, occupational, speech, and language therapy and special classes may be helpful. A detailed case report in 1991 noted that

the intelligence of children with WZS is generally within normal range, though they may have mild-to-moderate intellectual delay in the preschool period. The same report notes that physical growth should be normal by age five or six.

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ORGANIZATIONS

- Pierre Robin Network, 6304 Biscayne, Quincy, IL 62305, info@pierreroobin.org, <http://www.pierreroobin.org/index.html>
- Stickler Involved People (SIP), 15 Angelina, Augusta, KS 67010, (316) 259-5194, sip@sticklers.org, <http://www.sticklers.org>

Dawn A. Jacob, MS

Werner syndrome

Definition

Werner syndrome is a very rare, inherited disease that resembles premature aging. Since the gene responsible was discovered in the mid-1990s, Werner syndrome has greatly interested researchers as a possible model for the study of human aging. It is also being extensively studied for insights it may eventually supply into a number of other diseases, including cancer, diabetes mellitus, and atherosclerosis.

Description

This syndrome is named for the German physician C. W. Otto Werner (1879–1936). Werner was a medical

student in 1903 when he first observed the syndrome in four siblings, all about 30 years of age. The following year, Werner wrote about these observations in his “Inaugural Dissertation.”

The clinical signs and symptoms of Werner syndrome start to appear during the teen or early adult years, after which patients appear to age rapidly and have a greater-than-usual chance of developing cancer, cardiovascular disease, or diabetes mellitus. By the time the patient is 30–40 years old, he or she has the look of old age. The most common cause of death is heart attack.

While in many ways the signs and symptoms of Werner syndrome resemble those of premature aging (referred to in adults as progeria), there are also some significant differences. For instance, the tumors commonly seen in Werner syndrome patients are commonly derived from the cells of the mesoderm, a middle layer of the embryo that gives rise to a variety of tissues including cartilage, muscle, bone, kidneys, and connective tissue. In normal aging, tumors are more likely to be derived from the epithelial cells that cover the body’s exterior and line most of its hollow structures. Osteoporosis and soft-tissue calcium deposits are found both in Werner syndrome and normal aging, but the distribution of these conditions within the body is different in patients with Werner syndrome. In addition, patients with Werner syndrome do not generally experience symptoms of Alzheimer’s disease or premature cognitive decline, as do their aging counterparts in the general population.

Researchers are uncertain whether the symptoms of Werner syndrome are really a speeding-up of normal aging, or whether the many similarities are coincidental. There is nonetheless considerable optimism that further research into Werner syndrome may lead to a better understanding of aging, cancer, diabetes, systemic sclerosis, atherosclerosis, cataracts, and other conditions.

Genetic profile

Werner syndrome results from mutation of a single gene. In 1992, the gene responsible (*WRN*) was mapped to chromosome 8p11-12. In 1996, a research group based in Seattle cloned the *WRN* gene. It was also discovered that the syndrome resulted from an autosomal recessive mutation that affects a member of a family of enzymes known as helicases that unwind deoxyribonucleic acid (DNA) and, in some cases, ribonucleic acid (RNA).

Despite the discovery that Werner syndrome is caused by a genetic defect, researchers are unable to explain exactly how this defect causes the disease. The purpose of helicases in the body is not fully understood, but they are known to unwind DNA, splitting the double-stranded molecules into separate single-stranded

KEY TERMS

Atherosclerosis—Hardening of the arteries caused by cholesterol and fat deposits. Increases risk of heart disease, stroke, and other complications.

Progeria—Genetic abnormality that presents initially as premature aging and failure to thrive in children.

Systemic sclerosis—A rare disorder that causes thickening and scarring of multiple organ systems.

molecules. In this way, the enzymes are involved in the repair, recombination, replication, and transcription of DNA. There appear to be many damaged sites in DNA taken from patients with Werner syndrome. It has therefore been suggested that Werner syndrome may be caused by failure in these DNA-related processes, and that the somatic cells of those with Werner syndrome may be particularly prone to mutations.

The *WRN* gene is not known to bind to DNA damage, but recent research has suggested it might be able to sense the presence of damaged DNA. Since the discovery of the *WRN* gene, more than ten mutations have been uncovered. Many of these mutations were in the Japanese population. It has been suggested that the relatively high incidence of Werner syndrome in that country may be related to traditions of marriages between closely related individuals in some areas of Japan.

Researchers are still seeking to further study Werner syndrome and the *WRN* gene. Specifically, they hope to create mice with a genetic equivalent of the *WRN* gene, and to determine whether these mice would age more quickly than normal mice.

Demographics

Because of the limited number of cases, the demographic distribution of Werner syndrome is difficult to determine. Estimates of the number of people affected range from 1 in 95,000 to 1 in 1,000,000 people. Unlike progeria, which can be diagnosed at birth or soon after, Werner syndrome is not usually detected prior to adolescence. It is commonly noticed only after patients have failed to undergo the normal growth spurt associated with their teen years. The full range of symptoms is not usually seen until patients reach their 20s or 30s. Werner syndrome is more common in families in which a close biological relationship exists between parents. It occurs equally in both sexes. There is no evidence of a birth-order effect.

Signs and symptoms

The cardinal signs and symptoms of Werner syndrome start to appear after the age of ten. They are:

- Cataracts. These occur in both eyes, and usually develop by age 25 or 30.
- Skin problems including tight, shiny, smooth skin; ulceration; general wasting of the skin and localized wasting of the subcutaneous area underneath it; pigmentary changes; a thickening of the horny outer layer of the skin; and a characteristic bird-like facial appearance, including a beaked or pinched nose and unusually prominent eyes.
- Shortness of stature.
- An affected sibling or a close biological relationship between parents (third cousin or closer).
- Earlier-than-usual graying and/or thinning of scalp hair, usually by age 20.
- Excess amounts of hyaluronic acid (more commonly found in the body's connective tissues and in the fluids of the eyes and joints) in the urine.

Additional signs and symptoms of Werner syndrome include the following:

- Diabetes mellitus. This is usually mild, but can be found in between 44% and 67% of Werner syndrome patients.
- Impaired function of the ovaries or testes, as indicated by small or poorly developed genitalia or reduced fertility.
- Osteoporosis, most commonly in the upper limbs and spine, as well as in the lower limbs, feet, and ankles. In patients with Werner syndrome, osteoporosis is unlikely to be found in the skull or the torso.
- Unusually high bone density in the extremities of the finger and toe bones. This must be established by an x-ray examination.
- Deposits of calcium salts in soft tissues of the body. Common locations are around the Achilles tendon and the tendons of the elbow and the knee.
- Evidence pointing to earlier-than-usual arterial disease, such as a prior heart attack or abnormal electrocardiograms, etc.
- Rare or multiple tumors, or tumors derived from the mesoderm, the middle layer of the embryo. Werner syndrome is not marked by increased occurrence of all forms of tumors, but by selectively higher proportions of certain cancers that are relatively rare.
- Changes to the voice, rendering it squeaky, hoarse, or high-pitched.
- Flat feet.

QUESTIONS TO ASK YOUR DOCTOR

- What diagnostic criteria did you utilize to arrive at Werner syndrome?
- At what age should my child's heart be evaluated?
- Which family members should undergo genetic testing?
- What screenings for cancer should my child undergo?

In addition to the above signs and symptoms used for formal diagnostic purposes, other clinical observations have been reported, including loss of eyelashes and eyebrow hair, nail deformities, and the presence of thin limbs with a stocky trunk. A possible link to lung cancer has also been proposed.

In some cases, Werner syndrome can occur in a slower and milder partial form, with only some of the symptoms present.

Diagnosis

A definite diagnosis of Werner syndrome is established by the presence of all of the cardinal signs and symptoms listed above, plus at least two of the additional signs and symptoms.

A probable diagnosis is indicated by the presence of all of the first three cardinal signs, plus any two from the additional list.

A possible diagnosis is suggested by the presence of either cataracts or the skin manifestations, plus any four of the other signs or symptoms.

Werner syndrome may be ruled out if the signs and symptoms appear prior to adolescence. The exception to this rule is shortness of stature, because patterns of pre-adolescent growth are not sufficiently understood.

Diagnosis may involve x-rays to study hormone excretion, skin biopsies, and a blood-sugar test to determine whether diabetes mellitus is present. Werner syndrome can also be diagnosed by mutational analysis of the *WRN* gene.

Treatment and management

There is no known cure for Werner syndrome, so treatment is related to the specific symptoms present.

For example, cataracts can be corrected by surgery and skin ulcers can be treated with grafts.

Prognosis

Because it mimics the human aging process, Werner syndrome significantly reduces life expectancy in most patients. Average life expectancy for a Werner symptom patient is somewhere between 40 and 47 years. The most common causes of death are heart attacks, cerebrovascular accidents, and cancers.

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- International Progeria Registry, Progeria Research Foundation, PO Box 3453, Peabody, MA 01961, (978) 535-2594, (978) 535-5849, info@progeriaresearch.org, http://www.progeriaresearch.org/patient_registry.html
- International Registry of Werner Syndrome, Department of Pathology, School of Medicine, University of Washington, Box 357470, Health Sciences Center, Room K-543, 1959 NE Pacific St., Seattle, WA 98195, (206) 543-5088, picard@u.washington.edu, <http://www.wernersyndrome.org/registry/registry.html>
- March of Dimes, 1275 Mamaroneck Ave., White Plains, NY 10605, (914) 997-4488, <http://www.marchofdimes.org>

David L. Helwig

Whistling face syndrome see **Freeman-Sheldon syndrome**

Whole-exome and whole-genome sequencing

Definitions

Whole-exome sequencing (WES) is a genomic technique that has been developed since 2007 for identifying or determining the exact order of all the portions of the genes in an organism's genome that code for proteins. These gene portions are called exons, and the total of all the exons in a genome is called the exome. The human exome accounts for 180,000 exons, or 1% of all the DNA in an individual human's haploid genome—about 3.2 million base pairs. The word *exon* was formed from the words "EXpress" and "regiON", because the exon is the region of the gene expressed in the protein produced by the gene.

In most DNA sequences, the exons are separated by non-coding portions of the gene called introns. The word *intron* is derived from "INTragenic" and "regiON," because the introns are located inside the gene (intra-genic) between the exons. Prior to the process of amino acid transcription, the introns are spliced out of messenger RNA, leaving only the exons to transcribe the final gene product.

Whole-genome sequencing (WGS) is the sequencing of an organism's entire DNA at one time, including all of its chromosomal and mitochondrial DNA. WGS is also known as full genome sequencing, entire genome sequencing, or complete genome sequencing. Unlike WES, WGS can detect insertion or deletion mutations (indels), single nucleotide variants (SNVs), copy number changes, and large structural variations in the genome. It can also detect some variations in the exome that are missed by WES.

Until 2014, WGS was used primarily as a research tool, but it is increasingly used in clinical applications as of 2021. The first organism to have its entire genome sequenced was a bacterium, *Haemophilus influenzae*; its sequencing was completed in 1995 after automated methods sped up the process. In comparison to that of the human, the genome of *H. influenzae* is small—1,830,140 base pairs of DNA.

Description

Both WES and WGS utilize blood, skin, or saliva samples for DNA analysis related to human or animal disease or disease risk, although blood samples are preferred because they yield higher amounts of DNA and are less likely to be contaminated by bacteria. When bacterial DNA is to be analyzed, the organisms are taken from a laboratory culture plate and treated with chemicals



Scientists at the Food and Drug Administration's comparative genomics laboratory using the Pac-Bio whole-genome sequencing machine. (FDA/Michael J. Ermarth/Science Source)

to extract the DNA. Plant samples often require several steps of chemical treatment, followed by washing to free the DNA from the complex sugars and other materials found in plant matter.

Both WES and WGS are innovations in DNA sequencing that were developed shortly after 2005, when so-called next-generation sequencing—variously called high-throughput sequencing, massively parallel sequencing, and shotgun sequencing—technology was introduced. Next-generation sequencing was the first major breakthrough in sequencing DNA since the development of the Sanger method in 1977 by Frederick Sanger in the United Kingdom. The Sanger method was time-consuming, expensive, and limited to sections of DNA that were only about 1,000 base pairs (bp) in length. As a result, using the Sanger sequencing method—which was the state of the art in 1990—meant that the Human Genome Project required 13 years to complete its sequencing of a human genome, and the task had to be divided among several different research centers.

Next-generation sequencing is both faster and less expensive than the original Sanger method, as it can sequence many strands of DNA at the same time and also sequence longer sections of DNA than the Sanger method allowed. The phrase “shotgun sequencing” refers to the fact that next-generation sequencing methods break up, or shear, an organism’s entire genome into many small fragments, similar to the effect of a shotgun blast. The DNA segments are then copied millions of times by polymerase chain reaction (PCR). The population of DNA fragments ready for sequencing is called a DNA library. The library is loaded onto a sequencer, and the resulting millions of reads produced by the sequencer are read by a computer that identifies overlapping segments in the

fragments and uses them to place them in the correct order to reconstruct the full genome.

Whole-exome sequencing begins with shotgun shearing of a genome, followed by one of several so-called target-enrichment strategies to identify the exons in the genome and separate them from the noncoding regions. This step is called targeted capture. Several different biotech companies offer kits containing the reagents needed to capture the exons as well as the equipment to interpret the results. After the exons have been captured, the exome is sequenced. It can then be analyzed to identify disease-causing mutations that underlie rare Mendelian (monogenic) diseases.

High-throughput sequencing is used for whole-genome sequencing as well as whole-exome sequencing. WGS can be divided into large whole-genome sequencing (for genomes larger than 5 million bp) and small whole-genome sequencing (for genomes smaller than 5 million bp, which includes almost all bacteria and viruses). Since 2019, it has been possible to perform a WES run in as little as five minutes, and a WGS in about 55 minutes.

Purpose

Whole-exome sequencing

WES is often used to identify disease-causing gene mutations because it can identify variations in the protein-coding region of any gene rather than focusing on a few preselected genes. About 85% of all disease-causing mutations in humans can be found in the exome.

As of 2021, WES has a diagnostic utility of 20% to 30%, meaning that a diagnosis can be given to between a fifth and a third of individuals who had been previously undiagnosed but had traits or features that suggested a genetic disorder. The use of WES has increased since 2015, because improvements in high-throughput sequencing have lowered the cost, reduced laboratory turnaround time, and increased insurance coverage of WES testing. According to the Yale Center for Genome Analysis (YCGA), whole-exome sequencing can cost from \$176 to \$364, depending on whether the patient’s DNA is taken from a standard blood sample or from a cancerous tumor.

Whole-genome sequencing

WGS is used in research and in some clinical cases in which DNA variations outside the exome can lead to genetic mutations. As of 2021, WGS is most likely to be used when WES has not been helpful in identifying the location of a mutation or when time is critical. Some

KEY TERMS

Base pair (bp)—Any of the complementary nucleotide bases (adenine-thymine and cytosine-guanine in DNA; adenine-uracil and cytosine-guanine in RNA) held together by weak hydrogen bonds. Base pairs form links between the two strands of DNA.

Bioinformatics—An interdisciplinary scientific field that combines statistics, engineering, mathematics, and computer science to capture and understand biological data.

Cascade testing—A term that refers to performing genetic counseling and testing in blood relatives of a person identified as having a specific genetic mutation. It is most commonly recommended for the relatives of patients carrying a genetic mutation linked to cancer.

Ethics—The branch of philosophy that concerns questions of good and evil as well as moral duties and obligations in human society.

Exome—The part of a genome formed by all of its exons.

Exon—The DNA sequence of a gene that codes for a protein.

Genome—The complete genetic material of an organism.

Genome-wide association study (GWAS)—A method for identifying genes involved in human

disease by searching a number of human genomes for small variations that occur more commonly in people with a given disease than in those who do not have the disease.

Genomics—A subspecialty of genetics that focuses on the study of the genome.

Haploid—Referring to cells that have only one chromosome of each type, and therefore have only one complete set of genes. Gametes (sperm and eggs) normally have a haploid number of chromosomes.

Intron—Any of the portions of a gene that does not code for amino acids.

Mendelian disease—A disease caused by a single mutated gene; also called a single-gene disease. These diseases are named for Gregor Mendel (1822–1884), an Austrian monk who discovered the basic principles of inheritance of single-gene traits through experimentation with plants in his garden.

Monogenic disease—Another term for a single-gene disorder.

Next-generation sequencing—A general term for massively parallel sequencing of large portions of DNA base pairs, performed by first fragmenting the DNA, reading the individual fragments in parallel, and then reassembling the reads to obtain the sequence of the entire genome.

complex human disorders in which WGS has been used to arrive at a diagnosis include:

- intellectual disabilities and learning disorders
- developmental delays in walking and talking
- seizures and brain abnormalities
- hearing and vision disorders
- heart and lung disorders
- disorders of the digestive tract
- skeletal disorders, including short stature and abnormalities of the arms, legs, hands, and feet
- recurrent infections and immunodeficiencies
- severe unexplained illnesses

The advantages of WGS include the possibility of early intervention in the treatment of a diagnosed disorder, including a more personalized approach to the patient's therapy. In addition, WGS can provide the patient's family with information that they can use to decide whether other family members might benefit from genetic testing—an approach called cascade testing.

The cost of WGS has dropped considerably since the completion of the Human Genome Project in 2003. After 2006, a number of biotechnology companies began to compete to lower the price of a complete human genome to \$1,000, and “the \$1,000 genome” became a catchphrase among entrepreneurs interested in making WGS affordable to average persons. The National Human Genome Research Institute (NHGRI) began offering grant money to advance the development of a \$1,000 genome. Various companies, including Illumina and Veritas Genetics, claimed to have invented sequencing technologies that could produce a full human genome for \$1,000 by 2018. In 2019, the Yale Center for Genome Analysis charged \$949 for WGS. The price has dropped even further, with WGS being offered by one commercial company for as little as \$199 on the shopping holiday known as Black Friday in 2019.

Unlike WGS, however, insurance companies are less willing to share the cost of whole-genome sequencing. United Healthcare maintains in its most recent policy statement (issued on January 1, 2021) that “Whole

Nucleotide—A building block of a nucleic acid (DNA or RNA), consisting of a sugar molecule, a phosphate group, and one of the nitrogen-containing bases (adenine, cytosine, guanine, and thymine in DNA; adenine, cytosine, guanine, and uracil in RNA).

Personalized medicine—The tailoring of medical treatment to the individual patient based on his or her genetic profile. It is also called precision medicine.

Pharmacogenomics—The branch of medicine that studies the role of the human genome in response to medications.

Phenotype—The set of observable characteristics or traits of an organism. It includes physical form and structure, development, metabolic processes, movement, and behavior.

Polymerase chain reaction (PCR)—A method for replicating DNA fragments by using repeated cycles of heating and cooling to denature the DNA (separate it into two strands) and use an enzyme to make new copies of the original DNA.

PulseNet—A network of laboratories across the United States, overseen by the Centers for Disease Control and Prevention (CDC) to identify bacteria responsible for foodborne outbreaks by using whole-genome sequencing.

Sanger sequencing—The earliest method for sequencing DNA, devised by Frederick Sanger in the United Kingdom in 1977 and used as the primary method of sequencing until 2002. It is still used to validate the results of so-called next-generation sequencing. The Sanger method involves first separating the two strands of DNA and then adding chemically altered forms of the adenine, cytosine, guanine, and thymine bases. The altered bases stop the process of DNA replication as they are added to the strand of DNA, resulting in a series of short pieces of DNA. These short pieces are placed in order from shortest to longest to read the entire original sequence of DNA.

Secondary findings—Incidental or unanticipated findings, often of a previously unsuspected disease risk, resulting from the use of WES or WGS.

Throughput—In general, the rate at which data can be processed, or the work that a computer can do in a specific period of time. High-throughput sequencing refers to any of a set of technologies that can produce large numbers of DNA sequences concurrently.

Zoonosis (plural, zoonoses)—Any infectious disease of animals that can be transmitted to humans. A human disease that can be transmitted to animals is called a reverse zoonosis.

Genome Sequencing (WGS) is not medically necessary for evaluating any genetic disorder due to the availability of clinically equivalent diagnostic tests.” Other insurers will pay for WGS only for critically ill infants in a newborn intensive care unit (NICU).

Limitations

The primary limitation of WES is that it covers only a limited portion of the human genome; thus, DNA variations outside the exome that can influence genetic mutations will not be identified by WES. If a suspected disease-causing mutation is thought to be in the missing section of the exome, it must be identified by another method, most often whole-genome sequencing. This limitation of WES has led to a debate in the field of genomics regarding the future utility of exome sequencing. Some researchers are predicting that WES has a limited “shelf life,” and will be replaced entirely by WGS as the cost of whole-genome sequencing continues to drop. Others maintain that the shorter time frame required to perform WES (1/15 the time required to sequence an entire human

genome) and the smaller amount of data requiring storage (1/15 the volume required for WGS) will guarantee an ongoing place for whole-exome sequencing. The chief limitation of WGS is the much greater amount of computational power and data storage it requires.

Another limitation is that both WES and WGS sequencing identify a large number of single nucleotide variations (SNVs) of unknown significance as well as potentially disease-causing mutations. The number of such variations ranges from about 24,000 in African American samples to 20,000 in Caucasian Americans. Although there are several strategies for filtering out the non-problematic variations, there are usually several hundred SNVs remaining that require sorting and analysis by genetics professionals.

One related problem is the discovery of what are called secondary or incidental findings during whole-exome or whole-genome sequencing. A secondary finding is one that is not relevant to the condition for which the test was ordered but indicates the likelihood of future

disease in the person being tested; for example, the discovery of a mutation in one of the genes linked to breast cancer—an adult-onset disorder—in a small child being tested for mutations related to vision disorders. Secondary findings can cause considerable anxiety in patients. The risk of psychological distress is one that the genetic counselor should discuss with the patient before the sequencing is ordered.

Ethical concerns

The rapid pace of these new discoveries has led to a set of new ethical concerns for high-quality patient care as well as the most effective use of advanced technologies. In 2012, the American College of Medical Genetics and Genomics (ACMG) drew up a policy statement—which has not been updated as of 2021—regarding the clinical applications of whole-exome and whole-genome sequencing. Their first recommendation concerned the indications for WES and WGS in clinical diagnostic assessment. The ACMG recommended WES or WGS in the following situations:

- The patient's phenotype or family history suggests a genetic cause, but the patient's phenotype does not resemble that of a genetic disorder for which a clinical single-gene test currently exists.
- The patient has a genetic disorder with a high degree of genetic heterogeneity, making WES or WGS a more practical approach because both methods can analyze a number of different genes simultaneously.
- The patient is likely to have a genetic disorder, but the specific genetic tests presently available for that disorder have failed to yield a diagnosis.

The ACMG also recommended pre-test genetic counseling regarding the expected outcomes, the likelihood and reporting of secondary findings, and discussion of which results will or will not be disclosed to the patient. The patient is to be given the option of *not* receiving either diagnostically certain or secondary findings. In addition, the ACMG recommended obtaining informed consent from the patient for the use of findings of unknown significance that might be a subject for future research. Ongoing questions related to both WES and WGS include issues of permanent versus temporary data storage, patient confidentiality, obtaining informed consent from children and adolescent patients, and disclosure of WES and WGS findings to insurance companies.

In regard to using WES and WGS for health-screening purposes in asymptomatic patients, the ACMG stated that genomic sequencing should not be used for prenatal or newborn screening under present circumstances. Adult subjects should be given both pre-test and post-test counseling by a qualified medical geneticist or

QUESTIONS TO ASK YOUR DOCTOR

- Have any of your patients ever undergone WES or WGS?
- If so, were the results helpful in diagnosing or treating their health condition?
- Do you think that WES or WGS should be used routinely for health screenings in adults? Why or why not?
- What advances in personalized medicine do you expect to see in the next few years as a result of genomic sequencing?

genetic counselor. The counseling should cover both risks and benefits of genomic sequencing, plus the fact that the results will include “the virtual certainty of finding variants of uncertain significance.”

Epidemiology

Whole-genome sequencing has been used since 2013 by the CDC, and since 2018 by the FDA, in identifying foodborne bacteria and other biological contaminants. WGS has advantages over older methods of identifying disease-causing organisms in food, because it can distinguish genomic differences among bacteria or other contaminants, thus allowing scientists to trace the root source of a foodborne pathogen. The FDA has set up an open-access database called the GenomeTrackr, which archives WGS data for hundreds of thousands of bacterial samples. As of April 2021, there are over 600,000 WGS sequences in the GenomeTrackr, with an average of 12,000 new sequences added each month.

In 1996, the CDC established PulseNet, a network of 83 laboratories across the United States, in order to track outbreaks of foodborne illness and resolve them as quickly as possible. Until 2013, PulseNet used an older technology called pulsed-field gel electrophoresis (PFGE) to compare bacterial genomes. In 2013, WGS was introduced to solve outbreaks caused by *Listeria monocytogenes*, a virulent foodborne bacterium that can cause fatal illness in 20% to 30% of high-risk persons. The CDC found that the use of WGS resulted in solving more cases of *Listeria* outbreaks while simultaneously reducing the number of cases reported for each outbreak.

Another epidemiological application of WGS is its use in tracking infections passed between humans and other animals (zoonoses). A group of researchers in Texas concerned about the possibility of COVID-19

transmission between humans and household pets obtained samples of the virus from 76 cats and dogs sharing a household with at least one infected human, and analyzed the samples using WGS. Interestingly, the sequencing showed that humans were more likely to transmit the virus to their pets than the other way around—a form of transmission called reverse zoonosis.

Personalized medicine

Researchers are greatly interested in the use of WES and WGS to advance personalized medicine, also known as precision medicine. Personalized medicine is an approach to health care that uses genomic information about patients to make treatment decisions. These decisions could include the type of therapy offered to a patient, the choice of a specific medication, or careful monitoring of a patient known to be at increased risk of a specific disease or disorder. Personalized medicine allows for the use of information gained from WES and WGS to begin an intervention at an earlier stage in the patient's life. For example, a child who is revealed by WES to be at increased risk of developing type 2 diabetes in adult life can learn to eat a healthful diet, get adequate physical exercise, and make other lifestyle adjustments to lower the risk of adult-onset diabetes.

Pharmacogenomics, or the study of how a person's genome affects their response to medications, is a major part of personalized medicine. A growing number of cancer drugs, for example, are tailored to attack specific mutations, such as the three drugs currently used to treat melanomas caused by mutations in the *BRAF* gene. Other examples can be found in the field of psychiatry. Because a person's DNA affects how long an antidepressant or antipsychotic medication remains active in the body, genome sequencing can help identify the specific medication that is most likely to benefit the patient, as well as the most effective dosage of that medication.

Direct-to-consumer exome and genome sequencing

Various companies based in the United States and China began offering direct-to-consumer (DTC) exome sequencing tests as early as 2011. Whole-genome sequencing tests were offered a few years later. Although private individuals were able to purchase WGS for several years from such companies as Illumina, the whole-genome tests cost \$4,000 at that point in time and were marketed primarily to researchers. In 2011, a DTC genetic testing company called 23andMe offered a whole-exome sequencing test for \$999 but was forced to drop the health-related results formerly sent to customers

when the Food and Drug Administration (FDA) ordered the company to discontinue its personal genome service.

As of 2021, one company called Sequencing.com offers WGS to American consumers for \$399. According to the company, WGS testing in India is offered to consumers for prices ranging from \$338 to \$676. Another American company, Nebula, offers three tiers of WGS: “basic,” for \$149; “deep,” for \$299; and “ultra-deep” for \$999.

Genetics professionals are concerned about the trend toward DTC genomic sequencing, as it has already led to anxious consumers consulting genetic counselors on their own. As both whole-exome sequencing and whole-genome sequencing yield large amounts of complex data that are time-consuming to interpret, DTC marketing of sequencing tests is currently more likely to confuse and worry consumers than to help them. In addition, genetic counselors have noted the lack of adequate informed-consent provisions on many DTC genome-sequencing websites, along with incomplete or misleading information about the tests themselves.

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- American College of Medical Genetics and Genomics (ACMG), 7101 Wisconsin Avenue, Bethesda, MD 20814, (301) 718-9603, (301) 718-9604, acmg@acmg.net, <https://www.acmg.net/>
- Broad Institute, 415 Main Street, Cambridge, MA 02142, (617) 714-7000, <https://www.broadinstitute.org/contact>, <https://www.broadinstitute.org/>
- Illumina, Inc., 5200 Illumina Way, San Diego, CA 92122, (858) 202-4500, (858) 202-4766, <https://www.illumina.com/>
- National Human Genome Research Institute (NHGRI), Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000

Rockville Pike, Bethesda, MD 20892-2152, , (301) 402-0911, <https://www.genome.gov/about-nhgri/Contact>, <https://www.genome.gov/>

National Society of Genetic Counselors (NSGC), 330 North Wabash Avenue, Suite 2000, Chicago, IL 60611, (312) 321-6834, nsgc@nsgc.org, <https://www.nsgc.org>

NIH Intramural Sequencing Center (NISC), 5625 Fishers Lane, RM 5N-01, MSC9400, Bethesda, MD 20892-9400, (301) 451-0282, nisc@mail.nih.gov, <https://www.nisc.nih.gov/>

U.S. Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, Atlanta, GA 30333, (800) CDC-INFO (232-4636), <http://www.cdc.gov/cdc-info/requestform.html>, <http://www.cdc.gov>

U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993, (888) 463-6332, <https://www.fda.gov/>

Rebecca J. Frey, PhD

Williams-Beuren syndrome see **Williams syndrome**

Williams syndrome

Definition

Williams syndrome is a genetic disorder caused by a deletion of a series of genes on chromosome 7q11. Individuals with the disorder have distinctive facial features, mild intellectual disability, heart and blood vessel problems, short stature, unique personality traits, and distinct learning abilities and deficits.

Description

Williams syndrome, also known as Williams Beuren syndrome, was first described in 1961 by Dr. J. C. P. Williams of New Zealand. At that time it was noted that individuals with the condition had an unusual constellation of physical and mental findings. The physical features include a characteristic facial appearance, heart and cardiovascular problems, high blood calcium levels, low birth weight, short stature, and other connective tissue abnormalities. The intellectual problems associated with Williams include a mild intellectual disability and a specific cognitive profile. That is, individuals with Williams syndrome often have the same pattern of learning abilities and disabilities, as well as many similar personality traits.

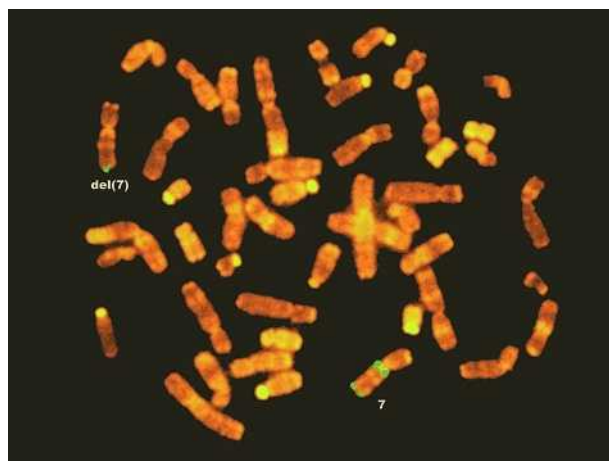
The findings in Williams syndrome are variable—that is, not all individuals with the disorder will have all of the described findings. In addition to being variable, the physical and mental findings associated with Williams syndrome are progressive—they change over time.

Genetic profile

Williams syndrome is a genetic disorder due to a deletion of chromosome material on the long arm of chromosome 7. A series of genes are located in this region. Individuals with Williams syndrome may have some or all of these genes deleted. Because of this, the condition is referred to as a contiguous gene deletion syndrome. Contiguous refers to the fact that these genes are arranged next to each other. The size of the deletion can be large or small, which may explain why some individuals with Williams syndrome are more severely affected than others. If you think of these genes as the letters of the alphabet, some individuals with the condition are missing A to M, some are missing G to Q, and others are missing A to R. While there are differences in the amount of genetic material that can be deleted, there is a region of overlap. Everyone in the example was missing G to M. It is thought that the missing genes in this region are important causes of the physical and mental findings of Williams syndrome.

Two genes in particular, *ELN* and *LIMK1*, have been shown to be important in causing some of the characteristic symptoms of Williams syndrome. The *ELN* gene codes for a protein called elastin. The job of elastin in the human body is to provide elasticity to the connective tissues such as those in the arteries, joints, and tendons. The exact role of the *LIMK1* gene is not known. The gene codes for a substance known as lim kinase 1 that is active in the brain. It is thought that the deletion of the *LIMK1* gene may be responsible for the visuospatial learning difficulties of individuals with Williams syndrome. Many other genes are known to be in the deleted region of chromosome 7q11 responsible for the disorder and much work is being done to determine the role of these genes in Williams syndrome.

Williams syndrome is an autosomal dominant disorder. Genes always come in pairs and in an autosomal dominant disorder, only one gene need be missing or altered for an individual to have the disorder. Although Williams syndrome is an autosomal disorder, most individuals with Williams syndrome are the only people in their family with this disorder. When this is the case, the chromosome deletion that causes Williams syndrome is called *de novo*. A *de novo* deletion is one that occurs for the first time in the affected individual. The cause of *de novo* chromosome deletions is unknown. Parents of an individual with Williams syndrome due to a *de novo* deletion are very unlikely to have a second child with the syndrome. However, once an individual has a chromosome deletion, there is a 50% chance that they will pass it on to their offspring. Thus individuals with Williams syndrome have a 50% chance of passing this deletion (and Williams syndrome) to their children.



Human chromosomes showing Williams syndrome. The chromosome marked 7 (lower right) shows four dots (genes). The chromosome marked del(7) [upper left] shows only one green area. (Addenbrookes Hospital/Science Source)

Demographics

Williams syndrome affects 1 in 10,000 people. Because Williams syndrome is an autosomal dominant disorder, it affects an equal number of males and females. It is thought that the condition occurs in people of all ethnic backgrounds equally.

Signs and symptoms

Williams syndrome is a multi-system disorder. In addition to distinct facial features, individuals can have cardiovascular, growth, joint, and other physical problems. They also share unique personality traits and have intellectual differences.

Infants with Williams syndrome are often born small for their family and 70% are diagnosed with failure to thrive during infancy. These growth problems continue throughout the life of a person with Williams syndrome and most individuals with the disorder have short stature (height below the third percentile). Infants with Williams syndrome can also be extremely irritable and have “colic-like” behavior. This behavior is thought to be due to excess calcium in the blood (hypercalcemia). Other problems that can occur in the first years include strabismus (crossed eyes), ear infections, chronic constipation, and eating problems.

Individuals with the condition can have distinct facial features sometimes described as “elfin” or “pixie-like.” While none of these individual facial features are abnormal, the combination of the different features is common for Williams syndrome. Individuals have a small upturned nose; a small chin; long upper lip with a

KEY TERMS

De novo deletion—A deletion that occurs for the first time in the affected individual. The cause of de novo deletions is not known.

Hypercalcemia—High levels of calcium in the blood.

Stellate—A star-like, lacy white pattern in the iris. Most often seen in light-eyed individuals.

wide mouth; small, widely spaced teeth, and puffiness around the eyes. As an individual gets older, these facial features become more pronounced.

People with Williams syndrome often have problems with narrowing of their heart and blood vessels. This is thought to be due to the deletion of the elastin gene and is called elastin arteriopathy. Any artery in the body can be affected but the most common narrowing is seen in the aorta of the heart. This condition is called supravalvar aortic stenosis (SVAS) and occurs in approximately 75% of individuals with the disorder. The degree of narrowing is variable. If left untreated, it can lead to high blood pressure, heart disease, and heart failure. The blood vessels that lead to the kidney and other organs can also be affected.

Deletions of the elastin gene are also thought to be responsible for the loose joints of some children with Williams syndrome. As individuals with the syndrome age, their heel cords and hamstrings tend to tighten, which can lead to a stiff awkward gait and curving of the spine.

Approximately 75% of individuals with the condition have mild intellectual disability. They also have a unique cognitive profile (unique learning abilities and disabilities). This cognitive profile is independent of their IQ. Individuals with Williams syndrome generally have excellent language and memorization skills. They can have extensive vocabularies and may develop a thorough knowledge of a topic that they are interested in. Many individuals are also gifted musicians. Individuals with Williams syndrome have trouble with concepts that rely on visuospatial ability. Because of this, many people with the disorder have trouble with math, writing, and drawing.

People with Williams syndrome also often share personality characteristics. They are noted to be very talkative and friendly—sometimes inappropriately—and they can be hyperactive. Another shared personality trait is a generalized anxiety.

Diagnosis

The diagnosis of Williams syndrome is usually made by a physician familiar with the disorder and based upon a physical examination of the individual and a review of his or her medical history. It is often made in infants after a heart problem (usually SVAS) is diagnosed. In children without significant heart problems, the diagnosis may be made after enrollment in school when they are noted to be “slow learners.”

While a diagnosis can be made based upon physical examination and medical history, the diagnosis can now be confirmed by a DNA test.

Williams syndrome is caused by a deletion of genetic material from the long arm of chromosome 7. A specific technique called fluorescent in situ hybridization testing, or FISH testing, can determine whether there is genetic material missing. A FISH test will be positive (detect a deletion) in more than 99% of individuals with the disorder. A negative FISH test for Williams syndrome means that no genetic material is missing from the critical region on chromosome 7q11.

Prenatal testing (testing during pregnancy) for Williams syndrome is possible using the FISH test on DNA sample obtained by chorionic villus sampling (CVS) or by amniocentesis. Chorionic villus sampling is a prenatal test that is usually done between 10 to 12 weeks of pregnancy and involves removing a small amount of tissue from the placenta. Amniocentesis is a prenatal test that is usually performed at 16–18 weeks of pregnancy and involves removing a small amount of the amniotic fluid that surrounds the fetus. DNA is obtained from these samples and tested to see if the deletion responsible for the condition is present. While prenatal testing is possible, it is not routinely performed. Typically, the test is only done if there is a family history of Williams syndrome.

Treatment and management

Because Williams syndrome is a multi-system disorder, the expertise of a number of specialists is required for management of this disorder.

The height and growth of individuals with Williams syndrome should be monitored using special growth curves developed specifically for individuals with the disorder. Individuals who fall off these growth curves should be worked up for possible eating or thyroid disorders.

A cardiologist should evaluate individuals with Williams syndrome yearly. This examination should include measurement of blood pressure in all four limbs and an echocardiogram of the heart. An echocardiogram is a special form of ultrasound that looks at the structure of the heart. Doppler flow studies, which look at how the blood

QUESTIONS TO ASK YOUR DOCTOR

- How does the Williams syndrome growth chart differ from other growth charts, and where does my child fall on it?
- Can you recommend a nutritionist?
- Is my child's blood pressure within the normal range?
- What are the risks and benefits of medications used to manage behavior?

flows into and out of the heart, should also be done. Individuals with supravulvar stenosis may require surgery to fix this condition. The high blood pressure caused by this condition may be treated with medication. Examinations should take place yearly as some of these conditions are progressive and may worsen over time.

Individuals with Williams syndrome should also have a complete neurological examination. In addition, the blood calcium levels of individuals with the disorder should be monitored every two years. High levels of calcium can cause irritability, vomiting, constipation, and muscle cramps. An individual found to have a high level of calcium should consult a nutritionist to make sure that their intake of calcium is not higher than 100% of the recommended daily allowance (RDA). Because vitamin D can increase calcium levels, individuals with Williams syndrome and high calcium should not take multivitamins containing vitamin D. If calcium levels remain high after limiting vitamin D and decreasing dietary intake of calcium, an individual with hypercalcemia should see a nephrologist for further management and to monitor kidney function.

Strabismus (crossed eyes) can be treated by patching or by surgery. Ear infections can be treated with antibiotics and surgical placement of ear tubes.

The developmental differences of individuals with Williams syndrome should be treated with early intervention and special education classes. Specific learning strategies that capitalize on the strengths of individuals with the condition should be used. Physical, occupational, and speech therapy should be provided. Behavioral counseling and medication may help with behavioral problems such as hyperactivity and anxiety.

Prognosis

The prognosis for individuals with Williams syndrome is highly dependent on the medical complications of a particular individual. Individuals with the disorder

who have no heart complications, or very minor ones, have a good prognosis. Good medical care and treatment of potential problems allows most individuals with Williams syndrome to lead a long life. The prognosis for individuals with more serious medical complications such as severe heart disease or hypertension is more guarded. Since the medical conditions associated with the condition are progressive rather than static, it is very important that individuals with Williams syndrome have yearly medical examinations with a health care provider familiar with the disorder.

The range of abilities among individuals with Williams syndrome is very wide, and the ultimate functioning of an individual is dependent on his or her abilities. While individuals do well in structured environments such as school, their unique abilities and disabilities do not permit them to do as well in unstructured surroundings. Some individuals live independently but most live with their parents or in a supervised setting. Many individuals can gain employment in supervised settings and do well at tasks that do not require mathematics or visuospatial abilities. It is important to encourage individuals with Williams syndrome toward independence but to recognize that their friendly and outgoing personalities may lead them into abusive situations.

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ORGANIZATIONS

- Williams Syndrome Association, 570 Kirts Blvd., Suite 223, Troy, MI 48064-4156, (248) 244-2229 or (800) 806-1871, info@williams-syndrome.org, <https://williams-syndrome.org>

Williams Syndrome Changing Lives Foundation, PO Box 76021,
Saint Petersburg, FL 33734, info@wschanginglives.org,
http://www.wschanginglives.org

Kathleen Fergus, MS, CGC

Wilson disease

Definition

Wilson disease is a rare, inherited disorder that causes excess copper to accumulate in the body. Steadily increasing amounts of copper circulating in the blood are deposited primarily in the brain, liver, kidneys, and the cornea of the eyes.

Description

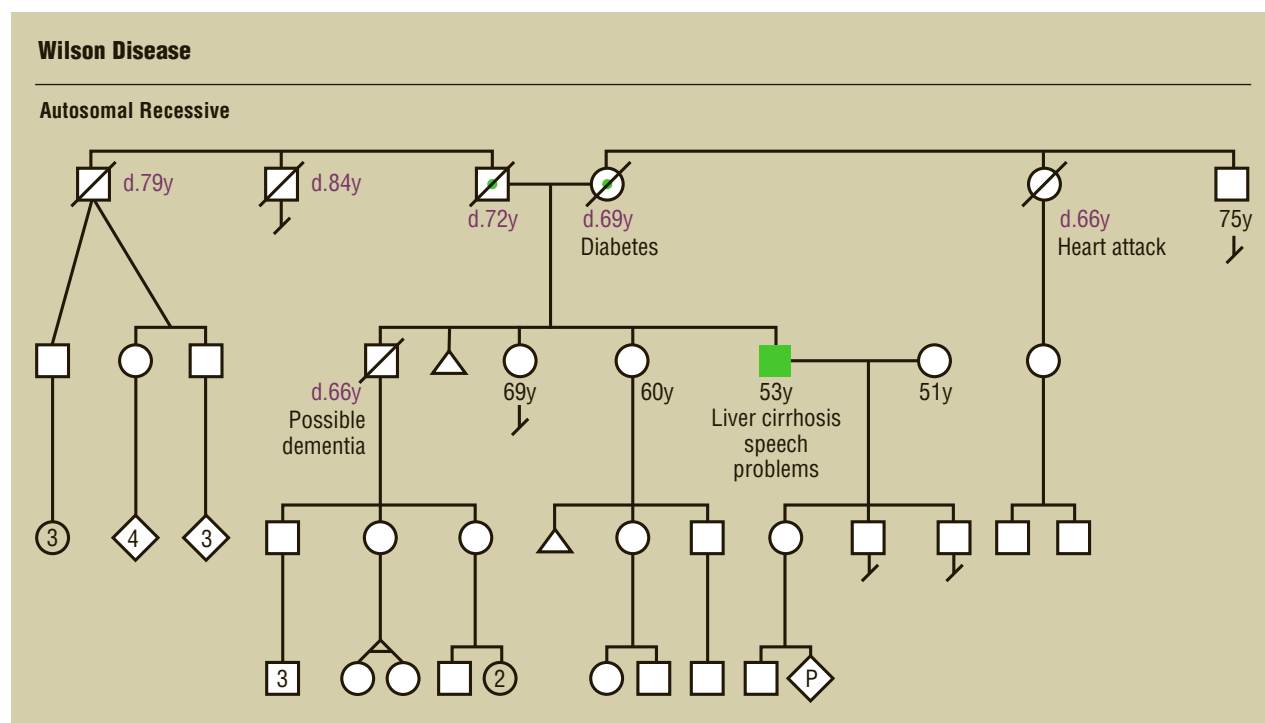
Under normal conditions, copper that finds its way into the body through the diet is processed within the liver. This processed form of copper is then passed into the gallbladder, along with the other components of bile (a fluid produced by the liver that enters the small intestine in order to help in digestive processes). When the gallbladder empties its contents into the first part of the small intestine (duodenum), the copper in the bile enters and passes through the intestine with the waste products

of digestion. In healthy individuals, copper is then passed out of the body in stool.

In Wilson disease, copper does not pass from the liver into the bile, but rather begins to accumulate within the liver. As copper levels rise in the liver, the damaged organ begins to allow copper to flow into the bloodstream, where it circulates. Copper is then deposited throughout the body, building up primarily in the kidneys, the brain and nervous system, and the eyes. Wilson disease, then, is a disorder of copper poisoning occurring from birth.

Genetic profile

Wilson disease is inherited in an autosomal recessive manner. "Autosomal recessive" refers to the pattern of inheritance in which each parent carries a gene mutation for the disease on one of his or her chromosome pairs. When each parent passes on the chromosome with the gene mutation for Wilson disease, the child will be affected with the disease. Both males and females can be affected by Wilson disease. If an individual is a carrier of the Wilson disease gene, he or she does not have any symptoms of the disorder. In order to be affected, an individual must inherit two copies of the gene, one from each parent. Many cases of Wilson disease may not be inherited but occur as a spontaneous mutation in the gene.



Wilson Disease: pedigree analysis chart (Gale)

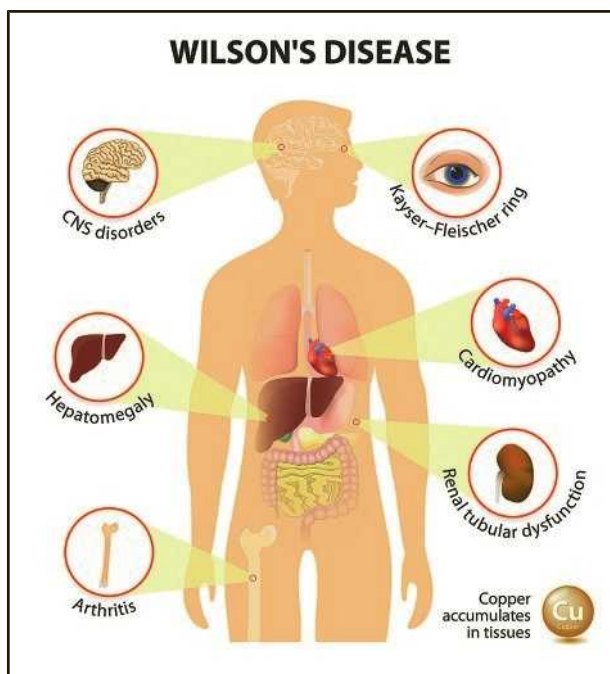


Illustration of the signs and symptoms of Wilson disease.
(Designua/Shutterstock)

The gene for Wilson disease, *ATP7B*, is located on chromosome 13 and is thought to be involved in transporting copper. More than 500 different mutations of this gene have been identified, making diagnosis by genetic testing difficult.

Demographics

Wilson disease affects approximately 1 in 30,000 to 1 in 100,000 individuals and can affect people from many different populations. In some isolated regions of Sardinia, the prevalence is reported to be 1 in 10,000 individuals. Approximately 1 in 90 individuals are carriers of the gene for Wilson disease.

Signs and symptoms

Symptoms typically present between the ages of 3 and 60, with age 17 considered to be the average age of diagnosis. About half of all patients experience their first symptoms in the liver. The illness causes swelling and tenderness of the liver, sometimes with fever, mimicking more common disorders such as viral hepatitis and infectious mononucleosis. Abnormal levels of circulating liver enzymes reveal that the liver is being seriously damaged. This form of damage is referred to as “fatty degeneration.” Without medical intervention, the liver damage will progress to actual cirrhosis. An often-fatal manifestation of liver disease is called fulminant hepatitis. This extremely severe inflammation of the liver (hepatitis)

results in jaundice, fluid leaking into the abdomen, low protein circulating in the blood, abnormalities of the blood clotting system, swelling of the brain, and anemia due to the abnormal destruction of red blood cells.

Neurological symptoms are the first to occur in half of all patients due to copper accumulation in the brain and nervous system. The average age of onset for neurological symptoms is 21 years. These symptoms include tremors of the hands, uncontrollable movements of the limbs, stiffness, drooling, difficulty swallowing, difficulty talking, and headache. There is no change in a patient’s intelligence.

About one-third of all patients with Wilson disease have a variety of psychiatric symptoms as the first signs of the disease. These symptoms include inability to cope, depression, irritability, increased anger, and inappropriate behavior. Patients often have trouble completing tasks at work or in school.

Other symptoms that can affect patients with Wilson disease, and that may occur before or after a diagnosis has been made, include joint disorders, symptoms of arthritis, and skeletal problems such as osteoporosis. Patients have occasionally been affected with kidney stones and abnormal handling of glucose in their body, and women have menstrual cycle irregularities including temporary stopping of their regular cycle.

Diagnosis

The diagnosis of Wilson disease can be performed relatively easily through several different tests that can be performed on patients who have or have not already shown symptoms of the disease. Although Wilson disease is so rare that diagnosis is often delayed, it is extremely important to make a diagnosis as soon as possible since liver damage can occur before there are any signs of the disease.

An easy way to diagnose Wilson disease is to measure the amount of a glycoprotein found in the blood called ceruloplasmin. Low levels of ceruloplasmin can diagnose the disease in about 80% of affected patients. This procedure is not as effective for women taking birth control pills, pregnant women, or infants less than six months of age.

A second test involving an eye examination to detect a characteristic ring of copper deposited in a membrane of the cornea (referred to as Kayser-Fleischer rings) is very easy to perform and is very useful in diagnosing patients who have already exhibited symptoms. This test is not as effective in persons without symptoms and cannot be used by itself to make a diagnosis because some patients with liver disease, but not Wilson disease, will test positive.

KEY TERMS

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Bile—A substance produced by the liver and concentrated and stored in the gallbladder. Bile contains a number of different substances, including bile salts, cholesterol, and bilirubin.

Biopsy—The surgical removal and microscopic examination of living tissue for diagnostic purposes.

Cell—The smallest living units of the body that group together to form tissues and help the body perform specific functions.

Ceruloplasmin—A protein circulating in the bloodstream that binds with copper and transports it.

Chromosome—A microscopic thread-like structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Cirrhosis—A chronic degenerative disease of the liver in which normal cells are replaced by fibrous tissue. Cirrhosis is a major risk factor for the later development of liver cancer.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Gallbladder—A small, pear-shaped organ in the upper right hand corner of the abdomen. It is connected by a series of ducts (tube-like channels) to the liver, pancreas, and duodenum (first part of the small intestine). The gallbladder receives bile from the liver and concentrates and stores it. After a meal, bile is squeezed out of the gallbladder into the intestine, where it aids in digestion of food.

Gene—A building block of inheritance that contains the instructions for the production of a particular protein and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Glucose—One of the two simple sugars, together with galactose, that makes up the protein lactose, found in milk. Glucose is the form of sugar that is usable by the body to generate energy.

Hepatitis—A viral disease characterized by inflammation of the liver cells (hepatocytes). People infected with hepatitis B or hepatitis C virus are at an increased risk for developing liver cancer.

Jaundice—Yellowing of the skin or eyes due to excess of bilirubin in the blood.

Toxic—Poisonous.

A third test for diagnosing Wilson disease involves measuring the amount of copper in the liver. This can be accomplished by sampling a portion of the liver in a procedure called a biopsy. This is one of the most effective ways to diagnose Wilson disease; however, the procedure itself is more difficult to perform than the others.

Other tests are also useful; for example, measuring the amount of copper passed into the urine daily (high in Wilson disease). Another lab test measures the ability of a patient's ceruloplasmin to bind with a form of copper (decreased in Wilson disease). Some patients can be diagnosed through a DNA test to determine whether or not they carry two genes for Wilson disease. This test does not always prove to be useful in certain patients and is used mostly to test the brothers and sisters of affected patients.

Treatment and management

Treatment involves life-long administration of either D-penicillamine or trientine hydrochloride. Both of these

drugs remove copper deposits throughout the body by binding to the copper, which is removed from the body in urine. Zinc acetate and a low copper diet are other ways to treat Wilson disease.

Penicillamine has a number of serious side effects:

- joint pain
- neurological problems
- systemic lupus erythematosus
- decreased production of all blood elements
- interference with clotting
- allergic reactions

Careful monitoring is necessary. When patients have side effects from penicillamine, the dose can sometimes be lowered to an effective level that causes fewer difficulties. Alternatively, steroid medications may be required to reduce certain sensitivity reactions. Trientine has fewer potential side effects, but it must still be carefully monitored.

QUESTIONS TO ASK YOUR DOCTOR

- Can you recommend a low copper diet?
- What are the side effects of penicillamine?
- What are the pros and cons of zinc treatment versus medication for removing copper?
- How accurate is the genetic testing for Wilson disease?
- Are there any new therapies available to treat Wilson disease?

Treatment with zinc is also an effective way to remove excess copper from the body. Zinc is a metal that works to block copper absorption and bind copper in the intestinal cells until it is all released into the stool approximately one week later. The benefit of treatment with zinc is that there are no toxic side effects; however, zinc is a slower acting agent than the other drugs. It takes four to eight months for the zinc to be effective in reducing the overall amount of copper in the body.

In special situations in which individuals with Wilson disease do not respond to these treatments, a liver transplant is considered.

Finally, patients with Wilson disease are encouraged to follow a diet low in copper, with an average copper intake of 1.0 mg/day. Foods to avoid due to their high levels of copper include liver and shellfish. Patients are also instructed to monitor their drinking water for excess levels of copper and drink distilled water instead.

Prognosis

Without treatment, Wilson disease is always fatal. With treatment, symptoms may continue to worsen for the first six to eight weeks. After this time, definite improvement should start to be seen. However, it may take several years (two to five) of treatment to reach maximal benefit to the brain and liver. Even then, many patients are not returned to their original level of functioning. Patients with Wilson disease need to maintain some sort of anti-copper treatment for the rest of their lives in order to prevent copper levels from rising in the body. Interruptions in treatment can result in a relapse of the disease that is not reversible and can ultimately lead to death.

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ORGANIZATIONS

- American Liver Foundation, 39 Broadway, Suite 2700, New York, NY 10006, (212) 668-1000 or (800) 465-4837, (212) 483-8179, <http://www.liverfoundation.org>
- Canadian Liver Foundation (CLF), 3100 Steeles Ave. E, Suite 801, Markham, ON Canada L3R 8T3, (416) 491-3353 or (800) 563-5483, (905) 752-1540, clf@liver.ca, <http://www.liver.ca>
- Wilson Disease Association, 1732 First Ave., No. 20043, New York, NY 10128, (414) 961-0533 or (866) 961-0533, info@wilsonsdisease.org, <http://www.wilsonsdisease.org>

Katherine S. Hunt, PhD, MS, CGC

Wiskott-Aldrich syndrome

Definition

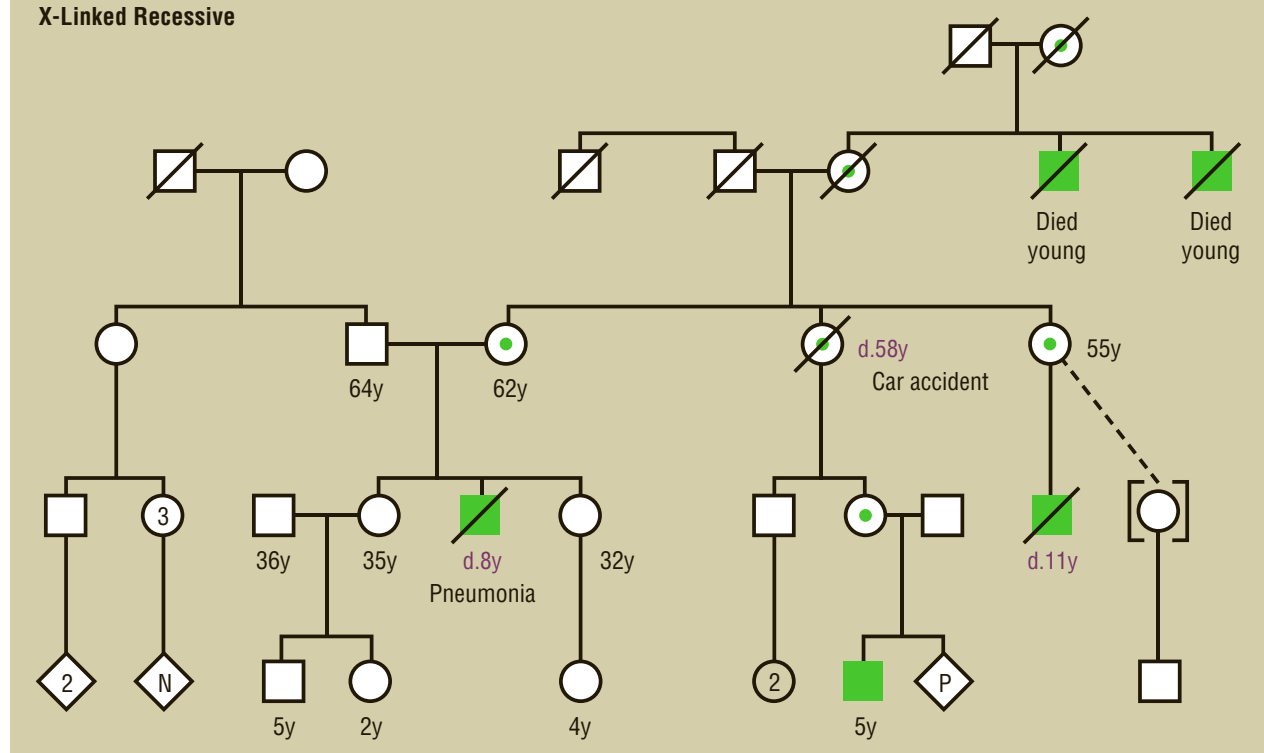
Wiskott-Aldrich syndrome (WAS) is a rare inherited disorder marked by a low level of blood platelets, eczema, immunodeficiency, and a high risk of leukemia or lymph node tumors.

Description

WAS was named for the two physicians who first reported the disorder. In 1937, Dr. Alfred Wiskott, a physician working in Munich, described two affected boys of German ancestry who had repeated infections, a skin

Wiskott-Aldrich Syndrome

X-Linked Recessive



Wiskott-Aldrich syndrome: pedigree analysis chart (Gale)

rash, and poor blood-clotting ability. Nearly 20 years later, Dr. Robert Aldrich reported similar symptoms in members of an American family of Dutch ancestry.

The syndrome is caused by a defect (mutation) in a specific gene called the *WAS* gene that normally codes for the Wiskott-Aldrich syndrome protein (WASp). This vital protein is a component of cells that are important in the body's defense against infection (lymphocytes). The same protein also functions in the cells that help prevent bleeding (platelets). A less severe form of the disease, X-linked thrombocytopenia, affects mainly the platelets.

Genetic profile

WAS is inherited as an X-linked genetic disorder and will therefore only affect males. The gene responsible for WAS is located on the short arm of the X chromosome. Since males have only one X chromosome, they only have one copy of the gene. If that copy carries the abnormal gene, they will have WAS. In contrast, females have two X chromosomes. They will have a normal copy of the gene on one chromosome even if an abnormal gene is on the other because the abnormal gene is very rare. The normal copy on one X chromosome is usually

sufficient to prevent females from having WAS. However, women who have one abnormal copy of the *WAS* gene are designated as carriers. While they will not have WAS, they have a 50% risk of passing the gene to each of their sons, who will then have WAS. Carrier females also have a 50% risk of passing the defective copy of the gene to their daughters, who then become carriers.

Researchers identified the gene for WAS in 1994 and pinpointed its location on the short arm of the X chromosome (Xp11.22-p11.23). More than 100 different mutations have been found in the gene among WAS patients. The fact that there are many mutations may explain some of the variability of symptoms among boys with WAS. However, even within the same family, affected individuals with the identical *WAS* gene mutation may have different degrees of severity of the disease. The mild form, X-linked thrombocytopenia, is also caused by mutations in this same gene. The *WAS* gene codes for the WASp protein, a protein necessary for blood cell development. A mutation in the *WAS* gene causes a disruption in the actin cytoskeleton, which is important for the structure of the cell itself. An alteration in the structure of the cell leads to an alteration in the function of the cell. White blood cells that have an alteration in the WASp protein,

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman’s abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Anemia—A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted through either the mother’s vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Eczema—Inflammation of the skin with redness and other variable signs such as crusts, watery discharge, and itching.

Gene—A building block of inheritance that contains the instructions for the production of a particular protein and is made up of a molecular sequence found on a section of DNA. Each gene is found at a precise location on a chromosome.

Immune system—The complex group of organs and cells that defends the body against infection and disease.

Mutation—An inherited or de novo change in the DNA sequence of the genome.

Platelets—Small disc-shaped structures that circulate in the blood stream and participate in blood clotting.

Prenatal diagnosis—The determination of whether a fetus possesses a disease or disorder while it is still in the womb.

Syndrome—A group of signs and symptoms that collectively characterize a disease or disorder.

Thrombocytopenia—A persistent decrease in the number of blood platelets; usually associated with hemorrhaging.

X-linked—A genetic trait that is carried on the X chromosome.

therefore, are unable to properly respond to pathogens, leading to a decrease in the overall function of the immune system. A lack of WASp protein in other blood cells such as platelets will result in an altered shape of the cell and cause early cell death, hence the low levels of platelets seen in WAS.

Demographics

WAS occurs worldwide and affects 1 in every 10 million male children. It is even less prevalent in women due to its X-linked inheritance pattern.

Signs and symptoms

Increased susceptibility to infections, eczema, and excessive bleeding are the hallmarks of WAS, although the symptoms can vary significantly from one patient to another. The immune system of a patient with WAS produces too few B and T cells. B cells are the cells in the body that make antibodies. There are many types of T cells. Both B and T cells are needed to defend the body against infection. Because both types of cells are affected, WAS patients are subject to repeated infections from bacteria, fungi, and viruses. Ear infections, meningitis, and pneumonia are common in boys with WAS.

WAS patients also have thrombocytopenia, a decreased number of platelets. Platelets are the specialized blood cells that help to form blood clots and prevent uncontrolled bleeding. The platelets may also be smaller than normal. Some of the earliest symptoms of the syndrome are hemorrhage from circumcision, bloody diarrhea, and a tendency to bruise very easily.

Anemia and an enlarged spleen (splenomegaly) are seen in some patients. About 10% of patients develop malignancies, usually leukemia or tumors in the lymph nodes (non-Hodgkin lymphoma).

Diagnosis

The diagnosis of WAS is usually suspected in male infants who have excessive bleeding, eczema, frequent bacterial or viral infections, bloody diarrhea, petechiae, or purpura. Special blood tests can then be ordered to confirm WAS. These blood tests are imperative because WAS may be confused with other bleeding disorders, and correct treatment given early is important for the prognosis of the individual. The blood of patients with WAS will show a low platelet count (less than 70,000/mL), a decreased amount of IgM and IgG with normal to high levels of IgA and IgE, and a decreased antibody response, particularly when assessed after routine vaccinations such as DPT (diphtheria, pertussis, and tetanus). It is also possible to confirm the diagnosis by obtaining a small sample of the patient’s blood and analyzing the

QUESTIONS TO ASK YOUR DOCTOR

- Which family members should undergo genetic testing for Wiskott Aldrich syndrome?
- Do you recommend removal of the spleen?
- What family members could be potential bone marrow donors?
- What are the risks and benefits of immune globulin?
- What are the treatment options for Wiskott Aldrich syndrome?
- What is the prognosis in this case?

DNA for a mutation in the WAS gene. Knowledge of the exact mutation combined with information about how much WASp protein the defective gene can produce may help predict how severe a form of the disease an individual will have.

Carrier testing

If the specific WAS gene mutation is identified in an affected child, that child's mother can then be tested to confirm that she carries the gene. Other members of the mother's family may also want to consider testing to find out if they carry the same gene mutation. The first step in studying other family members is for a geneticist or genetic counselor to obtain a detailed family history and construct a pedigree (family tree) to determine which family members should be offered testing.

Prenatal diagnosis

In families in which there has been one child born with WAS, prenatal testing should be offered in subsequent pregnancies. There is a 50% chance with each subsequent pregnancy that the mother, who is a carrier, will transmit the abnormal copy of the gene to her baby. The key is to first identify the particular WAS gene mutation in the child with WAS. Then, early in a pregnancy, cells can be obtained from the developing fetus by chorionic villus sampling or amniocentesis and checked for the same mutation. Women who carry the abnormal WAS gene and are considering prenatal diagnosis should discuss the risks and benefits of this type of testing with a geneticist or genetic counselor.

Treatment and management

Standard treatments for individuals with WAS include antibiotics for infections and platelet transfusions

to limit bleeding. Immune globulin replacement therapy is given every 4–6 weeks starting at age six months to strengthen the individual's immune system. Bloodwork should be evaluated routinely as well for the management of WAS. Eczema can be treated with corticosteroid creams applied directly to the skin. The spleen is sometimes removed to reduce the risk of bleeding. In individuals with WAS, however, removal of the spleen also increases the risk of infection unless antibiotics are given to prevent infections. About 50% of individuals with WAS are helped by treatment with transfer factor, which is a substance derived from the T cells of a healthy person. Transfer factor is given to improve both blood clotting and immune functions. Bone marrow transplantation has been successful in a number of cases. It has been most successful in boys under five years of age when the donor is a sibling whose tissue type closely matches that of the individual with WAS. As of 2015, the most effective treatment for WAS was the use of hematopoietic cell transplantation (HCT). Hematopoietic stem cell gene therapy using peripheral blood, umbilical cord blood, and/or bone marrow is also critical for the treatment of WAS in very young infants. Prenatal diagnosis is necessary to utilize this treatment method.

Prognosis

The prognosis for males diagnosed with WAS syndrome is poor. The average individual lives about four years. Forty percent of those who survive into adolescence often develop other autoimmune diseases typically causing liver and/or kidney failure, and/or cancer. Death usually occurs from severe bleeding or overwhelming infection in the first few years of life.

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ORGANIZATIONS

Immune Deficiency Foundation, 110 West Rd., Suite 300, Towson, MD 21204, (800) 296-4433, (410) 321-9165, info@primaryimmune.org, <http://primaryimmune.org>

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Wolf-Hirschhorn syndrome

Definition

Wolf-Hirschhorn syndrome (WHS) refers to a condition that is caused by a deletion of the short arm of chromosome 4. This missing genetic material results in severe developmental retardation and a characteristic facial appearance, and it may include a variety of other birth defects.

Description

This syndrome was reported in 1965 in published reports by Wolf and Hirschhorn, who associated specific physical characteristics with a deletion of part of the short arm of chromosome 4. The short arm of a chromosome is called the “p” arm. Thus, this syndrome is also known as 4p- syndrome or deletion 4p- syndrome, and occasionally as Wolf syndrome.

A normal human karyotype consists of 23 pairs of chromosomes. Each pair is numbered 1 through 22, and the 23rd pair is made by the sex chromosomes. On each chromosome are hundreds of genes that determine how human bodies look and function. WHS is a contiguous gene syndrome that is defined as a gene syndrome in which deletions or duplications in the same region of the chromosome occur, affecting the genes on those chromosomes. Each time a deletion or duplication of those genes occurs, they cause specific characteristics that define a particular syndrome. This is in contrast to having just one particular gene cause a syndrome. Some patients who have WHS may have a small deletion on 4p, while others may be missing up to half of 4p. For this reason, some individuals have a less severe case of WHS than others do. The band 4p16.3 needs to be deleted in order for an individual to have full expression of WHS.

WHS frequently presents prenatally with slow growth (intrauterine growth retardation). Some infants with WHS can be stillborn or die shortly after birth, and

as many as one-third of reported patients with WHS have died in the first year of life. Individuals with WHS have been described as having a characteristic facial appearance likened to a “Greek Helmet facies.” This can be described as having small head size (microcephaly), eyes spaced widely apart (ocular hypertelorism), downturned mouth, short upper lip, short groove between the upper lip and nose (philtrum), or bilateral cleft lip and small chin (micrognathia).

Children with WHS have severe developmental delays. Other significant problems can include heart defects, cleft lip and/or palate, hearing impairment, and eye problems. Approximately 90% of children who have WHS have seizures. These seizures begin between 5 and 23 months of age; however, approximately 50% of the individuals stop having seizures between age 3 and 11. Sleeping problems are also common in children who have WHS. Although it seems that most of the literature focuses on children who have WHS, there are adults who have the disease.

Genetic profile

With routine chromosome analysis, it is possible to identify missing parts of the short arm of chromosome 4. The size of the missing material may vary from patient to patient. At times, the deletion is so small that it cannot be detected by routine chromosome analysis. If a patient is suspected to have WHS and an obvious deletion is not detected by routine chromosome analysis, more detailed studies are warranted and may identify the missing genetic material. WHS may also present as mosaicism. Mosaicism for 4p- syndrome means that the individual has some cells that have normal number 4 chromosomes and other cells that are missing some of the genetic material from chromosome 4.

Approximately 85%–90% of cases of WHS occur as the result of a new deletion in the affected individual. This is also known as a *de novo* deletion and simply means that the affected individual’s parents did not have any chromosome arrangement that led to the deletion. In this case, the chance for recurrence in future pregnancies of a couple who has an affected child is not increased. In the remaining 10%–15% of cases, one of the parents of the affected individual carries a balanced translocation. A balanced translocation is a rearrangement in the individual’s chromosomes that causes that individual no problems since he or she has all the necessary genetic material needed. However, when the individual produces eggs or sperm, the eggs or sperm may end up with an unbalanced arrangement and could lead to the conception of a child who has missing or extra genetic material. This could lead to miscarriage or to the birth of a child with conditions like WHS.

When a parent is identified as being a carrier of a balanced translocation, with each pregnancy he or she has an increased chance of having a child with an unbalanced chromosome arrangement. This probability is determined by the individual's specific translocation, how it was identified, and which parent is the carrier of the translocation. Genetic counseling should be offered to any family in which a child is diagnosed with WHS. Other family members should also be offered counseling and chromosome analysis to determine if they are carriers of a balanced translocation.

Demographics

The incidence of this condition is rare and estimated to be approximately 1 in 50,000 births. As with many genetic conditions, WHS may be misdiagnosed or may not be diagnosed in all individuals who are affected, especially if the condition results in pregnancy loss or loss in the early newborn period. It has been estimated that approximately 35% of individuals who have WHS die within the first two years of life. Also, with the advent of prenatal diagnosis, some fetuses with ultrasound abnormalities may be detected early, and the parents may elect to terminate the pregnancy. Approximately two-thirds of reported cases have been females.

Signs and symptoms

It is important to remember that each individual who may have a particular genetic syndrome is a unique individual. Therefore, all individuals with WHS do not have all of the same signs and symptoms. An accurate diagnosis helps to determine the needs of each person, based on the histories available from other individuals affected with the same condition.

Signs and symptoms that can be associated with WHS include the following:

- slow growth before birth
- slow growth after birth (postnatal growth deficiency)
- small head size (microcephaly)
- weak cry in infancy
- poor muscle tone (hypotonia)
- seizures
- severe developmental delays
- severe delay of motor skills
- crossed eyes (strabismus)
- widely spaced eyes (hypertelorism)
- droopy eyelids (ptosis)
- skin folds in the corner of the eyes (epicanthal folds)
- cleft lip and/or palate

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen and into her uterus to draw out a small sample of the amniotic fluid from around the fetus. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted through either the woman's vagina or abdominal wall and a sample of cells is collected from around the fetus. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome translocation—The exchange of genetic material between chromosomes, which can lead to extra or missing genetic material.

Corpus callosum—A thick bundle of nerve fibers deep in the center of the forebrain that provides communications between the right and left cerebral hemispheres.

In vitro fertilization—A process by which a woman has her eggs surgically removed and fertilized in the laboratory. The developing embryos can then be transferred to her uterus to hopefully achieve a pregnancy.

- short upper lip and philtrum
- small chin (micrognathia)
- asymmetry of the skull (cranial asymmetry)
- skin tag or pit in front of the ear (preauricular tag or pit)
- downturned mouth
- prominent triangular area of the forehead (glabella)
- scalp defects on the center of the back of the head
- underdeveloped fingerprints (dermal ridges)
- a single crease across the palm of the hands (simian crease)
- misaligned bones in the front part of the foot/clubfoot (talipes equinovarus)
- turned up fingernails
- urinary opening on the underside of the penis (hypospadias)
- undescended testicles (cryptorchidism)
- dimple at the base of the spine
- heart defects

- curvature of the spine (scoliosis)
- underdeveloped bones of the hands and pelvis

Diagnosis

When WHS is suspected, chromosome analysis should be performed and the laboratory should be informed as to what syndrome is suspected. This ensures that the laboratory carefully looks at chromosome 4, and if the deletion is not visible, then fluorescent in situ hybridization (FISH) can be done specifically for the critical 4p16.3 region of chromosome 4. FISH analysis is a procedure that is used in the laboratory to identify pieces of genetic material that are too small to see by looking at the chromosome under a microscope. Instead, DNA that is specific to a particular area of a chromosome is fluorescently labeled so that it is visible under the microscope. This labeled DNA is then added to the sample and allowed to attach itself to the particular piece of DNA in question. This enables the laboratory technician to then look under the microscope for the fluorescent spot on the chromosome and identify extra or missing pieces of DNA that are too small to see by just looking at the chromosome alone. With this procedure, those individuals who have deletions so small that they cannot be detected by routine chromosome analysis may be able to have the deletion detected by FISH.

Interestingly, a syndrome called Pitt-Rogers-Danks syndrome (PRDS) has been reported to have similar characteristics to WHS. Several individuals who were initially diagnosed with PRDS subsequently had FISH analysis that detected a deletion of 4p, and thus the individuals were reclassified as having WHS. Some feel that PRDS is actually WHS without obvious deletions of 4p.

When a couple has had a child diagnosed with the inherited form of WHS, a member of that couple carries a balanced translocation, and genetic counseling should be offered to discuss reproductive options. One option is choosing sperm or egg donation so that the parent who has the translocation does not pass unbalanced genetic material on to his or her future child. Another option is preimplantation genetic diagnosis. Preimplantation genetic diagnosis is a very complex process that involves in vitro fertilization and diagnosing the embryos before they are placed into the mother's uterus. Thus, only unaffected embryos are transferred to the uterus. Lastly, the options of CVS and amniocentesis for prenatal diagnosis should be discussed. All of these options have allowed couples with balanced translocations to evaluate their choice of having more children.

If ultrasound examination reveals findings consistent with the possibility of WHS in a family with no history of WHS, genetic counseling and prenatal diagnosis should

QUESTIONS TO ASK YOUR DOCTOR

- At what point should my child be evaluated for a heart disorder?
- When should my child's hearing be evaluated?
- When should my child see an ophthalmologist?
- What developmental programs or resources do you recommend?
- What is my status as a carrier for WHS if other family members have the disease?

be offered. These ultrasound findings may include heart defects, microcephaly, agenesis of the corpus collosum (missing a specific part of the brain), micrognathia, cleft lip and palate, a hole in the diaphragm (diaphragmatic hernia), hypospadias, and clubbed feet. While all these symptoms are consistent with WHS, they can also be evidence of other genetic syndromes.

Treatment and management

There is no treatment for the underlying condition of WHS. Treatment and management for patients who have WHS are specific to each individual. For example, some individuals who have WHS may have heart defects or a cleft lip and/or palate that may require surgery, while others may not. Therefore, there is no specific treatment for individuals who have WHS; rather, the treatment and management are geared toward that particular individual's needs and are likely to include several medical specialists. Information about patients who have WHS has been compiled and provides a comprehensive look into the natural history of this condition. It also allows management guidelines to be recommended. The collection of this information has shown that many of these individuals may achieve more development than was previously believed possible.

The management recommendations that have been made include:

- Feeding problems should be addressed and may require intervention such as placement of a gastrostomy tube.
- Characterization of seizures is important, and treatment with antiepileptic medications such as valproic acid should be investigated and may help control the seizure activity in many individuals.
- Skeletal abnormalities such as clubfoot should be addressed, and treatment should be considered. It should not be assumed that clubfoot does not need to be

addressed because the child will never walk. Children with WHS have learned to walk unassisted.

- Approximately 30% of individuals may have congenital heart defects, so the heart should be examined. Usually the heart lesions are not severe and may be repaired easily or may not even require surgery.
- Hearing loss may occur, and because some children are able to learn to talk in short sentences, they should be screened for hearing problems.
- Eye abnormalities may be present; therefore, an ophthalmology exam should be performed to rule out any eye problems, even if no obvious signs are present.
- With regard to the development of patients with WHS, it is suggested that individuals participate in personal development programs to assist with social skills and occupational therapy for motor skills.

Prognosis

Infants who have WHS may be stillborn or die in the newborn period, and prognosis during the newborn period depends upon what birth defects are present. It has been estimated that approximately 35% of individuals who have WHS die within the first two years of life, but many individuals who have WHS survive to adulthood. Universally, children with WHS have severe or profound developmental retardation; however, there are many affected individuals who are able to walk and some who are able to talk in short sentences. It is evident that many patients seem to proceed farther than was previously thought possible. The actual lifespan for individuals who have WHS is unknown, although there are several individuals who have WHS who are in their 20s, 30s, and 40s.

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ORGANIZATIONS

- 4p- Support Group, <http://www.4p-supportgroup.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 746-6518, (203) 798-2291, <http://www.rarediseases.org>

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Wolman disease

Definition

Wolman disease is a rare inherited defect in the body's metabolism of fats (lipids) caused by a loss of function of the lysosomal acid lipase enzyme.

Description

Wolman disease, also known as lysosomal acid lipase disease, is a lethal genetic disorder caused by the lack of the enzyme lysosomal acid lipase. Lysosomal acid lipase is a cellular enzyme widespread throughout the body and is important in the breakdown of certain lipids called triglycerides and cholesteryl esters. Individuals without an active enzyme accumulate abnormally large amounts of these lipids in their cells. This build-up interferes with the normal cellular metabolic functions and leads to severe neurological and physical symptoms and early death. A milder disease, cholesteryl ester storage disease (CESD), is caused by mutations in the same gene but affected individuals may not show symptoms until adulthood.

Genetic profile

Inheritance pattern

Wolman disease is an autosomal recessive disorder affecting both males and females. In individuals with this disorder, both copies of the *LIPA* gene that codes for lysosomal acid lipase are abnormal. Both parents of an affected child have one abnormal copy of *LIPA* but usually do not show symptoms because they also have one normal copy. The normal copy provides approximately 50% of the usual enzyme activity, a level adequate for the body's needs. Individuals with one abnormal copy of the

KEY TERMS

Adrenal gland—A triangle-shaped endocrine gland, located above each kidney, that synthesizes aldosterone, cortisol, and testosterone from cholesterol. The adrenal glands are responsible for salt and water levels in the body, as well as for protein, fat, and carbohydrate metabolism.

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Chorionic villus sampling—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and

a sample of cells is collected from around the early embryo. These cells are then tested for chromosome abnormalities or other genetic diseases.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Heterozygote—Having two different versions of the same gene.

Lysosomal—Pertaining to the lysosomes, special parts (organelles) of cells that contain a number of enzymes important in the breakdown of large molecules such as proteins and fats.

Lysosomal acid lipase—An enzyme that catalyzes the hydrolytic breakdown of lipids in the lysosome. This enzyme is coded by the LIPA gene.

Mutation—A permanent change in the genetic material that may alter a trait or characteristic of an individual, or manifest as disease, and can be transmitted to offspring.

LIPA gene and 50% enzyme activity are said to be carriers or heterozygotes. Because both parents of a child with Wolman disease are carriers, they have a 25% risk in each subsequent pregnancy of having another child who is affected with the same disorder.

Gene location

The gene for acid lipase is located on the long arm of chromosome 10 at position 10q23.2-q23.3. A number of different types of mutations in this gene all result in a lack of enzyme function and have been identified in patients diagnosed with Wolman disease. These include deletions of small portions of the gene, as well as changes in the sequence of specific nucleotides. The different mutations may explain the variations in symptoms observed in Wolman patients. However, symptoms may vary even among siblings who have inherited the same mutations from their parents, suggesting there may be other genetic or environmental factors that affect the presentation of the disease. Milder forms, such as the related disorder CESD, appear to be associated with gene mutations that result in only partial loss of enzyme function.

Demographics

In the general population Wolman disease is exceedingly rare, with approximately 50 or fewer well-described cases to date. CESD is thought to be more common. Individuals with Wolman disease have been reported in various parts of the world including Western Europe, North America, Iraq, Iran, Israel, China, and Japan.

Signs and symptoms

Symptoms of Wolman disease appear in the first few weeks of life. Forceful vomiting and distention of the abdomen are usually the first symptoms presented. Other general symptoms in the early stages of this disease are watery diarrhea or fat in the stool, fever, and a yellow tint to the skin (jaundice). Medical examination can reveal massive enlargement of the liver and spleen (hepatosplenomegaly) due to a build-up of fats that cannot be broken down. Other common findings are severe anemia, calcium deposits in the adrenal glands, and a general decline in mental development.

QUESTIONS TO ASK YOUR DOCTOR

- Do you recommend a low-fat diet?
- What are the risks and expected benefits of cholesterol controlling medication?
- Have you heard reports of enzyme replacement for Wolman disease?
- Do you think liver transplant is a possibility?
- If I am a carrier of Wolman disease, what are the chances my children will have it?

Diagnosis

Diagnosis can be difficult because there are no general laboratory tests that point specifically to Wolman disease. Infants with hepatosplenomegaly and evidence of malnutrition should have a careful neurological examination and x-rays of the abdomen to check for calcium deposits in the adrenal glands. If Wolman disease is suspected on the basis of these tests, acid lipase activity can be measured in the laboratory using white blood cells or skin cells. An absence of acid lipase activity confirms the diagnosis.

Carrier testing

Individuals suspected of being a carrier of Wolman disease can have their diagnosis confirmed by measuring acid lipase activity in their white blood cells. Carriers will typically demonstrate 50% of normal enzyme activity.

Mutation detection

Specific DNA tests that check for changes in the normal sequence of nucleotides in the *LIPA* gene can usually detect the particular gene mutation in an affected individual or carrier. This type of test is only available in a few, very specialized DNA laboratories.

Prenatal diagnosis

Couples who have had one child with Wolman disease may be offered prenatal testing in future pregnancies. Prenatal testing is accomplished by measuring acid lipase activity either in cells from a chorionic villus sampling (CVS) at 10–12 weeks of pregnancy, or in amniotic fluid cells obtained by amniocentesis between 16–18 weeks of pregnancy. Alternatively, if specific gene

mutations have been identified in parents because they have already had an affected child, fetal DNA from chorionic villi cells or amniotic fluid cells can be studied to look for these same mutations in the fetus. Carrier couples that are considering prenatal diagnosis should discuss the risks and benefits of this type of testing with a geneticist or genetic counselor.

Treatment and management

There is no specific treatment for Wolman disease. There have been attempts to treat the milder CESD with low-fat diets and cholesterol-lowering drugs, and there has been at least one report of a liver transplant in a patient with CESD. Replacement of the missing enzyme has not been reported.

Prognosis

Infants diagnosed with Wolman disease usually die by six months of age. As of 2009, the oldest recorded ages of surviving Wolman patients were 4 and 11 years. Both patients had received stem cell treatments.

Resources

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ORGANIZATIONS

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>

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X-linked intellectual disability

Definition

X-linked intellectual disability (XLID), formerly known as X-linked mental retardation, broadly refers to a group of inherited disorders characterized by varying degrees of intellectual disability caused by mutations in various genes present on the X chromosome. Intellectual disability is defined as the failure to develop cognitive abilities and achieve a level of intelligence and adaptive behavior that is appropriate for a particular age group. XLID is mostly seen in boys, usually manifests before the age of 18, and is characterized by an overall intelligence quotient (IQ) of less than 70, along with functional deficits in adaptive behavior like daily living, social, and communication skills.

Description

The X chromosome was so named initially to mean unknown, as the functions of the genes carried on it were not clear. The United States Census of 1890 was the first to collect data that showed that more boys than girls were mentally disabled, and later it was suspected that this was due to the difference in the sex chromosomes present in males and females. It was only in 1970 that the most common cause of XLID, fragile X syndrome, was described in detail; its mutated gene (*FMR1*) was not identified until 1991. Mutations in the *MECP2* gene are the second most common cause of XLID, and result in Rett's syndrome. This gene was identified in 1999. Since 2004, about 200 XLID disease types have been described. With the help of the Human Genome Project, of the 150–200 candidate genes on the X chromosome, mutations in about 100 have been identified as being responsible for different XLID diseases.

XLID is broadly divided into syndromic and non-syndromic disorders. Syndromic XLID (S-XLID) refers to conditions in which intellectual disability is accompanied by characteristic and easily recognizable physical

and/or neurological features. In non-syndromic XLID (NS-XLID), intellectual disability is the only key feature without any other distinctive physical or neurological features. Two-thirds of XLID cases are thought to be non-syndromic. In both syndromic and non-syndromic XLID, affected persons are mostly boys who have developmental delay or intellectual disability of variable severity and who usually have another affected male maternal relative such as a maternal uncle. With rapid advances in genetics afforded by the Human Genome Project, it is now possible to detect most of the mutations known to cause intellectual disability even before the child is born, leading to effective counseling and prevention strategies.

X-linked intellectual disability was formerly called X-linked mental retardation; however, at the request of patient advocacy groups, in January 2013 the United States federal government proposed a terminology change in all official documents to replace “mental retardation” with the term “intellectual disability.” This change was enacted, and all documents from the U.S. government no longer use the term “mental retardation.” Most patients and parents welcomed this change and consider the use of “mental retardation” to be pejorative.

Genetic profile

The different diagnoses of X-linked intellectual disability are among the most common forms of inherited intellectual disability, with fragile X being the most common form of inherited intellectual disability after Down syndrome. There are more than 100 different specific mutations of genes on the X chromosome that cause intellectual disability.

As of August 2015, mutations on the following genes located on the X-chromosome were known to cause XLID: *ABCD1*, *ACSL4*, *ACTB*, *ACTG1*, *AFF2*, *AMMECR1*, *ARX*, *ARFGEF2*, *ARHGEF6*, *ATP6AP2*, *ATP7A*, *ATRX*, *BCAP31*, *BCOR*, *BRWD3*, *CACNA1F*, *CASK*, *CCDC22*, *CDKL5*, *CLCN5*, *CLIC2*, *CUL4B*, *DCX*, *DLAT*, *DLG3*, *FBXO25* (translocation X;8),

FGD1, FLNA, FMRI, FTSJ1, GDII, GPC3, GRIA3, HCFC1, HDAC8, HPRT1, HSD17B10, HUWE1, IDS, IGBP1, IKBKG, IL1RAPL2, IQSEC2, KCNE5, KDM5C, KDM6A, L1CAM, LAMP2, MAOA, MECP2, MED12, MID1, MID2, NHS, NIPBL, NLGN3, NLGN4X, NPDP, OCRL, OFD1, OPHN1, OTC, PAFAH1B1, PAK3, PDHA1, PDHB, PDHX, PDP1, PGK1, PHF6, PHF8, PLP1, PORCN, PQBP1, PRPS1, RAB39B, RAB40AL, RELN, RPL10, RPS6KA3, SHROOM4, SLC6A8, SLC9A6, SLC16A2, SMC1A, SMC3, SMS, SOX3, SPECC1L, SRPX2, SYP, TSPAN7, TUBA1A, UBE2A, UPF3B, USP9X, YWHAE, ZC4H2, ZDHHC9, ZDHHC15, ZMYM3, ZNF711, and ZNF81.

The complete sequence of the X chromosome was identified in 2005, and it confirmed that an unusually large number of its genes carry information for proteins important for brain functions. Most of the mutated genes in XLID are “intelligence” genes that influence development, cell migration, formation and maintenance of neural networks, and cell-to-cell communication in the brain. The majority of the genes identified are linked to syndromic XLID, while the majority of individuals with XLID do not have a known syndrome. Different mutations in the same gene can give rise to either S-XLID or NS-XLID.

Females have two X chromosomes, and males have one X and one Y chromosome (which determines the male sex). The X chromosome in the male is always derived from the mother. A female uses only one of her two X chromosomes in each cell and randomly inactivates the other X chromosome. Thus, if only one of her X chromosomes has a defective gene, only some of her cells will suffer. The severity of XLID in the female will consequently depend on the percentage of cells in which the mutated gene is expressed. On the other hand, men have only one X chromosome, so any defective genes from that chromosome are invariably expressed.

Demographics

About 2%–3% of the population has intellectual disability due to genetic and non-genetic factors such as birth injuries, infections, and developmental anomalies. XLID is thought to account for approximately 20% of genetic causes of intellectual disability and accounts for the 20%–30% excess of intellectual disability observed in males in comparison to females. Although accurate numbers are difficult to estimate, the prevalence of XLID may be approximately 1 in 600 males and 1 in 400 female carriers.

Signs and symptoms

There are many different conditions and syndromes associated with XLID. These can either be malformation syndromes, in which affected patients have intellectual

disability and multiple birth defects; neuromuscular syndromes, in which patients have intellectual disability and abnormalities in various nerves and muscles; metabolic syndromes have a defect in a specific biochemical pathway; or dominant syndromes in which the disorder is inherited in an X-linked dominant fashion with most affected males dying before birth.

The most common known cause of inherited intellectual disability is fragile X syndrome, which accounts for 20% of XLID. It was first described in the late 1970s; the gene was discovered in 1991. People from all ethnic and social backgrounds can be affected. It results from a mutation in the fragile X intellectual disability (*FMRI*) gene found on the X chromosome. This gene contains information needed for making the FMR protein, which is thought to regulate communication between various cells by eliminating unwanted communication neural pathways.

The *FMRI* gene contains two distinct regions, one of which is called the promoter region. This region is composed of repeating units or building blocks called nucleotides arranged in a specific sequence. A normal person has 30 such units and can make normal amounts of the FMR protein. When a person has between 55 and 200 units, the gene becomes partially inactivated. They can still make some amount of FMR protein and are said to have a pre-mutation. The pre-mutation occurs in 1 in 250–300 females and 1 in 1,000 males. The amount of FMR protein in the body determines the severity of effects due to fragile X. Therefore, patients with a pre-mutation may have few, if any, symptoms and may not even know that they are carrying an abnormal gene. A pre-mutation can be transmitted silently over generations, but with each generation, the number of units increases and there is a higher chance of manifesting the condition (anticipation).

When a person has more than 200 units, the gene itself becomes completely inactivated, making it impossible to produce any FMR protein. The full mutation occurs in 1 in 3,600 males and 1 in 4,000–6,000 females. As females have two X chromosomes in each cell, even if one X has the full mutation, the other X carries the normal *FMRI* gene, making it possible to produce at least some FMR protein. Therefore, females are less often and less seriously affected than males. Females who do not express the disease, but carry the abnormal gene are called carriers.

If a father carries the *FMRI* mutation, he will transmit the mutation to all his daughters but cannot transmit it to his sons, as males receive only the Y chromosome. On the other hand, if a mother carries the mutation on one of her X chromosomes, each of her children (boys

or girls) will have a 50% chance of inheriting the *FMR1* mutation, depending on which X chromosome they receive.

There is a considerable variability in disease severity of fragile X syndrome in males, with many of the physical symptoms becoming more apparent only after puberty. Prior to puberty, the most common findings include speech delay, developmental delay, and intellectual disability. The most noticeable and consistent effect is on intelligence. More than 80% of affected males have an IQ of less than 70, whereas the effect on IQ in an affected female is variable. It is uncommon for persons with fragile X to have severe intellectual disability, and most have IQ in the range of 40–85. Females may show normal cognitive development with only mild learning disabilities and a normal IQ. People with fragile X have good memory skills for pictures and visual patterns, but have poor verbal knowledge. They also have poor abstract thinking, organizational skills, and problem-solving capabilities. Despite such limitations, many of them can be trained to acquire jobs and skills to take care of themselves.

Children with fragile X tend to develop certain physical characteristics by the time of puberty. They have a long face or jaw, large protruding ears, and do not grow as tall as other members in the family. Males with fragile X have large testicles, but this does not affect sexual development. They also have problems with connective tissues. They may be flat footed, have loose hyper-extensible joints, and “floppy” heart valves. Later in life, they can manifest hand tremors and difficulty walking. Women with fragile X undergo menopause early due to premature cessation of ovarian function affecting their reproductive capabilities. About 25% of patients have seizures.

Most people with fragile X syndrome, especially boys, have anxiety in social situations and become nervous and uncomfortable. They also tend to be easily upset and overwhelmed by sensory stimulation due to sights and sounds and deviance from normal routine. This may emerge as aggression in adolescent boys. Females tend to have less anxiety and are not usually aggressive. Boys have language problems, including speaking, writing, and acquiring social communication skills. Common behavior disturbances include attention deficit disorder, repetitive hand flapping, autistic behaviors, and gaze aversion. Twenty percent of these individuals meet full criteria for autism.

Rett’s syndrome (RS) is the second leading cause of XLID and the leading cause of intellectual disability in girls. It was first described in 1966; the gene was identified in 1999. RS is caused by mutation in the *MECP2* gene that causes abnormal truncation of the gene. The *MECP2* gene contains information for production of

methyl cytosine binding protein 2, which normally helps to turn off other genes appropriately at various points along the process of brain development. If this does not occur, the overactive genes interfere with normal brain maturation and lead to abnormal “wiring” and overload of the brain’s electrical system. Other types of mutation in the same *MECP2* gene can result in mild intellectual disability, tremor, psychosis, or learning disability, both in boys and girls, without producing classic RS.

RS occurs almost exclusively in females and has a prevalence of 1 in 10,000–20,000. In males, the mutation is lethal, and most are severely affected or die before or soon after birth. There is also a phenomenon of preferential inactivation of the normal X chromosome leading to the disease expression even in the female. The affected girl develops normally during the first five months of life. During this period, the child exhibits autistic behaviors. She can be calm and quiet, without making good eye contact, and without showing much interest in toys. After this, head growth slows down and the child loses whatever purposeful hand movements that had already developed. Around three years of age, the girl develops repetitive hand washing or hand wringing gestures, loses ability to speak, has trouble sleeping, becomes irritable, and develops an unsteady gait. Varying degrees of intellectual disability are present. These children also have seizures.

West syndrome, also known as the infantile spasm intellectual disability syndrome, is caused by mutations in the *ARX* (aristaless-related homeobox) gene. This is the third most common genetic mutation leading to XLID. It can occur in both boys and girls and is characterized by developmental delay, intellectual disability, and a specific type of seizures called salaam fits or infantile spasms. During the seizures, the children either have a flexion spasm where the body is bent over in a self-hugging position or an extension spasm where the neck and body are arched backwards.

Mutations in the *ARX* gene can also result in various developmental defects like lissencephaly (smooth brain), absence of the corpus callosum, microcephaly, and urinary and genital abnormalities, without causing the classic West syndrome.

Non-syndromic X-linked intellectual disability (NS-XLID) is represented by a heterogeneous group of disorders in which the only recognizable abnormality is intellectual disability without other accompanying physical manifestations.

Diagnosis

The diagnosis of XLID should be considered in all children with autistic behaviors, intellectual disability,

KEY TERMS

Amniotic fluid—The liquid that surrounds and cushions the developing fetus inside the mother's womb.

Anticipation—The apparent tendency of certain diseases to appear at earlier age and with increasing severity in successive generations.

Anomaly—A malformation or abnormality in any part of the body.

Attention deficit disorder—Neurological condition that is often evident from childhood, characterized by restlessness, disorganization, hyperactivity, distractibility, and mood swings.

Autism—A chronic developmental disorder usually diagnosed between 18 and 30 months of age; symptoms include problems with social interaction and communication, as well as repetitive interests and activities.

Carrier—An individual who possesses an unexpressed abnormal gene of a recessive genetic disorder.

Chorionic villus—Cells that are present in the placenta that can be used for genetic analysis.

Chromosome—A thread-like structure that is present in the nucleus of all cells and contains DNA, which carries genetic information.

Cognitive—Brain functions involved in the ability to think, learn, and remember.

Connective tissue—Tissue that is the supporting framework of the body and its internal organs; made up of collagen, elastic fibers, and fat.

Corpus callosum—Tightly bundled nerve fibers that connect the right and left hemispheres of the brain.

Deoxyribonucleic acid (DNA)—A chemical found primarily in the nucleus of cells, which carries the instructions for making all the structures and materials the body needs to function.

Gene—The basic unit of heredity; a sequence of DNA nucleotides on a chromosome.

Human Genome Project—An international effort begun in 1990 to locate and identify the 100,000 genes on the 46 human chromosomes.

Lissencephaly—A developmental disorder where the brain is smooth without the normal surface convolutions.

Menopause—The transition in a woman's life whereby menstrual periods stop.

Microcephaly—A condition, present at birth, in which the head is much smaller than normal for an infant of that age and gender.

Mutation—A spontaneous change in the sequence of nucleotides in a chromosome or gene.

Neural—Pertaining to a nerve or the nervous system.

Nucleotide—A small molecule composed of three parts: a nitrogen base (a purine or pyrimidine), a sugar (ribose or deoxyribose), and phosphate; they serve as the building blocks of nucleic acids (DNA and RNA).

Placenta—A bag-like organ that partially surrounds the fetus during pregnancy; it delivers oxygen and nutrients to, and takes waste away from, the fetus during pregnancy, and is attached to the fetus by the umbilical cord.

Promoter—The region of a gene that initiates transcription of the genetic information.

Psychosis—A severe mental disorder characterized by loss of contact with reality, causing deterioration of normal social functioning.

Seizures—An abnormal electrical discharge from the brain that usually results in convulsion of the body.

Syndrome—The group or recognizable pattern of symptoms or abnormalities that indicate a particular trait or disease.

developmental delay, or unexplained speech delay; 80%–90% of patients with fragile X syndrome are not yet correctly diagnosed. Because the symptoms of fragile X can be quite subtle, especially in young children, and because it is so frequent in the general population, many medical specialists recommend routine testing for fragile X syndrome. This is, however, not a regular screening test for all children. Testing for *FMR1* mutation is possible in people of any age and even before birth.

A variety of diagnostic tests based on DNA, chromosomal, or protein analysis is available. Chromosomal tests look for the fragile, or broken, portion of the X chromosome under a microscope, but are generally not very sensitive. Protein tests measure the amount of FMR protein produced by the cells and can determine the severity of the disorder. A DNA-based test to diagnose fragile X was developed in 1992 and is based on detecting an increased number of repeating units. This test is quite

accurate, and it can detect both carriers and fully affected individuals. Samples from blood, hair root, or a scraping from inside the cheek can be used to carry out the test. In a pregnant woman, amniotic fluid or cells from the placenta, called chorionic villi, are used to detect the mutation. Similarly, genetic testing can be done in specialized laboratories for the other common gene mutations associated with XLID, such as Rett's syndrome.

With the advent of next-generation sequencing (NGS), a genetic screening that provides the ability to sequence an individual's entire genome, it is now possible to identify the exact X chromosome mutation involved in most cases of XLID.

Treatment and management

Currently, there is no cure for any of the conditions associated with XLID. Best results are obtained when medications are combined with educational, social, and occupational therapy. Early intervention when the child's brain is still developing is advocated in order to maximize its long-term potential. A team comprising of a neurologist, genetic specialist, psychologist, behavioral specialist, physical, occupational, and speech therapists should work with the family and caregivers to ensure that the child receives appropriate therapy based on individual needs. This team can also assess the patient's level of independence and ensure appropriate transition from adolescent to young adult.

The U.S. Food and Drug Administration Agency (FDA) has not approved any specific medication for treatment of fragile X or its symptoms. But several medications have been tried on an empiric basis to ameliorate specific symptoms and problems associated with this disorder. Seizures and mood instability can be treated with drugs used primarily in epilepsy, such as carbamazepine, valproate, gabapentin, and topiramate.

The Individuals with Disabilities Act of 1997 ensures free education for children with intellectual disability and special cognitive needs until high school or until they reach 21 years. This law also ensures that children are taught in a non-restrictive environment tailored to their special needs. Speech therapists can help in language acquisition and devise innovative ways for nonverbal communication. Occupational therapists can assist the child with adaptive equipment to help overcome physical disabilities. Physical therapists help in designing programs and activities to promote posture, gait, and balance. Behavioral therapists can work with the family and the child in identifying strategies and coping skills to deal with social situations and avoiding aggression.

The Fragile X Research Foundation (FRAXA) funds several endeavors to help find a cure for this disease.

Ongoing research is focused on repairing the defective gene, replacing the defective gene, supplying the deficient protein, or substituting the deficient protein with another protein.

Prognosis

The prognosis for children with XLID varies depending on whether they have a syndrome with other features that may limit life expectancy. Children with fragile X syndrome, like most children with XLID, have a fairly normal life expectancy. With early diagnosis and treatment, they can grow into independent individuals. Similarly, children with Rett's syndrome usually survive to adulthood and middle age.

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ORGANIZATIONS

- The Arc, 1825 K St. NW, Suite 1200, Washington, DC 20006, (202) 534-3700 or (800) 533-5255, (202) 534-3731, <http://www.thearc.org>
- Eunice Kennedy Shriver National Institute of Child Health and Human Development, 31 Center Drive, Building 31, Room 2A32, Bethesda, MD 20892-2425, (800) 370-2943, (866) 760-5947, NICHDIInformationResourceCenter@mail.nih.gov, <http://www.nichd.nih.gov>
- Fragile X Research Foundation (FRAXA), 10 Prince Place, Suite 203, Newburyport, MA 01950, (978) 462-1866, info@fraxa.org, <http://www.fraxa.org>

International Rett Syndrome Association, PO Box 706143,
Cincinnati, OH 45270-6143, (800) 818 7388, (513)
874-2520, admin@rettsyndrome.org, <http://www.retttsyndrome.org>

National Fragile X Foundation, 2100 M St. NW, Suite 170, Box
302, Washington, DC 20037-1233, (800) 688-8765, (202)
747-6208, natlfx@fragilex.org, <https://fragilex.org>

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X-linked severe combined immunodeficiency

Definition

X-linked severe combined immunodeficiency (X-SCID) is a genetic disorder of the immune system that primarily affects males. It is the most common of the various forms of severe combined immunodeficiency (SCID). Symptoms can be present at birth. Males with the disorder are prone to recurrent and persistent infections due to their compromised immune systems.

Description

X-SCID is a hereditary disease, meaning it is passed from parent to child. It is considered a rare disorder by the National Institutes of Health (NIH). It is often called “Bubble Boy” disease based on a Texas boy who spent his entire life inside a germ-free environment, or “bubble.” The boy, David Vetter, died in 1984 at age 12 after a bone marrow transplant failed. Boys with X-linked SCID are susceptible to opportunistic infections that can occur over and over and are resistant to standard antibiotic treatment. The infections are called opportunistic because they do not normally cause sickness in healthy people. In people with the disorder, the body’s immune system, which normally fights off infections, is severely compromised or does not work at all, making any infection serious and potentially life-threatening. Without treatment, infants with the disorder usually die within the first couple of years after birth. The primary treatment is a bone marrow transplant.

The disorder is genetic, meaning it is inherited from a parent. Yet more than half of boys with the disease have no family history of early deaths in male relatives on their mother’s side, according to the NIH.

Genetic profile

X-SCID is an X-linked condition, meaning the gene for the disorder is found on the X chromosome. This is also known as a sex-linked condition affecting primarily males. Males and not females are affected because males

KEY TERMS

Bone marrow—The soft and spongy center of the bones where blood cells are made.

Chromosomes—Structures inside cells that carry an individual’s genetic information.

DNA—Deoxyribonucleic acid, the basic building blocks of all life on Earth. DNA stores genetic information that is passed from parents to their offspring.

Flow cytometry—A method of analyzing cells in which cell properties are detected as they flow in a narrow stream through a measuring device.

Hereditary—The passing of traits from parents to their offspring.

Immune system—The complex group of organs and cells that defends the body against infection and disease.

Lymphocytes—White blood cells that fight infection and disease.

Mutated gene—A change of DNA sequence that causes a change of the function of the gene and a subsequent disease.

Opportunistic infections—Infections that would not usually cause illness in people with a healthy immune system.

Preimplantation genetic diagnosis—Genetic testing performed on a developing embryo conceived through in vitro fertilization (IVF). The unaffected (non-disease carrying) embryos are transferred back into the womb for implantation.

Prenatal testing—Testing for a disease such as a genetic condition in an unborn baby.

are born with an X chromosome passed from their mother and a Y chromosome passed from their father. Women are born with two X chromosomes, one from their mother and one from their father. When women have a mutation for a genetic condition on one X chromosome, the other X chromosome will compensate for the mutated gene. Males who inherit the X chromosome with a gene mutation for SCID from their mother will not have a complementary copy of the gene since they have only one X chromosome.

The gene that is mutated in X-SCID is known as the *IL2RG* gene. A woman who carries an *IL2RG* mutation has a 50% chance of transmitting the gene to each child she bears. Her sons who inherit the mutation will get the

disorder, but any daughters will become carriers; they will not get the disorder. In contrast, men who have the mutated gene will pass it on to their daughters but not their sons. Prenatal testing is available for pregnant women who are known carriers of the gene mutation.

Demographics

The prevalence of X-SCID is unknown but likely affects at least 1 in 50,000 to 1 in 100,000 newborns in the United States and worldwide. However, since there are no routine screening programs to determine the true incidence, some experts say the estimate may be too small. All ethnic groups are affected equally by the disorder.

Signs and symptoms

X-SCID is caused by mutations in the *IL2RG* gene, which provides information for making a protein that is required for the immune system to function normally. It is the immune system's job to fight infections in the body using a variety of cells, including lymphocytes (a type of white blood cells in the immune system.) Mutations in the *IL2RG* gene prevent lymphocyte cells from developing normally. With damaged lymphocytes, the immune system cannot fight off infections.

Symptoms can start at birth, but more commonly problems are first noticed between three and six months of age. By one year of age, virtually all males with the disorder express symptoms. They include persistent and frequent infections caused by bacteria, viruses, and fungi that a healthy immune system would fight off. Common infections in infants include influenza, pneumonia, and infections of the ear and urinary tract. Other symptoms include rashes, diarrhea, cough, congestion, fever, other autoimmune conditions, failure to thrive, and short stature. Infants are often born without tonsils and lymph nodes.

Diagnosis

Diagnosis is usually made by measuring the amount of lymphocytes in the body, lymphocyte cell surface staining and counting by flow cytometry, and lymphocyte functional tests. When the number of absolute lymphocytes is low, the number of T cells is extremely low, B cells do not work, and the number of natural killer cells is low or zero. T cells are a type of white blood cell involved in rejecting foreign tissue, regulating immunity, and controlling the production of antibodies to fight infection. B cells are a class of lymphocytes, released from the bone marrow, that produce antibodies. Natural killer cells are specialized immune system cells that kill target cells infected with viruses or host cells that have become cancerous.

QUESTIONS TO ASK YOUR DOCTOR

- Do you know of any recent research or medical breakthroughs concerning my child's condition?
- Would alternative or complementary treatments be useful in treating any of my child's symptoms?
- Are there any current or planned clinical trials or studies of this disorder that my child might be eligible to participate in?
- What are the chances of having another affected child?

Examination

Diagnosis of the disorder is only through specific tests, not physical examination.

Genetic tests

X-SCID can also be diagnosed with genetic testing. Molecular genetic testing allows extra time to search for bone marrow transplant donors. It can also allow treatment to begin shortly after birth rather than waiting a few months for symptoms to appear. More than 99% of affected males will carry a mutation on the *IL2RG* gene found on the X chromosome. Many states now include X-SCID on a newborn screening panel. Prenatal testing and pre-implantation genetic diagnosis are also possible when the *IL2RG* gene mutation has been identified in a family.

Treatment and management

Bone marrow transplant is the primary treatment for X-SCID, although gene therapies have been successfully used since 1990. Since then, several European studies have shown that gene therapy is a successful treatment, although in a few cases, the side effects included leukemia, a potentially fatal cancer of the blood.

The primary treatment is usually a bone marrow transplant from a parent or other relative.

Interim treatment while the immune system is being restored includes treating infections with antibiotics and immunoglobulin infusion. Immunoglobulin is a class of proteins that act as antibodies in the immune system. Long-term treatment includes continued infusions of immunoglobulin and gene therapy using stem cells. Gene therapy is primarily used in children who are either unable to have a bone marrow transplant or in whom bone marrow transplantation has failed.

Prognosis

Infants and children with X-SCID need quick action to restore a healthy or healthier immune system to survive. Untreated infants usually do not live beyond a year.

The survival rate is not clear, and the oldest survivors have lived into their 30s, according to the National Center for Biotechnology Information. This may be changing as more research is done and new treatment possibilities are studied. Further advancement in gene therapy, especially stem cell research, may increase life expectancy. Children who have had successful bone marrow transplants should be evaluated by a physician every 6 to 12 months.

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ORGANIZATIONS

Canadian Immunodeficiencies Patient Organization (CIPO), 8516–18 Ave. SW, Edmonton, AB Canada T6X 0R7, info@cipo.ca, <http://www.cipo.ca>

Immune Deficiency Foundation (IDF), 110 West Rd., Suite 300, Towson, MD 21204, (800) 296-4433, info@primaryimmune.org, <http://www.primaryimmune.org>

Jeffrey Modell Foundation, 780 Third Ave., New York, NY 10017, (212) 764-4180, info@jmfworld.org, <http://www.info4pi.org>

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X-linked sideroblastic anemia

Definition

X-linked sideroblastic anemia is a hereditary enzyme disorder in which the body has adequate iron but is unable to incorporate it into hemoglobin. This inability results from the production of ring sideroblasts in the bone marrow instead of normal erythroblasts, the precursors of mature normal red blood cells.

Description

X-linked sideroblastic anemia is one form of congenital sideroblastic anemia (CSA), also known as iron overload anemia or sideroblastosis. There are three other congenital forms of sideroblastic anemia caused by mutations in different genes. All hereditary forms of sideroblastic anemia are very rare disorders with only a few hundred cases reported in the medical literature.

In sideroblastic anemia, iron enters an immature red blood cell called a sideroblast and is not incorporated properly into the hemoglobin molecule (the cell's oxygen carrier). This failure causes iron to accumulate in the mitochondria surrounding the cell nuclei of the sideroblasts. The defective hemoglobin then transports oxygen poorly, resulting in decreased tissue oxygenation. In addition, the buildup of iron in the sideroblast gives the cell nucleus a ringed appearance. A sideroblast that contains five or more iron granules in its mitochondria is called a ring sideroblast. This is the primary sign of sideroblastic anemia.

Children with X-linked sideroblastic anemia typically develop symptoms early in life, most often as early as the first few months or years of life, but sometimes as late as the early adult years. The most common signs of the condition are pale skin, difficulty breathing, dizzy spells, fatigue, and enlargement of the spleen and liver. Sideroblastic anemia is often mistaken for iron deficiency anemia, but tests usually reveal normal or increased levels of iron in the blood.

Another more common type of sideroblastic anemia is called acquired sideroblastic anemia. This condition develops in later life, most often as the result of myelodysplastic syndromes (blood disorders characterized by inefficient production of blood-forming cells in the bone marrow). It can also develop as the result of lead poisoning, alcoholism, or certain antimicrobial medications. Most cases of acquired sideroblastic anemia develop in adult life. The average age of patients with anemia resulting from a myelodysplastic syndrome is 68. Comparatively, acquired sideroblastic anemia resulting from alcoholism or exposure to toxins begins in the mid-fifties. The goal of treatment is the removal of the toxin and may involve therapy for the underlying disorder.

KEY TERMS

Ataxia—Difficulty in coordinating voluntary muscular movements, particularly those involving gait, speech, hand movements, and eye movements.

Chelation therapy (pronounced key-LAY-shun)—A form of therapy in which chelating agents are administered to remove heavy metals from the body. Chelating agents are chemicals that have a special affinity for metal ions.

Erythroblast—The immediate precursor of a normal red blood cell.

Erythrocyte—The scientific name for a normal mature red blood cell. Erythrocytes do not contain cell nuclei.

Ferritin—An intracellular protein that stores iron and releases it in a controlled manner. Ferritin in blood plasma is an indirect marker of the total amount of iron stored in the body.

Heme—The iron-containing molecule in hemoglobin that serves as the site of oxygen binding.

Hemochromatosis—Accumulation of large amounts of iron in the tissues of the body.

Hemoglobin—The protein-iron compound in the blood that carries oxygen to the cells and carries carbon dioxide away from the cells.

Hemosiderin—An iron storage complex found only within cells (not in blood plasma) and

consisting of ferritin, denatured ferritin, and other materials.

Mitochondria (singular, mitochondrion)—Organelles within the cell responsible for energy production.

Myelodysplastic syndrome (MDS)—A bone marrow disorder that can develop into aplastic anemia, requiring bone marrow or stem cell transplantation.

Nucleus—The central part of a cell that contains most of its genetic material, including chromosomes and DNA.

Red blood cells (RBCs)—Hemoglobin-containing blood cells that transport oxygen from the lungs to tissues. In the tissues, the red blood cells exchange their oxygen for carbon dioxide, which is brought back to the lungs to be exhaled.

Ring sideroblast—A sideroblast that contains five or more iron granules in its mitochondria, enough to form a ring surrounding a third or more of the cell nucleus. It is also called a ringed sideroblast.

Sideroblast—An abnormal erythroblast that contains a cell nucleus with iron granules accumulated in mitochondria around the nucleus.

Transferrin—An iron-binding glycoprotein found in blood plasma that controls the level of iron in biological fluids. The serum transferrin level can be used to check for iron deficiency and hemochromatosis.

X-linked sideroblastic anemia

The hereditary form of the disorder is rare. The primary type of inherited sideroblastic anemia was first described in 1945 by Thomas Cooley, a Detroit pediatrician and hematologist. He identified cases of X-linked sideroblastic anemia in two brothers from a family with a six-generational history of the inherited disease. The genetic abnormality that causes X-linked sideroblastic anemia was identified almost 40 years later. Identification has aided diagnosis of this disorder.

X-linked sideroblastic anemia is caused by a mutation in the *ALAS2* gene at Xp11.21, which codes for an enzyme called erythroid ALA-synthase. This enzyme is necessary for the first step in the production of heme, the iron-bearing molecule in hemoglobin. Some patients have a mutation in the *HFE* gene, which encodes a protein that regulates the amount of iron

absorbed from the diet, in addition to the mutation in the *ALAS2* gene. Those who have mutations in both genes develop a more severe form of the disorder. This severe form is characterized by the absorption of very large amounts of iron from the diet resulting in hemochromatosis, an iron overload disorder.

Another form of X-linked sideroblastic anemia was identified in 1985 and traced to a mutation in the *ABCB7* gene on the X chromosome at Xq13.3. This form of the disorder is characterized by ataxia (uncoordinated gait and lack or loss of coordination in hands and speech) as well as sideroblastic anemia. However, affected males lack the excessive levels of iron storage in their tissues in adult life that is typically found in patients with the more common form of X-linked sideroblastic anemia. Only a few cases of this form of X-linked sideroblastic anemia have been reported and only males appear to be affected.

Other inherited forms of sideroblastic anemia

There are other inherited forms of sideroblastic anemia, which are also rare. Two rare autosomal recessive forms of inherited sideroblastic anemia occur in both males and females of affected families. One type of autosomal recessive sideroblastic anemia is called pyridoxine-refractory because it does not respond to treatment with vitamin B6. It has been linked to two mutations, one in the *SLC25A38* gene on chromosome 3 at 3p22.1 and the other in the *GLRX5* gene on chromosome 14 at 14q32.13.

The other type of sideroblastic anemia inherited in an autosomal recessive pattern is called pyridoxine-responsive because affected individuals do respond to treatment with vitamin B6. As of 2015, this form of congenital sideroblastic anemia has not been traced to a specific gene, but researchers have found that it is not inherited in an X-linked pattern.

Autosomal dominant inheritance has also been reported. Also, Pearson's syndrome, an inherited disorder caused by abnormal mitochondria, is sometimes called sideroblastic anemia with marrow cell vacuolization and exocrine pancreatic dysfunction.

It is likely that other syndromes in which congenital sideroblastic anemia coexists with other disorders will be identified. In 2013 and 2014, a team of researchers in Belgium, Canada, France, Portugal, the United Kingdom, and the United States reported on a syndrome in which sideroblastic anemia is combined with immunodeficiency, fever, and developmental delay (SIFD). The disorder has been linked to a mutation in the *TRNT1* gene.

Genetic profile

Hereditary sideroblastic anemia is most commonly inherited as an X-linked recessive trait, although some rare forms are inherited in an autosomal recessive pattern.

Typical genetic transmission of X-linked disorders

The following concepts are important to understanding the inheritance of an X-linked disorder. All humans have two chromosomes that determine their gender. Females have an XX pattern; males have XY. X-linked recessive, also called sex-linked, inheritance affects the genes located on the X chromosome. It occurs when an unaffected mother carries a disease-causing gene on at least one of her X chromosomes. Because females have two X chromosomes, they are usually unaffected carriers. The X chromosome that does not have the disease-causing gene compensates for the X chromosome that does. For a woman to show symptoms of the disorder, both X chromosomes must have the disease-causing gene. That is

why women are less likely to show such symptoms than males. However, women with one inactivated X chromosome are often symptomatic. In fact, two families with X-linked sideroblastic anemia that appeared in female as well as male members were reported in 1962 and 1965 respectively.

If a mother has a female child, the child has a 50% chance of inheriting the disease gene and being a carrier who can pass the disease gene on to her sons. On the other hand, if a mother has a male child who inherits the disease-causing gene, he will be affected and has a 100% chance of passing the mutated gene on to his children. Because the gene is defective and there is no normal gene in a male with a standard XY chromosome pattern, the singular flawed gene is expressed.

Demographics

X-linked sideroblastic anemia occurs in young men and in some young women with an inactivated X chromosome. It may be seen in maternal uncles and male cousins of men with the disorder. Although the disorder is rare, it has been found in families from different countries and ethnic groups, including African American, Dutch, Italian, Korean, and Japanese families as well as Caucasian Americans. There is no evidence as of 2015 that X-linked sideroblastic anemia is more common in some racial or ethnic groups than in others.

Autosomal recessive forms of the disease may occur in both men and women.

Hereditary sideroblastic anemia affects patients in all age groups. It is most likely to be diagnosed during the first three decades of life, especially during adolescence. However, it has been first diagnosed in patients over 70 years old.

Signs and symptoms

General weakness, fatigue, dizziness, and difficulty breathing are associated with the disorder. Exertion may cause chest pains similar to angina.

The mucous membranes and the skin of the hands and arms of affected patients may be pale, possibly with a lemon-yellow cast. Subcutaneous bleeding may occur, causing a brownish-red discoloration.

Excess iron accumulation, known as hemochromatosis, accumulates over years in the bone marrow, liver, heart, and other tissues. This progressive deposition of toxic iron may result in an enlarged spleen or liver, liver disease, diabetes, impotence, arthritic signs, and heart disease, particularly cardiac arrhythmia.

Diagnosis

Diagnosis of X-linked sideroblastic anemia can be made through an examination of bone marrow aspirate. Ring sideroblasts are visible under microscopic examination of bone marrow when Prussian blue staining is used. The disorder can also be diagnosed by molecular genetic testing, either sequence analysis of the entire coding region or deletion/duplication analysis.

A blood test can indicate the presence of sideroblastic anemia. Indicative laboratory results of an iron panel test include:

- High levels of serum iron, serum ferritin, and transferrin iron saturation.
- Low levels of total iron binding capacity and transferrin.
- Normal to high levels of serum transferrin receptor.

Other signs of sideroblastic anemia include:

- Hemoglobin generally lower than 10.0g/dL.
- Hypochromic (reduced color) cells coexisting with normal cells.
- Stainable marrow and hemosiderin increased.
- Ring sideroblasts visible with Prussian blue staining and observable under microscopic examination of bone marrow.
- Increased width of red cell distribution.
- Normal white blood cells and platelets.

Treatment and management

The main objective in treatment of X-linked sideroblastic anemia is to prevent the development of diabetes, cirrhosis, and heart failure from hemochromatosis.

X-linked sideroblastic anemia often improves with pyridoxine (vitamin B6) therapy. Dosage is 50–200 mg. However, pregnant or nursing mothers may wish to limit intake to 100 mg daily. About 80% of patients respond to treatment with vitamin B6. Phlebotomy (periodic withdrawal of units of blood to prevent hemochromatosis) has also been used successfully to manage X-linked sideroblastic anemia.

In cases of extreme anemia, whole red blood cell transfusion may be required. Repeated whole red blood cell transfusion, however, will contribute significantly to existing iron burden in sideroblastic anemia patients. It will likely require chelation therapy with deferoxamine (Desferal), a drug with iron chelating properties. Deferoxamine binds excess body iron and promotes excretion by the liver and kidneys. It is administered by intravenous infusion from a small portable pump. The pump is worn nine to twelve hours daily, usually at night while

QUESTIONS TO ASK YOUR DOCTOR

- What type of congenital sideroblastic anemia does my child have?
- Is it the X-linked form or an autosomal recessive form?
- Would you recommend bone marrow transplantation?
- What do you expect the chance of improvement to be if pyridoxine is taken?
- What are the most common side effects of pyridoxine?
- What are the early signs of heart failure?
- How often should blood iron levels be monitored?

sleeping. Side effects vary and include pain and swelling at the injection site.

Certain drugs are sometimes associated with treatment of acquired sideroblastic anemia: progesterone, copper chelating drugs, and anti-tuberculosis drugs among others. In other cases, acquired sideroblastic anemia may be secondary to another disorder or disease. Other predisposing causes may be inflammatory disease such as rheumatoid arthritis, cancerous conditions such as leukemia and lymphoma, kidney disorders such as uremia, endocrine disorders such as hyperthyroidism, and metabolic disorders such as porphyria cutanea tarda. With these conditions, it is important to treat the primary disease or disorder in order to reverse the anemia.

Development of leukemia is associated with the acquired form of the disease, often first showing up in the form of a myeloproliferative disorder. These disorders are characterized by abnormal growth of bone tissue and related cells.

Prognosis

Congenital sideroblastic anemia can often be kept in check with regular medical supervision. In a few cases, bone marrow transplantation has been beneficial. Many individuals with X-linked sideroblastic anemia require chronic transfusions to maintain acceptable hemoglobin levels. Over a lifetime, problems related to iron overload, including congestive heart failure and cirrhosis, can become life-threatening issues.

Death can result from hemochromatosis if the disease is untreated or if blood transfusions are inadequate to account for the iron overload.

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ORGANIZATIONS

American Society of Hematology (ASH), 2021 L St. NW, Suite 900, Washington, DC 20036, (202) 776-0544, (202) 776-0545, <http://www.hematology.org>

Iron Disorders Institute, PO Box 675, Taylors, SC 29687, info@irondisorders.org, <http://www.irondisorders.org>

Madisons Foundation, PO Box 241956, Los Angeles, CA 90024, (310)264-0826, (310) 264-4766, getinfo@madisonsfoundation.org, <http://madisonsfoundation.org>

National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>

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Xeroderma pigmentosum

Definition

Xeroderma pigmentosum is a rare inherited genetic disease. People with this condition develop skin and eye cancers at young ages because their DNA is extremely susceptible to damage caused by ultraviolet radiation. "Xeroderma" (dry, scaly skin) and "pigmentosum" (freckling and abnormal skin coloring) refer to changes that occur after exposure to sunlight or other ultraviolet radiation.

Description

Xeroderma pigmentosum refers to a group of similar conditions. Each subgroup is designated by a letter or a roman numeral. Xeroderma pigmentosum is also often abbreviated XP. XP A and XP I are the same, as are XP B and XP II, XP C and XP III, etc. There are seven types of xeroderma pigmentosum designated A–G or I–VII. An eighth type of XP is called the "variant" type. XP VIII/XP

H was once a separate subgroup; now it is known to be part of XP D/XP IV.

Each of the eight types of xeroderma pigmentosum has its own DNA defect. However, each section of DNA affected is involved in the same process. These defects affect the body's ability to repair DNA damage, especially DNA damage to the skin caused by exposure to ultraviolet radiation. Sunlight is the most common source of ultraviolet radiation. Everyone's DNA is damaged when it is exposed to sunlight. However, the body has complex and very effective methods to repair the DNA damage. This repair mechanism does not work properly in people with xeroderma pigmentosum. They quickly accumulate damage to their DNA if they are exposed to ultraviolet radiation. Cumulative DNA damage leads to cancer, especially of the skin and the eyes.

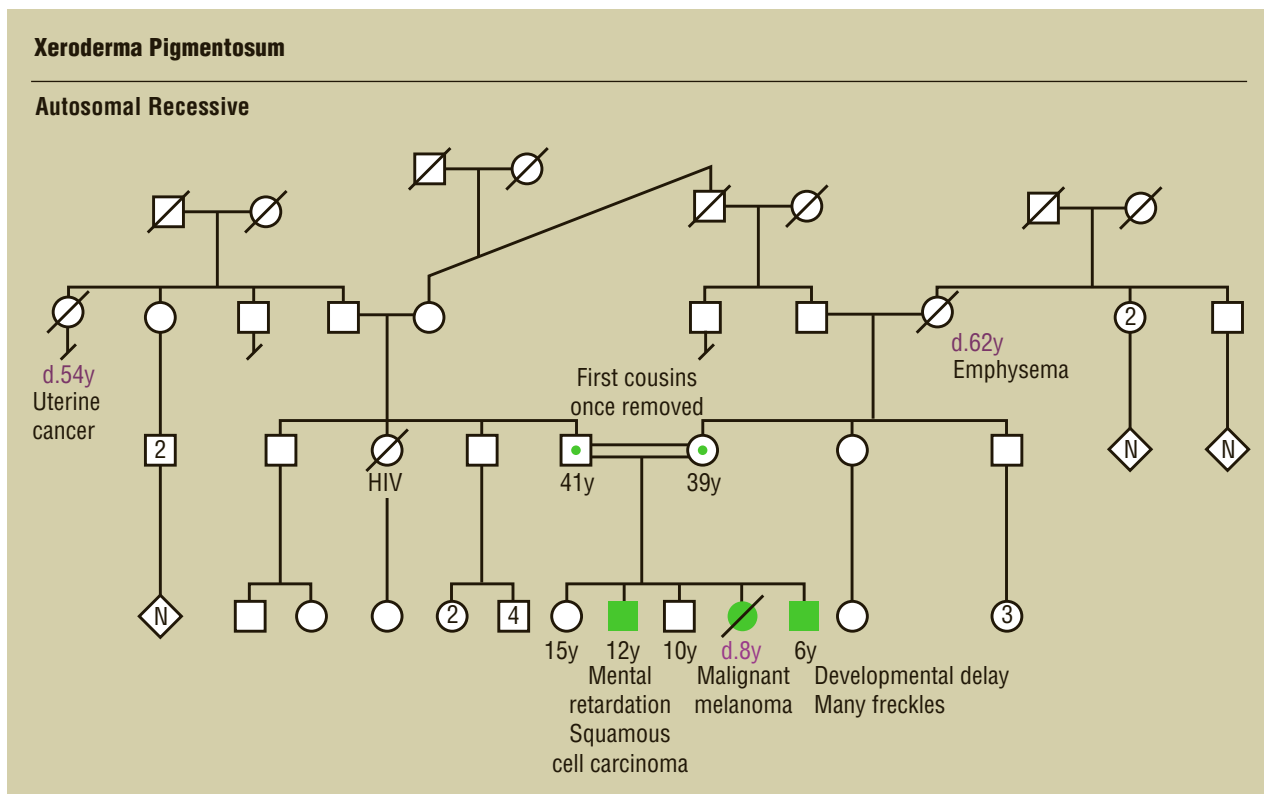
DeSanctis-Cacchione syndrome refers to the combination of xeroderma pigmentosum with intellectual disability, short stature, and other symptoms. Trichothiodystrophy (TTD) is sometimes caused by the same DNA change that causes XP D and, rarely, XP B. People with TTD also have brittle hair and nails, physical retardation, and intellectual disability.

Genetic profile

Xeroderma pigmentosum is inherited as an autosomal recessive condition. Everyone inherits one set of genetic material from each parent. People with xeroderma pigmentosum inherited one nonfunctional XP gene from each parent. Their parents have one normal gene and one abnormal gene (of that particular pair); they are called "carriers." Carriers do not have the autosomal recessive conditions because the normal gene in the pair protects them. Two carrier parents have a one in four chance with each pregnancy to have an affected child. A person with xeroderma pigmentosum will have an



Dr. Sulamita Chaibub assists Djalma Antonio Jardim who has xeroderma pigmentosum. (Eraldo Peres/AP Images)



Xeroderma Pigmentosum: pedigree analysis chart (Gale)

affected child only if the child's other parent is a carrier or affected with XP.

The genetics of xeroderma pigmentosum are a bit complicated. The genetic defect in seven of the subgroups has been identified. Each subgroup (A–G) has its own abnormal gene. Each person with xeroderma pigmentosum has a particular subtype, which is associated with one specific abnormal gene. For example, a person with XP type A has no normal XP A gene but does not have XP type B and does not have the abnormal genes associated with XP type B. The genes for types A, B, C, D, E, F, and G are on chromosomes 9, 2, 3, 19, 11, 16, and 13, respectively. The gene for the “variant” type is on chromosome 6. If two people with different forms of xeroderma pigmentosum had a child, the child would not have xeroderma pigmentosum. But if two people with the same type of xeroderma pigmentosum had children, all of the children would also have xeroderma pigmentosum.

This discussion involves two different types of DNA changes. The first DNA change is the change that the person with xeroderma pigmentosum inherits from both parents. This change (mutation) affects the repair enzymes and is present in every cell in the person's body. The second type of change discussed is additional DNA

mutations that result from exposure to ultraviolet radiation. Since the skin and eyes are commonly exposed to ultraviolet radiation that damages DNA and since the body's repair system is not working, people with this condition have a high rate of mutation in the exposed organs. These mutations often manifest themselves as cancers—abnormal, uncontrolled growths. Thus, it is the combination of genetic defect and environmental exposure that causes the manifestations of this disease. The first DNA change would not be nearly as problematic if it did not predispose the person with it to accumulate many additional DNA mutations.

Demographics

Xeroderma pigmentosum occurs in every ethnic group, and it occurs equally in men and women. Approximately 1 in 1,000,000 people in the United States have xeroderma pigmentosum. Approximately 1 in 22,000 Japanese individuals have xeroderma pigmentosum. The most common types are A, C, D, and the variant type.

Signs and symptoms

People with xeroderma pigmentosum have photosensitive skin. This means that their skin is hypersensitive to the effects of sunlight. Development of cancer at a young age

KEY TERMS

Autosomal—Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomes and one pair of sex chromosomes.

Cancer cells—These cells have characteristics that distinguish them from normal cells and non-cancerous cells; they are threatening, harmful, and resistant to treatment.

Carcinoma—Any cancer that arises in the epithelium, the tissue that lines the external and internal organs of the body.

Chromosome—A microscopic thread-like structure found within each cell of the body and consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Deoxyribonucleic acid (DNA)—The genetic material in cells that holds the inherited instructions for growth, development, and cellular functioning.

Malignant—A tumor growth that spreads to another part of the body, usually cancerous.

is the most serious consequence. The eyes are also affected. Some people with xeroderma pigmentosum are affected intellectually, but not all. The symptoms a person will have are somewhat predictable based on which mutation he or she has.

Cutaneous symptoms

Skin manifestations usually begin in infancy. Early effects of skin exposure to minimal ultraviolet radiation include acute sunburn, blistering, freckles, increased or decreased pigment, birthmark-like spots, inflammation, dryness, and rough spots. The face, hands, neck, and arms are more severely affected because of increased sun exposure. Multiple scars may develop. The skin is normal at birth.

The average age at which people with xeroderma pigmentosum develop the first skin cancer is eight years. The risk to develop skin cancer is increased 1,000 times over the risk of the general population. A cell accumulates multiple abnormalities in its transition from a normal cell to a cancer cell. Cancers that occur frequently in people with xeroderma pigmentosum include squamous cell carcinoma, basal cell carcinoma, and malignant melanoma. Basal cell cancers are malignant and, if untreated, are characterized

by relentless local invasion but not metastasis elsewhere in the body. Squamous cell cancers are also malignant and, like basal cell carcinomas, tend to be local, although they are occasionally capable of metastasis. Malignant melanoma, as the name implies, is also malignant, but it is much more aggressive than either basal cell or squamous cell cancers of the skin. It is especially threatening because, if not diagnosed and treated early, it commonly will spread to internal organs and can be fatal. Cancer may occur on the eyes, lips, and tongue.

Ocular symptoms

Most people with xeroderma pigmentosum also have extremely light-sensitive eyes. Their eyes easily become irritated, red, and swollen. Abnormal growths may appear. Cataracts may occur at an unusually young age.

Other symptoms

The other symptoms associated with xeroderma pigmentosum are variable. Many people who are affected only have eye and skin manifestations. Mental deterioration may occur; when it does, it usually worsens over time. Neurological symptoms are not believed to be associated with sun exposure. Some people have one or a combination of deafness, poor reflexes, lower intelligence, or spasticity (in addition to ocular and cutaneous symptoms).

Diagnosis

Xeroderma pigmentosum may be suspected based on a person's history of skin changes that occurred after minimal exposure to sunlight. The diagnosis is confirmed by a blood test or a skin test. The skin or blood cells are sent to a specialty laboratory. Studies are performed to determine whether the cells are hypersensitive to ultraviolet radiation. Scientists may examine whether abnormal changes can be seen in the chromosomes. The type of xeroderma pigmentosum may be determined by genetic studies or other specialized studies.

Genetic testing for xeroderma pigmentosum is complicated because there are eight different genes involved. Genetic tests are usually very specific, looking for a change in one gene. To confirm a diagnosis of xeroderma pigmentosum by DNA testing, scientists must look for multiple changes in eight different genes.

Prenatal diagnosis may be possible, especially if genetic studies have already been performed on an affected sibling and the parents.

Treatment and management

The only treatment for xeroderma pigmentosum is avoiding harmful exposure to ultraviolet radiation and

QUESTIONS TO ASK YOUR DOCTOR

- How can avoidance of UV light best be accomplished?
- What are the risks and benefits of treatment with medication?
- How often should my child be screened for abnormal growths?
- Which family members should undergo genetic testing?

treating/removing growths as they occur. The DNA damage caused by exposure to ultraviolet light accumulates over time and the resulting DNA damage is irreversible.

Life is changed dramatically when a family member has xeroderma pigmentosum. Extreme measures must be taken to completely avoid exposure to the sun. Preventative measures include sunglasses, tightly woven long-sleeved clothing, wide brim hats, sunblock, and protective window coverings (at home, in the car, and at school). Children do not play outside during the day. All sources of ultraviolet radiation are avoided, even exposure to certain light bulbs. These precautions are critical to survival. Levels of ultraviolet radiation at home and at school can be measured with special instruments. Abnormal skin growths and other symptoms are treated/removed as they arise. Regular visits are made to the eye doctor, dermatologist, and neurologist. Often psychosocial support is also helpful.

Treatments that would deliver DNA repair proteins into the skin of affected patients are under investigation. Some people with xeroderma pigmentosum may be offered other types of medication, like isotretinoin. The dermatologist weighs the benefit of prescribing a medication against the side effects associated with that medication.

Because our bodies have different mechanisms for fixing different forms of DNA damage, people with xeroderma pigmentosum are most susceptible to DNA damage by ultraviolet radiation. Some other exposures have been associated with the type of DNA damage caused by ultraviolet radiation. Therefore, people with xeroderma pigmentosum should also avoid exposure to tobacco and certain other drugs.

Prognosis

Life expectancy is significantly reduced due to morbidity associated with the cancers. Researchers have not

determined how effective preventative measures are (e.g., avoidance of ultraviolet radiation).

In the 1990s scientists discovered a great deal about DNA repair mechanisms and about the genes associated with xeroderma pigmentosum. The range of symptoms associated with each type have been better defined. The media has also been interested in XP, giving it more attention than is typical for such a rare condition. Advocates in the XP community have developed helpful resources for other affected families, such as Camp Sundown.

Resources

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ORGANIZATIONS

- National Cancer Institute, BG 9609 MSC 9760, 9609 Medical Center Dr., Bethesda, MD 20892-9760, (800) 422-6237, <http://www.nci.nih.gov>
- Skin Cancer Foundation, 149 Madison Ave., Suite 901, New York, NY 10016, (212) 725-5176, <http://www.skincancer.org>
- Xeroderma Pigmentosum Society, 437 Snyderstown Rd., Craryville, NY 12521, (518) 851-3466, xps@xps.org, <http://www.xps.org>

Michelle Queneau Bosworth, MS, CGC
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XMEN

Definition

XMEN is a rare genetic disorder classified as a primary immune deficiency disease or PIDD. The term "primary" means that the immune disorder arises by itself and

KEY TERMS

B cells—Lymphocytes that originate in the bone marrow and make antibodies in response to antigens.

CD4+ cells—A type of T cell that secretes small proteins (called cytokines) that regulate the body's active immune response to infections.

CD8+ cells—A type of T cell that kills cancer cells, cells infected with viruses, or cells that are damaged in other ways. CD81 cells are also known as cytotoxic T cells, killer T cells, and cytolytic T cells.

Epstein-Barr virus (EBV)—A human herpesvirus (HHV-4) that causes infectious mononucleosis and is associated with certain types of cancer and complications of HIV infection.

Latency—The ability of some viruses to remain dormant in the body after the acute infection has subsided.

Loss-of-function mutation—A genetic mutation in which the protein encoded by the gene has little or no effectiveness.

Lymphocyte—Any of three types of white blood cells that play an important role in the immune system. They include T cells, B cells, and natural killer (NK) cells.

Lymphoma—A general term for a group of cancers that affect the immune system; they develop from lymphocytes, cells in the lymphatic system.

Lymphopenia—A condition marked by an abnormally low level of lymphocytes in the blood.

Neoplasia—An abnormal proliferation of cells, which results in an abnormal mass of tissue known as a neoplasm.

Neutropenia—An abnormally low level of neutrophils in the blood. Neutrophils are the most common type of circulating white blood cells and are the first line of defense in the body's response to inflammation.

Primary immune deficiency diseases (PIDDs)—A group of rare genetic disorders caused by inherited defects in specific cells of the immune system. XMEN is one of about 200 known PIDDs.

Splenomegaly—Enlargement of the spleen.

T cells—A type of lymphocyte that plays an important role in cell-mediated immunity. There are several different subtypes of T cells, including helper (CD41) cells and cytotoxic (CD81) cells. T cells are so called because they mature in the thymus gland.

is not secondary to another disease, drug treatment, or exposure to environmental toxins. The acronym XMEN stands for “X-linked immune deficiency with magnesium defect, Epstein-Barr virus (EBV) infection, and neoplasia.” The word “neoplasia” in the name of the disorder refers to the abnormal proliferation of cells characteristic of lymphomas and other cancers.

Description

XMEN is a genetic disorder that affects only males. It is characterized by severe recurrent upper respiratory and ear infections, persistent EBV activity, an abnormally low number of T helper lymphocytes (also called CD4+ lymphocytes), defective activation of another type of T cell (CD8+ T cells), and eventual development of lymphomas, which are cancers that develop in cells of the immune system. The disorder was identified in 2011 by a team of researchers at the National Institute of Allergy and Infectious Diseases (NIAID), and much is still unknown about it. Its discovery has, however, led to a new understanding of the role of magnesium in cellular signaling within the human immune system.

Genetic profile

XMEN, as its name indicates, is an X-linked disorder, which means that it is sex-linked. The gene associated with XMEN, the *MAGT1* gene, is located on the X chromosome, which is a sex chromosome. Only males are affected by X-linked disorders because they have only one X chromosome and will develop the disorder if they inherit an X chromosome with the defective gene from the mother. Females, who have two X chromosomes, are carriers of X-linked disorders but will not develop symptoms because their second X chromosome is usually normal. Another characteristic of X-linked disorders is that fathers with X-linked disorders cannot pass them on to their sons.

The specific gene associated with XMEN, the *MAGT1* gene, is located on the long arm of the X chromosome at Xq21.1. The gene codes for a protein that is a magnesium transporter, which moves magnesium ions into T cells—particularly the CD8+ T cells, which help to control infections like EBV infections. CD8+ T cells normally take in magnesium when they detect the presence of a virus or other foreign invader. In addition to the CD8+ T cells, some researchers think that the

magnesium transporter protein also plays a role in the production of CD4+ T cells in the thymus gland.

The mutation in the *MAGT1* gene that causes XMEN is a loss-of-function mutation, which means that it results in insufficient amounts of the magnesium transporter protein. This lack, in turn, reduces the amount of magnesium that enters the T cells, preventing effective activation of the CD8+ cells. When these cells are not activated, they cannot attack the Epstein-Barr virus, and the uncontrolled presence of EBV in the patient's body increases his risk of developing lymphoma. In regard to the CD4+ cells, the insufficiency of the magnesium transporter protein means that the thymus will produce too few of these cells, which accounts for the low number of CD4+ T cells in patients diagnosed with XMEN.

Demographics

XMEN is a very rare disorder, with only seven cases reported in the medical literature as of 2015, and an eighth diagnosed in Canada that year. One patient, a 45-year-old man, was diagnosed only after his death. Because the disorder has been identified only recently and so few cases have been diagnosed, very little is known about the frequency of XMEN worldwide or whether it is more common in some racial or ethnic groups than others.

Signs and symptoms

The signs and symptoms of XMEN include a history of recurrent ear, sinus, and respiratory infections, and the persistence of infections caused by the Epstein-Barr virus (EBV). This virus, which causes infectious mononucleosis and is associated with such cancers as Burkitt lymphoma and Hodgkin's lymphoma, is also a common cause of childhood infections. About 50% of five-year-olds and 90% of adults in the United States have been infected with EBV. In people with a normal immune system, the virus remains latent within the B cells of the immune system for the rest of the patient's life after the acute infection subsides. In patients with XMEN, however, the EBV virus does not enter latency but remains active; the EBV infections do not resolve but persist, increasing the patient's risk of developing lymphoma as an adult.

Other symptoms associated with XMEN include splenomegaly (enlargement of the spleen), recurrent diarrhea, and other infections associated with a weakened immune system, including pneumonia, streptococcal throat infections, and whooping cough (pertussis).

QUESTIONS TO ASK YOUR DOCTOR

- Have you ever treated a patient with a primary immune deficiency disease?
- Have you ever referred a patient to the Primary Immune Deficiency Clinic at NIAID?
- Do you think that researchers will develop an effective therapy for XMEN in the near future?

Diagnosis

The diagnosis of XMEN is based on observation of the patient's symptoms, particularly a history of recurrent ear, sinus, or other upper respiratory infections. The patient's spleen may be sufficiently enlarged to be felt during the doctor's examination of the patient's abdomen. Laboratory test results suggest XMEN includes the presence of a large number of cells infected with the EBV virus, a very low number of CD4+ T cells (CD4+ lymphopenia), a low ratio of CD4+ T cells to CD8+ T cells, and mild neutropenia (a low number of neutrophils in the blood).

The diagnosis can be confirmed by molecular genetic testing for the defective *MAGT1* gene. As of 2015, testing for this gene was available at the Primary Immune Deficiency Clinic at the National Institute of Allergy and Infectious Diseases (NIAID) and at the Molecular Genetics Laboratory of the Cincinnati Children's Hospital Medical Center in Ohio.

Treatment and management

Treatment options for XMEN were limited as of 2015. Bone marrow transplantation is one possible treatment for the disorder, but its effectiveness is unknown. Another treatment that shows promise is supplementation with an oral form of magnesium threonate, a compound that appears to be safe for long-term use provided that the therapy is carefully supervised by a physician. Further research is needed, as it is not yet known whether magnesium supplements will prevent the development of lymphoma in patients with XMEN. Patients suspected of having XMEN should consult the Primary Immune Deficiency Clinic at NIAID for an examination, diagnosis, and treatment recommendations.

Prognosis

The prognosis of XMEN is uncertain, in part because so little is known about this disorder and whether current treatment options will slow or prevent progression to lymphoma.

Resources

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- "XMEN Disease." NIAID. <https://www.niaid.nih.gov/sites/default/files/XMEN%20Factsheet.pdf> (accessed June 26, 2021).

ORGANIZATIONS

- Cincinnati Children's Hospital Medical Center, Molecular Genetics Laboratory, 3333 Burnet Ave., NRB 1042, Cincinnati, OH 45229, (513) 636-4474, (513) 636-4373, moleculargenetics@cchmc.org, <http://www.cincinnatichildrens.org/service/d/diagnostic-labs/molecular-genetics/default>
- Immune Deficiency Foundation (IDF), 110 West Rd., Suite 300, Towson, MD 21204, (800) 296-4433, (401) 321-9165, info@primaryimmune.org, <http://primaryimmune.org>
- National Institute of Allergy and Infectious Diseases (NIAID), 5601 Fishers Lane, MSC 9806, Bethesda, MD 20892, (301) 496-5717 or (866) 284-4107, (301) 402-3573, ocpostoffice@niaid.nih.gov, <http://www.niaid.nih.gov>
- NIAID Primary Immune Deficiency Clinic, NIH, 10 Center Dr., Building 10, Room 12C-103, Bethesda, MD 20892, (301) 402-1006 or (866) 857-5274, (301) 451-5680, <http://www.niaid.nih.gov>

Rebecca J. Frey, PhD

XO syndrome see **Turner syndrome**

XXXX Syndrome

Definition

XXXX syndrome is a genetic disorder in girls in which they have four X chromosomes rather than two. Also known tetra-X, tetrasomy X syndrome, and 48-X

syndrome, the condition may cause lowered intelligence, increased height, speech and language disorders, and infertility.

Description

Humans normally have 46 chromosomes, 23 from each parent. In XXXX syndrome, girls are born with 2 extra chromosomes, for a total of 48. Symptoms range from mild to severe. Some children with the disorder are never able to lead independent lives, although others play sports and attend college. The physical characteristics may be slight and not readily observable. Health problems associated with the syndrome also range from quite mild to more severe. XXXX syndrome was first reported in the medical literature in 1961. Research on XXXX syndrome has been limited, but there has been more interest in the topic in recent years.

Girls with XXXX syndrome generally do not have the obvious appearance of a chromosomal disorder. Their faces appear normal, and if differences are noted they are usually minor. The features that they may possess include epicanthal folds (creases next to the inner corner of the eye), eyes that may slant upward, and extra folds on the back of their neck. Their eyes may be widely spaced apart.

The speech and language disorders associated with XXXX syndrome are believed to be at the root of some of the behavioral problems described with this population. While many of the girls are described as pleasant and easy going, they also may have issues with anger management, mood swings, and shyness. Some girls experience psychiatric problems such as bipolar disorder and depression. Social difficulties have been reported among this group, although this issue is not consistently found among girls with XXXX syndrome.

Because there are so few cases in the world, studies are based on relatively small numbers. There are reports of four women with XXXX syndrome having a total of seven children. All were normal babies—a mixture of boys and girls—with the exception of one stillbirth and one baby born with Down syndrome.

Risk factors

XXXX syndrome is extremely rare. In a rare number of cases, mothers of XXXX syndrome girls have been found to have an extra X chromosome in some cells.

Genetic profile

XXXX syndrome occurs when a girl inherits either three X chromosomes from her mother and one X chromosome from her father, or when she inherits both extra

KEY TERMS

Epicanthal fold—A wrinkle in the skin extending from the nose up to the eyebrow and sometimes associated with genetic anomalies.

Renal—Pertaining to the kidney.

chromosomes from her mother. It is believed that, in the formation of the mother's egg, errors in cell division cause the egg to contain multiple X chromosomes rather than only one. In some cases it is believed that the mother's child may first develop five X chromosomes, but one chromosome dies and the baby is left with four. XXXX syndrome can also be caused during conception, if there are errors in cell division at that time or if the mother carries an extra X chromosome in some of her cells.

An environmental cause for XXXX syndrome has not been found, and it is believed that neither environment nor maternal lifestyle causes this condition.

Demographics

XXXX syndrome only affects girls, and is extremely rare. It is estimated that there are 100 girls and women in the world with the condition. A Penta-Tetra X registry has been established in the United Kingdom. Sex chromosome disorders in which a baby is born with 47 to 49 chromosomes include a variety of conditions affecting boys and girls, and occur in 1 out of 400 births. There may be a number of cases of girls with this disorder who have not been diagnosed.

Signs and symptoms

The clinical symptoms of XXXX syndrome vary from one girl to the next. Some have milder symptoms, while others face more severe issues. The following is a list of symptoms that appear to be more prevalent with this population:

- Delayed physical development (mild)
- Delayed speech development
- Difficulty learning (mild to moderate)
- Tall stature (in some cases)
- Tendency toward stress
- Higher risk of dysfunctioning ovaries
- Higher incidence of respiratory infections (during younger years) than most girls of same age
- High arched palate

- Epicanthal folds, upward slanted eyes, and extra folds in the back of the neck
- Heart conditions of varying levels (affects approximately one-third of the girls)
- Kidney disorders
- Joint problems

As babies, girls with XXXX syndrome exhibit delays in physical development such as sitting and walking. Some of the girls experience weaker muscle tone and abnormally loose ligaments, factors that contribute to such delays. However, it is important to note that when the children gain the ability to walk and run, girls with XXXX syndrome can be quite active. They typically jump and play, and by their teenage years enjoy swimming and other sports.

Kidney disorders range from mild to severe. In some cases, the kidneys are fused together; in others, the girl is born with only one kidney. Because of a defect in valves regulating urine flow that may occur, there may be difficulty with the flow of urine from the kidneys to the bladder.

The palate may be highly arched, leading to a susceptibility toward ear infections as bacteria moves readily from the mouth to the ears. It is important that hearing is monitored to determine if hearing loss occurs, and it is also essential to monitor and treat ear infections promptly. The arch of the palate may also lead to problems with teeth; some girls experience teeth that erupt too early, while others have a delay in tooth eruption.

Approximately half of the girls experience normal menstruation; the other half lack menstruation (or have irregular menstruation) as well as underdeveloped sexual features.

Approximately one-third of the girls may have varying degrees of heart conditions, ranging from murmurs to holes in either the septum (dividing partition) of the atria (upper chambers) or ventricles (lower chambers).

Problems with joint structure and movement seem to be an issue with this population. Some girls suffer with joints that are stiff or even fused, while others experience joints with hyper-rotation.

At birth, girls with XXXX syndrome are of slightly lower weight, with an average birth weight of 6.2 pounds. The girls tend to eat well and grow at a healthy pace; in fact, they tend to be tall children. Researchers believe it is possible that the extra chromosome adds to height. Another potential rationale for the increase in height among these girls is the lower levels of estrogen secretion. The range in height, although the sample is small because of the rarity of this disorder, is 5 foot 3 inches to 6 foot 2 inches.

QUESTIONS TO ASK YOUR DOCTOR

- Is my child considered to have a mild or severe case of XXXX syndrome?
- What supportive measures can I take to enhance my daughter's life?

In 1979, researchers at the University of California at Los Angeles reported on the first incident of a girl with XXXX syndrome lacking ovaries. The 16-year-old girl had a uterus and fallopian tubes but no ovaries. Consistent with the syndrome, the girl had intellectual disability, although mild, as well as other mild characteristics associated with the condition.

The disorder affects intellectual development. A “rule of thumb” is that intelligence decreases 10–15 points for every extra chromosome. The average intelligence quotient (IQ) for the girls ranges from 60 to 80. While some girls attend schools with supportive environments, others go on to college. It has been said that the most representative features of the syndrome are learning disability and delay in speech development. On average, they learn to speak at age three years. Issues with complex speech and vocabulary may persist into the upper grades.

Diagnosis

Examination

The clues that a baby has XXXX syndrome may be subtle at first. Symptoms of a chromosomal disorder, including epicanthal folds, may be present, but slight. In many cases, the baby's low birth weight, failure to meet developmental milestones, and sometimes the lack of muscle tone ultimately prompt the pediatrician to suggest genetic testing. The diagnosis often comes after parents face an extended period during which their baby does not perform activities that are appropriate for her age.

Tests

Genetic testing may be performed on body tissues such as blood or skin.

Procedures

XXXX syndrome may be diagnosed with prenatal chromosome testing such as chorionic villus sampling or amniocentesis.

Treatment and management

XXXX syndrome cannot be prevented. Regular medical testing throughout the girl's life, however, plays an important role in preventing complications of the syndrome, such as serious heart or kidney issues.

It is important to monitor kidney function because some girls have defects in the renal system. Kidney ultrasounds are recommended, as frequent infections of the kidney may impair kidney function later in life.

Some girls may require ear tubes if they experience recurrent infections.

Prognosis

Intellectual disability of varying degrees limits the chance of an independent life for those who have more severe forms of XXXX syndrome. Girls with mild intellectual disability may live independently, but others must live in a setting that offers supervision and support.

Girls who have XXXX syndrome are more likely to have a daughter with the disorder; therefore, genetic counseling is strongly suggested if pregnancy is considered.

Infections caused by this syndrome may lead to serious consequences later in life. Infections of the ears, due to the high palate, may lead to deafness. Kidney infections may lead to high blood pressure and kidney damage.

Hormonal problems may also create problems later in life. Low estrogen production can hasten osteoporosis, making the girls and women more susceptible to bone fractures.

Resources

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- “Tetrasomy X.” GARD. <https://rarediseases.info.nih.gov/diseases/7754/tetrasomy-x> (accessed June 26, 2021).

ORGANIZATIONS

Support Organization for Trisomy 18, 13, and Related Disorders (SOFT), 2982 S. Union St., Rochester, NY 14624, (800) 716-7638, <http://trisomy.org>

Unique Understanding Chromosome Disorders, The Rare Chromosome Disorder Support Group, G1 The Stables, Station Road West, Oxted, Surrey UK RH8 9EE, +44 (0) 1883 723356, info@rarechromo.org, rarechromo@aol.com, <http://www.rarechromo.org/html/home.asp>

Rhonda Cloos, RN

XXXXX syndrome

Definition

XXXXX syndrome (also called pentasomy X, penta X syndrome, or 49,XXXXX) is a rare genetic disorder in girls in which they have five X chromosomes rather than two. The disorder may cause lowered intelligence, physical deformities, and psychological problems.

Description

XXXXX syndrome is an extremely rare chromosomal condition affecting only girls. Researchers first described the condition in the *Journal of Pediatrics* in 1963. Seventeen years later, there had been only 12 cases noted in professional scientific publications. As of 2015, only 26 cases had been reported in medical journals.

During the 1960s and 1970s, there was a burst of scientific research in XXXXX syndrome and related disorders. After that time period passed, research on the disorder became rare; however, in the early 2000s, scientific interest in XXXXX syndrome grew. In 2009, the National Institutes for Health in Bethesda, Maryland, was accepting participants for a study of XXXXX syndrome. The study hoped to determine the effect of the disorders on the development of the brain, and whether brain imaging methods can identify the biological features of the brain that are associated with the disorders.

The most common characteristics of this syndrome are short height, short neck, round face, microcephaly, intellectual disability, fifth finger clinodactyly, and heart and kidney defects.

Infants with XXXXX syndrome share a number of characteristic features such as a round face, flat nose bridge, deformities of the ears, and upward slanting eyes. The girls also might have mild to severe intellectual disability. As a general rule there is a 10- to 15-point reduction in Intelligence Quotient (IQ) for each extra sex chromosome. Additionally, the chance of intellectual disability and dysmorphism rises with each extra sex

KEY TERMS

Clinodactyly—Curving of the finger to the left or right.

Epicanthal folds—Crease in the skin extending from the nose to the eyebrow.

Microcephaly—Abnormal smallness of the head; it often is associated with intellectual disability.

Missegregation of chromosomes—The faulty segregation of chromosomes into the appropriate daughter cells, in either mitosis (cell division) or meiosis (reproductive cell [sperm or egg] production).

chromosome. In the case of XXXXX syndrome, girls have three extra X chromosomes. Scientists believe that the presence of one extra X chromosome in a mother creates a slightly higher risk of having a daughter with XXXXX syndrome. Only females are at risk.

Genetic profile

XXXXX syndrome is caused by an aneuploidy (the presence of extra chromosomes) of the X chromosome. XXXXX syndrome is believed to be the result of a non-disjunction error in cell division during the process of chromosome splitting within the mother's ova that causes missegregation of the chromosomes. As a result of this error, the ovum contains more than 23 chromosomes. The occurrence of defects in the chromosome segregation during meiosis can result in several forms of chromosome duplication. Additional sex chromosome missegregation defects include the trisomy, tetrasomy, or other karyotypes that can occur in both males and females.

Demographics

XXXXX syndrome is very rare. It is estimated that the syndrome is present in 1 out of 85,000 female births, though this is considered to be an overestimation. The condition only affects girls.

Signs and symptoms

The most common symptoms associated with XXXXX syndrome include growth delays before birth and a failure to grow and gain weight following birth. The developmental deficiencies include short height, short neck, round face, microcephaly, moderate to severe intellectual disability, fifth finger clinodactyly, and heart and kidney defects.

Girls with XXXXX syndrome may exhibit any number of classic signs, such as:

- Developmental delays: physical and intellectual delays are possible
- Microcephaly (abnormal smallness of the head)
- Facial features: round face, upward slanting eyes, wide-set eyes, epicanthal folds, ear and tooth abnormalities, and short neck length
- Musculoskeletal: deformities in the elbow, foot (club foot may be present), overlapping toes, and larger space between first and second toes, fifth finger clinodactyly, weak muscle tone (hypotonia)
- Heart: defects in the heart may be present (atrial septal defect, ventricular septal defect, patent ductus arteriosus)
- Kidneys: horseshoe kidneys

Psychiatric symptoms have been described in girls with XXXXX syndrome. It is believed that the psychiatric symptoms are related to the presence of extra chromosomes.

In 1980, one case was reported in which a three-year-old girl with XXXXX syndrome had one underdeveloped kidney and was missing one ovary. The present ovary was believed to function normally, suggesting to researchers that the girl would be able to reproduce.

In 1999, the first case of XXXXX syndrome along with hyper IgE syndrome (HIE) was reported in a ten-year-old girl. The girl experienced a history of eczema as well as recurrent pneumonia and staphylococcal abscess in addition to the features commonly associated with XXXXX syndrome. This was the first case in which the presence of these two distinct chromosome disorders appeared together in one individual.

The syndrome has also been described in the medical literature as having similar attributes to Down syndrome.

Diagnosis

Diagnosis of XXXXX syndrome is usually made during childhood, as the symptoms become more pronounced. Diagnosis is confirmed through karyotyping, a chromosome number assessment test, and may include blood or skin tests. As of 2015, five cases had been diagnosed through prenatal testing procedures. The syndrome, if present, will appear on chorionic villus sampling or amniocentesis. The symptoms of XXXXX syndrome become more apparent as the girl progresses through early childhood. Ultimately, suspicions lead the parents and health care practitioner to seek testing.

Treatment and management

Girls with XXXXX syndrome experience medical conditions that range from mild to severe. The level of

QUESTIONS TO ASK YOUR DOCTOR

- What are my chances of having another child with XXXXX syndrome?
- How will I know if my daughter's condition is a mild or severe form of XXXXX syndrome?

severity dictates the treatment needed. If medical conditions such as atrial septal defect are present, heart surgery may be needed.

Because the syndrome is associated with poor muscle tone and speech abnormalities, physical, speech, and occupational therapies are recommended.

Atrial septal defect

If a child has an atrial septal defect, treatment to close the hole in the septum may be necessary. In the past, open-heart surgery was the only surgical option; however, methods of closing certain types of holes without surgery have been developed. Parents will need to discuss the options with their child's physician.

Ventricular septal defect

A ventricular septal defect, which may occur, is a hole in the membrane that separates the two ventricles, which are the lower chambers of the heart. Treatment depends on the size of the hole. If it is small, it may not require any treatment. If the hole is large, open heart surgery may be required. If serious symptoms develop in the first months of life, surgery on the baby may be essential. If the symptoms are mild, surgery may be delayed a few years. Surgery involves closing the hole with a patch.

Prognosis

There is no way to prevent XXXXX syndrome. The long-term prognosis depends on the severity of the syndrome in the individual girl. A more positive prognosis is generally associated with earlier diagnosis, sound treatment for medical conditions, and modalities such as occupational, physical, and speech therapies. If cardiac defects are present, treatment for such defects improves the prognosis.

Resources

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ORGANIZATIONS

Chromosome Disorder Outreach, PO Box 724, Boca Raton, FL 33429-4252, (561) 395-4252, info@chromodisorder.org, <http://www.chromodisorder.org>

Unique: The Rare Chromosome Disorder Support Group, G1 The Stables, Station Road West, Oxted, Surrey UK RH8 9EE, +44(0)1883 723356, info@rarechromo.org, <http://www.rarechromo.org>

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XXY syndrome

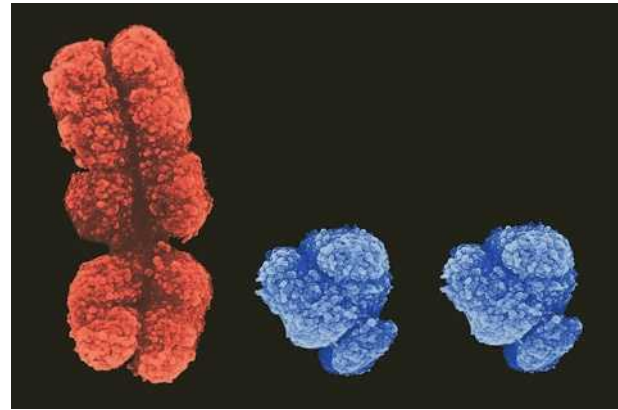
Definition

XXY syndrome is a chromosome disorder that affects males. Males with this disorder have an extra Y chromosome.

Description

The XYY syndrome was previously considered the *super-male* syndrome, in which men with this condition were thought to be overly aggressive and more likely to become criminals. These original stereotypes came about because several researchers in the 1960s found a high number of men with XYY syndrome in prisons and mental institutions.

These original observations did not consider that the majority of males with XYY syndrome were not in prisons or mental institutions. Since then, broader, less biased studies have been done on males with XYY syndrome. Though males with XYY syndrome may be taller than average and have an increased risk for learning difficulties, especially in reading and speech, they are not overly aggressive. Unfortunately, some text books and many people still believe the inaccurate stereotype of the *super-male* syndrome.



Scanning electron micrograph of human chromosomes, showing one X and two Y chromosomes, or XYY syndrome. People with this disorder are slightly taller and may have learning disabilities. (Biophoto Associates/Science Source)

Genetic profile

Chromosomes are structures in the cells that contain genes. Genes are responsible for instructing our bodies how to grow and develop. Usually, an individual has 46 chromosomes in each cell, or 23 pairs. The first 22 pairs are the same in males and females, and the last pair, the sex chromosomes, consist of two X chromosomes in a female and an X chromosome and a Y chromosome in a male.

XYY syndrome occurs when an extra Y chromosome is present in the cells of an affected individual. People with XYY syndrome are always male. The error that causes the extra Y chromosome can occur in the fertilizing sperm or in the developing embryo.

XYY is not considered an inherited condition. An inherited condition usually is one in which the mother and/or father has an alteration in a gene or chromosome that can be passed onto their children. Typically, in an inherited condition, there is an increased chance that the condition will reoccur. The risk of the condition reoccurring in another pregnancy is not increased above the general population incidence.

Demographics

XYY syndrome has an incidence of 1 in 1,000 newborn males. However, since many males with XYY syndrome look like other males without XYY syndrome, many males are never identified.

Signs and symptoms

There are no physical abnormalities in most males with XYY syndrome. However, some males can have one or more of the following characteristics. Males who have XYY syndrome are usually normal in length at

birth, but have rapid growth in childhood, typically averaging in the seventy-fifth percentile (taller than 75% of males their same age). Many males with XYY syndrome are not overly muscular, particularly in the chest and shoulders. Individuals with XYY syndrome often have difficulties with their coordination. As a result, they can appear to be awkward or clumsy. During their teenage years, males with XYY syndrome may develop severe acne that may need to be treated by a dermatologist.

Men with XYY syndrome have normal, heterosexual function, and most are fertile. However, numerous case reports of men with XYY syndrome presenting with infertility have been reported. Most males with XYY syndrome have normal hormones involved in their sperm production. However, a minority of males with XYY syndrome may have increased amounts of some hormones involved in sperm production. This may result in infertility due to inadequate sperm production. The true incidence of infertility in males with XYY syndrome is unknown.

When XYY men make sperm, the extra Y chromosome is thought to be lost resulting in a normal number of sex chromosomes. As a result, men with XYY syndrome are not at an increased risk for fathering children with chromosome abnormalities. However, some men with XYY syndrome have been found to have more sperm with extra chromosomes than what is found in men without XYY syndrome. Whether these men have an increased risk of fathering a child with a chromosome abnormality is unknown.

Men with XYY syndrome usually have normal intelligence, but it can be slightly lower than their brothers and sisters. Approximately 50% of males with XYY syndrome have learning difficulties, usually in language and reading. Speech delay can be noticed in early school years. Males with XYY syndrome may not process information as quickly as their peers and may need additional time for learning.

Males with XYY syndrome have an increased risk of behavior problems. Hyperactivity and temper tantrums can occur more frequently than expected, especially during childhood. As males with XYY syndrome become older, they may have problems with impulse control and appear emotionally immature.

From a psychosocial standpoint, males with XYY syndrome may have low self-esteem due to mild learning disabilities and/or lack of athletic skills due to lack of coordination. Males with XYY syndrome are at risk in stressful environments and have a low ability to deal with frustration.

Men with XYY syndrome are not thought to be excessively aggressive or psychotic. However, because some men with XYY syndrome can have mild learning

KEY TERMS

Amniocentesis—A procedure performed at 16–18 weeks of pregnancy in which a needle is inserted through a woman's abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from the fluid can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

Cell—The smallest living units of the body which group together to form tissues and help the body perform specific functions.

Chorionic villus sampling (CVS)—A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the early embryo. These cells are then tested for chromosome abnormalities or other genetic diseases.

Chromosome—A microscopic thread-like structure found within each cell of the body and consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Embryo—The earliest stage of development of a human infant, usually used to refer to the first eight weeks of pregnancy. The term “fetus” is used from roughly the third month of pregnancy until delivery.

Hormone—A chemical messenger produced by the body that is involved in regulating specific bodily functions such as growth, development, and reproduction.

difficulties and/or have difficulty controlling behavior problems such as lack of impulse control, their actions may lead to criminal behavior if placed in the right environment. It is important to emphasize that this only occurs in a small percentage of men with XYY syndrome. Most men with XYY syndrome are productive members of society with no criminal behavior.

Diagnosis

Most individuals with XYY syndrome (or 47,XYY) go through their entire lives without being diagnosed with this condition. Chromosome studies can be done after birth on a skin or blood sample to confirm the condition.

QUESTIONS TO ASK YOUR DOCTOR

- When should my son be evaluated for a learning disability?
- Do you recommend physical, occupational, or speech therapy?
- Is genetic testing recommended, and on whom?
- What supportive stress-reducing measures should I implement at home?

This syndrome can also be diagnosed coincidentally when a pregnant mother undergoes prenatal testing for other reasons, such as being age 35 or older at the time of delivery. Prenatal tests that can determine whether or not an unborn baby will be affected with 47,XXY are the chorionic villus sampling and amniocentesis procedures. Both procedures are associated with potential risks of pregnancy loss and therefore are only offered to women who have an increased risk of having a baby born with a chromosome problem or some type of genetic condition.

Treatment and management

Treatment and management for most men with XYY syndrome is not indicated. However, early identification and intervention of learning disabilities and/or behavior difficulties is necessary. Speech therapy, physical therapy, and occupational therapy may be helpful for males with XYY syndrome. Also, because males with XYY syndrome are at risk in stressful environments, a supportive and stimulating home life is important.

Prognosis

Most males who have learning disabilities and/or behavior problems due to XYY syndrome have an excellent prognosis. Learning disabilities are mild, and most affected males learn how to control their impulsiveness and other behavior problems. XYY syndrome does not shorten lifespan.

Resources

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- García-Velasco, Juan, et al., eds. *Human Reproductive Genetics*. London: Academic Press, 2020.
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- Jones, Kenneth Lyons, et al., eds. *Smith's Recognizable Patterns of Human Malformation*. 8th ed. Philadelphia: Elsevier, 2021.

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- "47,XXY syndrome." MedlinePlus. <https://medlineplus.gov/genetics/condition/47xyy-syndrome/> (accessed June 27, 2021).
- "XYY Syndrome." NORD. <https://rarediseases.org/rare-diseases/xyy-syndrome/> (accessed June 27, 2021).

ORGANIZATIONS

- Chromosome Disorder Outreach, PO Box 724, Boca Raton, FL 33429, (561) 395-4252, info@chromodisorder.org, <http://www.chromodisorder.org>

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YY syndrome

Definition

The YY syndrome is an unusual disorder in the history of pathology. The underlying genetic condition and cause were discovered before any evidence of the syndrome was observed. YY syndrome was discovered through the study of the diversity in the chromosomes of the chromosome pair 46. While most males have an X and a Y chromosome, some were observed to have an extra Y chromosome. The question then arose: How does the presence of an extra chromosome influence the normal development of the affected male?

The differences that distinguish the YY male are subtle and are usually not seen before the age of ten. Many males grow up without even realizing that they have the YY condition. Most of those affected tend to be taller and thinner than age-related norms. There is some evidence of speech delay and learning disabilities. Although the YY male is more aggressive than average, there is no noticeable increase in behavioral problems.

Description

The YY syndrome is a very mild disorder; it is certainly not considered a disease. It is best to know as early as possible if a boy has it, because the mild learning disabilities and the slight language delay can be accommodated better at a young age. However, most boys realize they have the YY condition only after they have grown taller than their peers in late childhood. Many who have it never know they are YY susceptible.

In the usual fertilization of the egg, the father contributes a sperm with either an X chromosome which determines that the resulting zygote will be female or with a Y chromosome which determines that the resulting zygote will be male. For an unknown reason, in some cases, the Y chromosome in the sperm splits in two before fertilization. The resulting zygote is male with

KEY TERMS

Amniocentesis—A procedure that extracts fluid from the amniotic sac in order that the chromosomes of the fetus can be examined. This test can determine lung maturity and the possibilities of birth defects.

Chromosome—A threadlike linear strand of DNA and associated proteins in the nucleus of eukaryotic cells that carries the genes of an organism.

Fertile—Able to reproduce.

Insemination—The process by which sperm is placed into the female reproductive tract for the purpose of impregnation.

Zygote—The sperm and egg combined to form the initial cell when a new organism is produced by means of sexual reproduction.

two Y chromosomes instead of one. The age of either parent is inconsequential in contributing to this disorder. This condition is not considered to be inherited, as the fathers with YY syndrome do not have sons with YY in any greater frequency than the general population.

The studies documenting the severity of the symptoms constantly note how mild and close to average all of the distinctive differences are. The most notable condition is the tendency to grow very tall earlier than peers and the tendency to be thinner than peers. However, the final height and body weight are still within normal range. Most of these boys have a language delay but eventually catch up to peers. Most have a learning disability but also have normal measured intelligence. They tend to be more aggressive than other boys and like physical activities. However, most adapt to the classroom and behavioral problems are no greater than the normal population. As a group they are distinctive but as individuals few are abnormal.

When the condition was first discovered, there was the assumption that such boys would grow up to be infertile. However, longitudinal studies have concluded that as an adult, the YY male is no less fertile than the general population. However, the semen of a YY male is slightly weak because of the presence of more than average dead sperm.

While this is a very mild disorder, it is beneficial to discover its presence in a young boy. The earlier that it is detected contributes to the sooner that more serious conditions can be ruled out. Furthermore, with appropriate treatment, the boy can overcome the effects of the language delay and learning disability. If the boy is forewarned, he will not become apprehensive when the rapid growth takes place.

Genetic profile

The condition is caused by an unusual split in the Y chromosome of a pre-insemination human sperm that manages to fertilize a human egg. The resulting zygote evolves over nine months of gestation and is born as a male infant with two Y chromosomes instead of one.

Demographics

The prevalence rate in the United States is 12 per 10,000 male births, with the rate for those of African descent being slightly lower. Studies from Norway and Japan suggest similar rates. The condition only affects males.

Signs and symptoms

The symptoms as noted above include unusual height and thinness, language delay, learning disability, and aggressive physical activity. Measured intelligence is within normal limits. The cases of behavioral problems within this population of boys are also within normal limits.

Diagnosis

There are no signs of this disorder at birth. Therefore, there would be no observable sign of this disorder through a prenatal ultrasound. This disorder can be detected through a prenatal amniocentesis; however, analysis of amniotic fluid does not usually look for the signs of YY syndrome.

Most boys are diagnosed with this disorder as a result of parental concerns for language delay or excessive growth. Diagnosis can take place through noting evidence for all of the usual symptoms. However, confirmation of this diagnosis must be done through

QUESTIONS TO ASK YOUR DOCTOR

- How can we help our son have a normal life?
- How serious are the conditions?
- What should I watch for in a baby suspected of having the YY syndrome?
- How much should we accept or discourage his aggressive physical activity?
- What kind of problems might be associated with his excessive height?
- What will he need to understand when he wants to start a family?

testing blood samples for the presence of the YY chromosome.

The main test for recognizing chromosomal disorders is the fluorescence in-situ hybridization (FISH). This method of analyzing the structures of human genetics relies on fluorescent probes designed to link to specific genetic particles such as proteins, genes, or chromosomal material. If the correlating probe cannot link to the material for which it is designed, then the result is accepted as an absence of the material. In testing for YY syndrome, the probes specific to the Y chromosome would be injected into genetic material from the affected person. If examination of the probes detects two Y chromosomes, then the test confirms the person has the YY syndrome.

Treatment and management

There is no treatment to cure the YY syndrome. Because of the mildness of the condition, even treatment specific to the symptoms may not be necessary. The most immediate treatment for the boy with YY syndrome may be speech therapy to address the language delay. However, some of the affected boys have been shown to overcome the language problem eventually, without therapy. The boy may need special services in the school years to alleviate the learning disorder. Again, this may not be necessary. In one study, almost all boys who were identified early with YY syndrome responded well to preschool as their only treatment for learning disability.

It is important for parents and teachers to be understanding and supportive of the YY syndrome boy. Clear limits should be set regarding the aggression; however, those limits should be made in consideration of the boy's need for physical activity. The boy should be encouraged to take part in organized sports.

Prognosis

There is no evidence of lower life expectancies for the YY male. There are no increased threats; particularly, there is no increased susceptibility to disease. As noted above, many YY males go through life not even realizing their condition. As an adult, the YY male can expect to father children; the population tends to be within normal expectancies of fertility.

Resources

BOOKS

- García-Velasco, Juan, et al., eds. *Human Reproductive Genetics*. London: Academic Press, 2020.
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- "Y Chromosome Fact Sheet." NIH. <https://www.genome.gov/about-genomics/fact-sheets/Y-Chromosome-facts> (accessed June 27, 2021).

ORGANIZATIONS

- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://www.rarediseases.org>
- Unique: Understanding Chromosome Disorders. The Rare Chromosome Disorder Support Group, G1 The Stables, Station Road West, Oxted, Surrey UK RH8 9EE, +44 (0) 1883 723356, info@rarechromo.org, rarechromo@aol.com, <http://www.rarechromo.org/html/home.asp>

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Z

Zebrafish studies

Definition

Zebrafish studies are research papers and clinical reports based on genetic experiments with zebrafish (*Danio rerio*) in order to better understand and treat human diseases and disorders. Zebrafish are considered to be model animals for this purpose because they share 70% of their genome with humans and 82% of the genes known to cause disease in humans. In addition, because zebrafish are vertebrates, they have the same major organs as humans; they have eyes and mouths, brains, bones and spinal cords, intestines, livers, bile ducts, kidneys, hearts, ears, noses, muscles, blood, and teeth.

Description

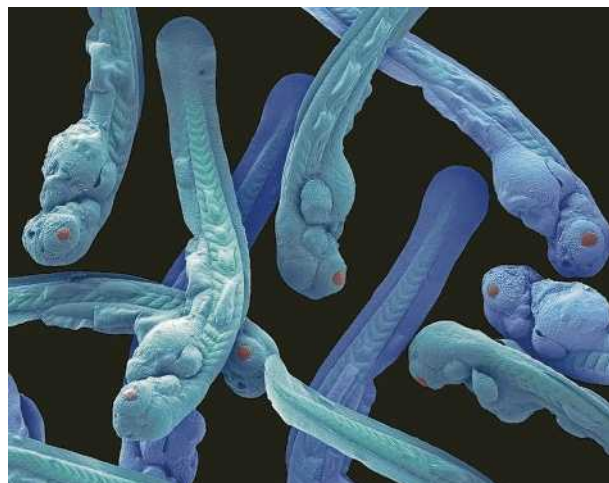
Zebrafish biology

Zebrafish are freshwater fishes belonging to the minnow or carp family (Cyprinidae) that are native to southern Asia. They were given their scientific name (*Danio rerio*) in 1822 by Francis Buchanan-Hamilton, a Scottish physician and zoologist who lived in India for many years. Zebrafish are plentiful in the wild; they live in slow-flowing shallow streams or stagnant fresh water in rice paddies or ponds. They can tolerate water as cold as 12.3 °C (54.1 °F) or as warm as 38.6 °C (101.5 °F). Because of their hardiness and adaptability, zebrafish are considered a species of least concern for risk of extinction by the International Union for Conservation of Nature (IUCN).

Zebrafish are small animals, averaging 1.8–3.7 cm (0.7–1.5 in) in length in the wild, although they can grow as long as 5 cm (2 in) in laboratory settings. Their name comes from the five uniform horizontal blue stripes on the side of the body. Male zebrafish have gold stripes between the blue ones and are shaped somewhat like a torpedo; females have silver stripes instead of gold and have larger bellies than the males. Zebrafish live about a

year in the wild, two to three years in captivity, and up to five years in a laboratory or specialized aquarium.

Zebrafish have a generation time of three months, which means that they can produce four consecutive generations of fish within a year. They reproduce by spawning, in which the adults release eggs and sperm into the water, which is where fertilization occurs. There must be a male zebrafish present for the female to ovulate (produce eggs). Unlike most fish species, zebrafish spawn around daybreak, which makes it easier for researchers to collect the embryos. Female zebrafish can lay a clutch of hundreds of eggs every two or three days. When fertilization occurs, the eggs become transparent, which is one reason why zebrafish are popular with researchers. The embryos develop very rapidly, compared to most mammals; after three hours, the embryo already contains



Colored scanning electron micrograph (SEM) of newly hatched zebrafish. These fish are used to study embryonic development. The eyes (red) can be seen in the heads. Zebrafish eggs develop rapidly (2-4 days), are transparent, and they develop outside the mother's body, allowing observation of the differentiation of the cells into different body organs. Zebrafish live in fresh water and are found in India. (Steve Gschmeissner/Science Source)

thousands of cells. The fish's head and tail begin to form 16 hours after fertilization, and the tail separates from the body by 24 hours. The zebrafish is sexually mature at three months of age.

History of zebrafish research

Zebrafish were brought to Europe and North America along with other subtropical fish species in the 1850s, when families as well as scientists began to keep small freshwater fish in aquariums as pets as well as for study. In the United States, zebrafish were accidentally released into the wild in Connecticut, New Mexico, Florida, and California. As the fish multiplied in their new habitats, they became popular with aquarium hobbyists, particularly with inexperienced fish keepers. Zebrafish were and still are inexpensive additions to a home aquarium; as of 2021 they cost between \$1.89 and \$2.10 each in most American pet stores.

Scientific research using zebrafish began with George Streisinger (1927–1984), a molecular biologist at the University of Oregon who became interested in the fish after purchasing some from a local pet store in Eugene. Streisinger was the first scientist to clone a vertebrate, and the zebrafish was the vertebrate he chose to clone; he described his procedure in a 1981 article published in *Nature*. Much of Streisinger's research into genetic engineering in zebrafish was not published until after his death. His last paper, on the use of ultraviolet light to induce mutations in zebrafish, appeared in *Genetical Research* in 1992. Streisinger was, however, almost singlehandedly responsible for the explosion of interest in zebrafish as model animals in the 1980s and following. Many well-known researchers in the field studied under him at the University of Oregon; subsequently, the number of journal articles on zebrafish listed by the National Library of Medicine rose from four per year in 1980 to 48 in 1990; 657 in 2000; 1,895 in 2010; and 4,383 in 2020. A peer-reviewed journal titled *Zebrafish* began publication in 2004 and is still actively seeking contributors as of 2021.

In addition to Streisinger's leadership, it was the technological changes in the fields of gene editing and next-generation sequencing that led to the establishment and funding of the zebrafish laboratories and research cores spread across the United States. The Zebrafish Information Network (ZFIN) was started after a meeting at Cold Spring Harbor in 1994 to establish an online database of information about zebrafish as a model organism. Scientists at the National Human Genome Research Institute (NHGRI) successfully created transgenic zebrafish using genetically modified sperm in 2004. The Zebrafish Core at NHGRI was started in 2006, as was the Zebrafish International Resource Center (ZIRC) at the University of

Oregon. Sequencing of the zebrafish genome began in 2001; the complete genome was published in 2013. There are about 1.5 billion base pairs in the zebrafish genome, spread over 25 chromosomes. By contrast, the human genome contains over three billion base pairs.

In 2015, researchers at NHGRI developed transgenic zebrafish that can be used as animal models of melanoma, leukemia, and pancreatic cancer. In 2014, the NIH began to fund the Undiagnosed Diseases Network (UDN), a consortium of clinical sites, a central biorepository, and animal research centers. One of the network's two Model Organism Screening Centers (MOSCs) is located at the University of Oregon and focuses on zebrafish research. In 2016, ZFIN joined together with five other model organism databases to form the Alliance of Genome Resources.

Purpose

As of 2021, zebrafish are most intensively researched as model organisms for gaining a better understanding of a wide range of disorders in humans and some possible pharmacological treatments for those disorders. The small size of these fish, their speed of reproduction, the high numbers and transparency of their embryos, and their preference for living in groups (shoaling) make it much easier and less expensive to store zebrafish in a laboratory than an equivalent number of mice. In addition, zebrafish eggs are fertilized outside the female's body, which makes their embryos much easier to manipulate genetically than mouse embryos. Zebrafish eggs can be fertilized in vitro (in a laboratory container), and the fertilized eggs can be injected with DNA or RNA to permanently alter their genetic makeup. The genetically engineered embryos can then be allowed to mature, reproduce, and generate a new line of zebrafish.

As of 2021, the most recent technology used to edit the zebrafish genome is CRISPR/Cas9, a molecular technique that involves the introduction of Cas9, a nuclease (specialized enzyme) attached to a synthetic guide RNA (gRNA) into a cell in a living organism. The Cas9 can be directed to cut the genome at a specific spot and remove, add, or replace the DNA at the location of the cut. The CRISPR/Cas9 technique was introduced in 2009; it is less expensive, more accurate, and easier to use than older genome editing methods. It can also target several genes at the same time. Most zebrafish researchers now use CRISPR/Cas9.

The zebrafish genome can be edited to produce transgenic zebrafish, whose DNA has been altered by the introduction of DNA from another species, including human DNA. Transgenic zebrafish can be used to model certain human diseases. Genome editing can also be used

KEY TERMS

Animal disease model—A living nonhuman animal used during the research and investigation of human disease. The animal model may or may not be genetically engineered.

Base pair (bp)—Any of the complementary nucleotide bases (adenine-thymine and cytosine-guanine in DNA; adenine-uracil and cytosine-guanine in RNA) held together by weak hydrogen bonds. Base pairs form links between the two strands of DNA.

Clustered regularly interspersed short palindromic repeats (CRISPR)—A technique for genome editing that involves creating a short RNA sequence called guide RNA (gRNA) that matches a targeted sequence of DNA in the organism's genome. The gRNA guides an enzyme called Cas9 to the target DNA sequence. The enzyme cuts the genome at this location, and the researcher can either remove DNA, add new DNA, or modify the DNA.

Clutch—The name for a group of eggs laid by zebrafish, other fish, amphibians, or birds.

Generation time—The average length of time elapsed between two consecutive generations in an animal population. The generation time for zebrafish is about three months.

Genome—The total amount of genetic information within an organism's chromosomes, including its genes and DNA sequences.

Genome editing—A type of genetic engineering in which DNA can be inserted, changed, deleted, or replaced within the genome of a living organism.

Knock-in—Referring to an organism that has been genetically engineered to alter a specific genetic locus by a one-for-one substitution of DNA sequence information or by the addition of DNA sequence information that is not found on the genetic locus in question.

Knockout—Referring to an organism that has been genetically engineered to lack one or more specific genes.

Mendelian disease—A disease caused by a single mutated gene; also called a single-gene disease.

Model organism—A nonhuman species (which may be a plant, animal, or bacterium) that is studied to

yield understanding of particular biological events or processes in the expectation that discoveries made in the model organism can be applied to other species.

Monogenic disease—Another term for a single-gene disorder.

Next-generation sequencing—A general term for massively parallel sequencing of large portions of DNA base pairs, performed by first fragmenting the DNA, reading the individual fragments in parallel, and then reassembling the reads to obtain the sequence of the entire genome.

Nuclease—A type of enzyme responsible for breaking the chemical bonds between the subunits (nucleotides) that make up DNA and RNA. A specific nuclease called Cas9 is used in CRISPR genome editing technology.

Oncogene—A gene that has the potential to cause cancer.

Phenotype—The set of externally observable characteristics or traits of an organism.

Poikilotherm—A term applied to any animal that cannot regulate its core body temperature and has a body temperature that varies with its surroundings. The opposite is a homeotherm, which refers to an organism (including humans) that can maintain a warm and fairly constant body temperature independent of the surrounding temperature.

Spawning—The process of releasing both eggs and sperm into water by fish and other aquatic animals.

Transgenic—Referring to an organism in which one or more sequences of DNA from another species have been introduced by artificial means. Animals are typically made transgenic by having a small segment of the other species' DNA injected into an egg or developing embryo.

Vertebrate—Any animal with a segmented spinal column and a distinct head. Vertebrates include fishes, amphibians, reptiles, birds, and mammals.

Wild type (WT)—The typical phenotype of a species as it exists in nature, without any genome editing.

to produce so-called knockout zebrafish, in which one or more specific genes have been removed from the genome. This is done in the zebrafish to determine whether loss of that gene's function causes the same

symptoms as those observed in the human patient. The opposite is knock-in genome editing, in which additional DNA sequences are inserted into the genome. Knock-in engineering is more complicated than its knockout

counterpart, but it is thought to be more promising in using zebrafish to understand human disorders.

Known disorders

There are a number of known human diseases and disorders affecting the organs and body systems that humans share with zebrafish that are under investigation:

- **Cancer.** Since 2011, mutated zebrafish have been used to study leukemia, melanoma, liver cancer, and pancreatic cancer. Zebrafish with mutated forms of the *BRAF* and *NRAS* oncogenes will develop melanoma. Zebrafish have also been used to study cancer predisposition genes (CPGs), which are genes whose mutations increase an individual's risk of developing cancer in later life. Mutated zebrafish have been used to study the genes associated with Li-Fraumeni syndrome, familial adenomatous polyposis, Peutz-Jeghers syndrome, and Cowden syndrome.
- **Developmental disorders.** Zebrafish can be used to study the role of genes in the development of the brain and nervous system. For example, researchers have discovered the gene (*ZC4H2*) responsible for an X-linked disorder known as Miles-Carpenter syndrome by working with zebrafish models. Knockout zebrafish lacking the *PHF21A* gene have been used to study Potocki-Shaffer syndrome, a microdeletion syndrome characterized by intellectual disability, defects in the bones that form the skull, vision disorders, and abnormal facial features.
- **Mental disorders.** Zebrafish subjected to inbreeding, coupled with environmental stress, develop a form of depression comparable to human depression. Inbred male zebrafish have fewer offspring, and the embryos have a high mortality rate.
- **Disorders of blood formation (hematopoiesis) and the circulatory system.** The transparency of zebrafish embryos allows researchers to observe the formation of blood cells and their circulation in the fish's body. In addition, the discovery that zebrafish can regenerate heart muscle tissue after injury offers promise for developing treatments for human heart disease.
- **Eye disorders.** Researchers at the National Eye Institute (NEI) are studying support cells in the zebrafish's eye that start multiplying in response to damage to the retina, the light-sensitive tissue at the back of the eye. A detailed understanding of this repair process may offer clues to repairing retinal damage in the human eye.
- **Immune system disorders.** The close similarities between the zebrafish and human immune systems, as well as the transparency of zebrafish embryos, assist researchers in imaging the interactions that occur between zebrafish bodies and a wide range of viruses, bacteria, and parasites. One specific disease that has been extensively studied in

QUESTIONS TO ASK YOUR DOCTOR

- What is your opinion of zebrafish studies? Do you think they will continue to contribute to scientific understanding of human disorders?
- Which human disease or body system do you think is best suited to zebrafish studies?
- Do you think that zebrafish will be useful in identifying diseases that are currently undiagnosed?

zebrafish is tuberculosis; another is influenza. Zebrafish can be used to analyze the effectiveness of various anti-infective drugs as well as the effectiveness of the innate immune system in fending off infections.

- **Musculoskeletal disorders.** Zebrafish are frequently used to study muscular dystrophies, a group of disorders characterized by muscle wasting, abnormal contractions of the muscles, and general weakness. Because zebrafish embryos readily absorb chemicals, they are a model organism for analyzing the effectiveness of possible drug therapies for the muscular dystrophies.

Unknown diseases

In addition to their versatility in studying known genetic syndromes, infectious diseases, and developmental disorders, zebrafish are being used to identify genes responsible for rare disorders. Of the 20,000 genes in the human genome, only about 4,000 have been linked to monogenic (single-gene or Mendelian) disorders or rare diseases. It is estimated that there may be as many as 6,000 additional genes remaining to be identified for Mendelian disorders and rare diseases. While a specific rare disease may affect only a few hundred people in the general American population, there are at least 25 million Americans coping with these diseases as of 2021, according to the CDC.

As noted above, the NIH established and began to fund the Undiagnosed Diseases Network (UDN) in 2014. The network includes two Model Organism Screening Centers or MOSCs, one of which contains a zebrafish core. The zebrafish core identified 16 candidate genes for unknown diseases during Phase I of the NIH funding. To date, almost 5,000 Americans with rare disorders have applied to be study participants, and 470 have received diagnoses of their diseases.

The Zebrafish International Research Center (ZIRC) at the University of Oregon makes mutant and transgenic strains of zebrafish available to qualified scientists in

other institutions. These fish are much more expensive than their pet shop counterparts; ZIRC currently charges \$20 for a pair of wild-type zebrafish, and \$200 for a pair of mutant or transgenic zebrafish. Mutant or transgenic embryos cost \$125 for a set of 100. These are the prices charged to academic institutions; the prices are doubled for commercial buyers.

Limitations

In spite of the widespread use of zebrafish as model animals, there are limitations on the research that can be done with them. To begin with, about 18% of the genes known to cause diseases in humans do not exist in zebrafish. Another limitation is that zebrafish cannot be used to model tissues or body parts in humans that zebrafish lack, such as external genitalia, mammary glands, lungs, and the prostate gland. In regard to mental and behavioral disorders, the human brain is far more complex than the zebrafish's brain.

Still another limitation of zebrafish as model animals is that they are not mammals; they are poikilotherms, which means that they must adapt to a wider variety of external temperatures, because they cannot regulate their internal body temperatures as mammals do. This factor means that zebrafish metabolize drugs at a different rate and possibly in a different manner than mammals do, which complicates evaluating the findings of drug studies in zebrafish. In humans, the presence of a placenta moderates the effects of drugs on a human fetus before birth, whereas zebrafish embryos absorb drugs directly from the surrounding water without any modification by the mother's metabolism.

Clinical trials

There are seven clinical trials that involve the use of zebrafish registered with the NIH as of mid-2021. One study is based on the findings of zebrafish studies of trifluoperazine as a possible treatment for a rare genetic blood disorder called Diamond Blackfan anemia or DBA. Another study used zebrafish to study the ability of human leukemia cells to survive in zebrafish embryos and evaluate the effectiveness of newer anticancer drugs. A third clinical trial being conducted in Italy will use zebrafish embryos transplanted with cancer cells from patients with liver, pancreatic, stomach, colorectal, esophageal, and gall bladder cancer to predict the chemotherapy regimen best suited to each patient.

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ORGANIZATIONS

Alliance of Genome Resources, help@alliancegenome.org,
<https://www.alliancegenome.org>

American College of Laboratory Animal Medicine (ACLAM),
c/o Dr. Melvin W. Balk, 96 Chester Street, Chester, NH
03036, (603) 887-2467, (603) 887-0096, mel.balk@aclam.org, <https://www.aclam.org>

National Center for Biotechnology Information (NCBI), U.S.
National Library of Medicine, 8600 Rockville Pike,
Bethesda, MD 20894, [no telephone number given], <https://www.ncbi.nlm.nih.gov/home/about/contact/>, <https://www.ncbi.nlm.nih.gov/>

National Human Genome Research Institute (NHGRI), Building
31, Room 4B09, 31 Center Drive, MSC 2152, 9000
Rockville Pike, Bethesda, MD 20892-2152, (301)
402-0911, <https://www.genome.gov/about-nhgri/Contact>,
<https://www.genome.gov/>

NICHD Zebrafish Core, Building 6, Room B140, 6 Center
Drive, Bethesda, MD 20892-2759, (301) 435-5556,
bfeldman@mail.nih.gov, <https://www.nichd.nih.gov/about/org/dir/other-facilities/cores/zebrafish>

Undiagnosed Diseases Network (UDN) Coordinating Center, c/
o Department of Biomedical Informatics, 10 Shattuck
Street, Suite 514, Boston, MA 02115, (844) 746-4836,
UDN@hms.harvard.edu, <https://undiagnosed.hms.harvard.edu/>

Zebrafish Information Network (ZFIN), 5291 University of
Oregon, Eugene, OR 97403-5291, [no telephone number
given], zfinadmin@zfin.org, <http://zfin.org>

Zebrafish International Resource Center (ZIRC), 5274 Univer-
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Rebecca J. Frey, PhD

Zellweger spectrum

Definition

Zellweger spectrum is a group of inherited disorders characterized by the reduction or absence of structures within the cell called peroxisomes, and by the accumulation of various unmetabolized substances in the blood and bodily tissues. Peroxisomes are a type of organelle or structure within the cell. They produce more than 80 different enzymes that are essential for cells to break down waste and remove it from the cell. When there are too few peroxisomes in a cell, waste products and other toxins build up and eventually kill the cell. When enough cells die, the tissue in which they live dies.

The disorder arises in infancy and results in visual and hearing impairments, decreased muscle tone, poor growth, intellectual disability, decreased coordination, liver damage, and abnormal development of facial



Sixteen-month-old Adrian Alfaro (left) looks up at his father, Jose. Adrian has Zellweger syndrome, a disease that stunts muscle development and takes away mobility. (Modesto Bee/Getty Images)

structures. There is no cure for the disorder, and treatment is limited to the relief of symptoms.

Description

Living bodies are made of millions of individual cells specifically adapted to carry out particular functions. Within cells are even smaller structures, called organelles, which perform different jobs and enable the cell to serve its ultimate purpose. One type of organelle is the peroxisome, whose function is to break down waste materials or to process materials that, if allowed to accumulate, would prove toxic to the cells.

Peroxisomes break down various materials through the use of enzymes (proteins that assist in biochemical reactions), and 80 different peroxisomal enzymes have been identified. These enzymes are made by the cell and transported into the peroxisome by a complex process, requiring at least 15 other proteins. In some cases, an absence or deficiency of these proteins results in a failure to transport enzymes into peroxisomes, leaving the cell unable to metabolize various substances. These substances build up in the blood stream and deposit in various tissues, causing damage.

Zellweger spectrum results from an abnormality in the transport of enzymes into the peroxisome, manifesting as absent or reduced functioning peroxisomes. As a consequence of peroxisome deficiency, various substances accumulate in the bloodstream, including phytanic acid, pipecolic acid, hydroxycholestanic acids, glyoxylate, and substances called very-long-chain fatty acids (VLCFA). Mutations in at least two different genes that encode proteins that participate in the transport of enzymes to the peroxisome have been identified in Zellweger spectrum.

Zellweger spectrum disorder is a group of conditions that affect many parts of the body and have similar signs and symptoms. The Zellweger spectrum includes Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD). These conditions were once thought to be distinct disorders but are now considered to be part of the same condition spectrum. Zellweger syndrome is the most severe form of the Zellweger spectrum disorder, NALD is intermediate in severity, and IRD is the least severe form.

The most severe form of Zellweger spectrum is Zellweger syndrome. Signs and symptoms of the condition develop during the newborn period and include weak muscle tone (hypotonia), feeding problems, hearing and vision impairment, and seizures. These problems are caused when a substance called myelin, the protective covering of nerves that promotes transmission of nerve impulses, is broken down. Destruction of myelin (demyelination) leads to loss of white matter, the part of the brain that contains the most myelin. Other symptoms of Zellweger syndrome include lethal problems in the liver, heart, and kidneys, and skeletal abnormalities, including a large space between the bones of the skull (fontanel) and characteristic bone spots known as chondrodysplasia punctata that can be seen on x-ray. Affected individuals have distinctive facial features, including a flattened face, broad nasal bridge, and high forehead. Children with Zellweger syndrome typically do not survive beyond the first year of life.

Neonatal adrenoleukodystrophy (NALD) is a moderate form of Zellweger spectrum. Individuals with this disorder have abnormalities of the adrenal glands, the white matter of the brain, and the testes. Symptoms of this disorder include seizures, hyperactivity, strabismus (crossed eyes), paralysis, hearing loss, and muscular weakness.

IRD is the least severe of the Zellweger spectrum disorders. The disorder arises in infancy and results in visual and hearing impairments, decreased muscle tone, poor growth, intellectual disability, decreased coordination, liver damage, and abnormal development of facial structures. There is no cure for the disorder, and treatment is limited to the relief of symptoms.

Genetic profile

Zellweger spectrum is a genetic condition and is inherited or passed on in a family. The genetic abnormality for the disorder is inherited as an autosomal recessive trait, meaning that two mutant genes are needed to display the disease. A person who carries one mutant gene does not display the disease and is called a carrier. A carrier has a 50% chance of transmitting the gene to their

children. A child must inherit the same abnormal gene from each parent to display the disease.

There are at least 12 known genetic mutations that cause the Zellweger spectrum disorders. These mutations alter production of a protein called peroxin that is essential to the production of peroxisomes, the organelles responsible for removing waste and toxins from the cell. When peroxisomes are not produced normally, the symptoms of Zellweger spectrum arise.

Mutations in the *PEX1* gene are responsible for most cases of Zellweger spectrum and are found in 70% of people who have this disorder.

Demographics

The combined incidence of all Zellweger spectrum disorders is estimated to be approximately 1 in 50,000. It is unclear whether these disorders are distributed equally among different geographical areas and ethnic groups.

Signs and symptoms

Symptoms associated with Zellweger spectrum arise at birth or very early infancy and affect many different organ systems and tissues, resulting in severe disease. Babies with Zellweger spectrum show decreased muscle tone and a failure to grow at appropriate rates. Characteristic facial features are often present, including prominent forehead and folds at the inner aspect of the eye, flat face and bridge of the nose, and low-set ears. While affected children are able to walk, the gait may be irregular due to abnormalities in muscle coordination.

High levels of unmetabolized substances can deposit in the fatty sheaths surrounding nerves, causing damage and resulting in peripheral neuropathy. "Peripheral neuropathy" is the term for dysfunction of the nerves outside of the spinal cord, causing loss of sensation, muscle weakness, pain, and loss of reflexes. Nerves leading to the ears can be affected, resulting in hearing loss or deafness. IRD also results in cerebellar ataxia, an abnormality in a specific part of the brain (the cerebellum), resulting in loss of coordination and unsteadiness. People with Zellweger syndrome have extensive impairments in cognitive function resulting in severe intellectual disability.

Zellweger spectrum often affects the eyes, causing retinitis pigmentosa, a degeneration of the retina resulting in poor nighttime vision, followed by loss of peripheral vision and eventually loss of central vision late in the course of the disease. Nystagmus (uncontrollable movements of the eye) may also be present due to related nervous system damage. Other manifestations of Zellweger spectrum include enlargement of the liver, poor digestion,

and abnormally low blood cholesterol. Early osteoporosis (decalcifications of the bone) may also develop, leading to bone fractures or compression of the spinal bones.

Diagnosis

Zellweger spectrum is diagnosed through a combination of consistent medical history, physical exam findings, and laboratory and genetic testing. Typically, parents bring newborns to their physicians because of the signs of low muscle tone. Other times, the characteristic facial abnormalities or a failure to grow at appropriate rates is noted. These findings raise suspicion for a genetic syndrome or metabolic disorder, and further tests are conducted.

Laboratory tests reveal several abnormalities. Blood samples from patients with Zellweger spectrum show accumulation of various substances including phytanic acid, pipecolic acid, hydroxycholestanic acids, glyoxylate, and VLCFA. Other measurements demonstrate low levels of plasmalogen, a substance normally produced by action of the peroxisomal enzymes. Immunoblot tests that measure levels of specific proteins will show deficiencies in many peroxisomal enzymes. Additional studies will reveal abnormal electrical responses from the retina and various nerve groups.

Finally, genetic testing can be performed. When a diagnosis of Zellweger spectrum is made in a child, genetic testing of the *PEX1* gene can be offered to determine if a specific gene change can be identified. If a specific change is identified, carrier testing can be offered to relatives. In families where the parents have been identified to be carriers of the abnormal gene, diagnosis of Zellweger spectrum before birth is possible. Prenatal diagnosis is performed on cells obtained by amniocentesis (withdrawal of the fluid surrounding a fetus in the womb using a needle) at about 16–18 weeks of pregnancy or by chorionic villus sampling (CVS) where cells are obtained from the chorionic villi (a part of the placenta) at 10–12 weeks of pregnancy.

Treatment and management

There is no cure or standard course of treatment for Zellweger spectrum. Currently, treatment of patients has generally involved only supportive care and symptomatic therapy. Several studies suggest that a diet that is free of phytanic acid can limit symptoms of Zellweger spectrum. A useful adjunct to dietary treatment is plasmapheresis. Plasmapheresis is a procedure by which determined amounts of plasma (the fluid component of blood that contains the unmetabolized substances) is removed from the blood and replaced with fluids or plasma that are free of accumulated substances. While treatment strategies

KEY TERMS

Autosomal recessive—A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

Carrier—A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

Cerebellar ataxia—Unsteadiness and lack of coordination caused by a progressive degeneration of the part of the brain known as the cerebellum.

Enzyme—A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

Mutant—A change in the genetic material that may alter a trait or characteristic of an individual or manifest as disease.

Organelle—Small, sub-cellular structures that carry out different functions necessary for cellular survival and proper cellular functioning.

Peripheral neuropathy—Any disease of the nerves outside of the spinal cord, usually resulting in weakness and/or numbness.

Peroxisome—A cellular organelle containing different enzymes responsible for the breakdown of waste or other products.

Retinitis pigmentosa—Progressive deterioration of the retina, often leading to vision loss and blindness.

may mitigate some of the symptoms experienced by the patient with Zellweger spectrum, they do not slow the progression of the disorder.

Experimental studies are underway to investigate whether several different agents can be of additional use. Patients with Zellweger spectrum have reduced levels of docosahexaenoic acid and arachidonic acid that can be corrected with the administration of oral supplements. There are some reports of improvement in symptoms with these therapies, and trials to formally investigate these claims are now in progress. Other scientific laboratories are investigating the usefulness of agents that stabilize peroxisomes in the treatment of Zellweger spectrum, but the experiments are still in their early stages.

Patients with Zellweger spectrum should be seen regularly by a multidisciplinary team of health care providers, including a pediatrician, neurologist, ophthalmologist, cardiologist, medical geneticist specializing in metabolic disease, nutritionist, and physical/occupational therapist. Genetic

QUESTIONS TO ASK YOUR DOCTOR

- What are the most common symptoms of Zellweger spectrum?
- What changes in the body are responsible for these symptoms?
- What treatments are recommended for this disorder?
- Are there organizations that provide support and information for families with a child affected by Zellweger spectrum?

counseling can help people with Zellweger spectrum, those who are carriers of the abnormal gene, or those who have a relative with the disorder, learn more about the disease, inheritance, testing, and options available to them so they can make informed decisions appropriate to their families.

Prognosis

For patients with Zellweger spectrum, some success has been achieved with multidisciplinary early intervention, including physical and occupational therapy, hearing aids, alternative communication, nutrition, and support for the parents. Although most patients with Zellweger syndrome continue to function in the profoundly or severely intellectually disabled range, some make significant gains in self-help skills, and a small percentage may reach stable condition in their teens. Despite these few successes, the prognosis for individuals with Zellweger spectrum and NALD is poor, with death generally occurring by six months of age. For individuals with IRD, death generally occurs before the second decade of life.

Resources

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ORGANIZATIONS

United Leukodystrophy Foundation, 224 N. 2nd St., Suite 2, DeKalb, IL 60115, (815) 748-3211 or (800) 728-5483, (815) 748-0844, office@ulf.org, <http://www.ulf.org>

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Zimmermann-Laband syndrome

Definition

Zimmermann-Laband syndrome (ZLS) is a rare genetic disorder characterized by dysmorphic abnormalities of the face and oral cavity, and malformations of the hands and feet. It is named for the German anatomist Karl Wilhelm Zimmermann (1861–1935), who identified the first two cases in 1928, and P. F. Laband, an American dentist and oral surgeon who published a case series in 1964. Alternate names for the disorder include Laband syndrome; gingival fibromatosis with abnormal fingers, nails, nose, and ears, and splenomegaly; and gingival fibromatosis, hepatosplenomegaly, and other anomalies.

Description

At the time of birth, infants with ZLS have abnormally long phalanges (the bones in the fingers and toes), and deformed or absent fingernails and toenails (anonychia). Other signs and symptoms of the disorder do not appear until later childhood, particularly gingival fibromatosis. This is a condition in which the gums become unusually large and overgrown, often preventing the eruption of the permanent teeth. Some children with ZLS will also start to show signs of intellectual disability.

Other changes that take place as the child matures into puberty include abnormal flexibility (hyperextension) in the joints of the fingers and toes; coarsening of the facial features, especially the ears and nose; hypertrichosis (excessive amounts of body hair); abnormalities of the skeleton and spine; and hepatomegaly (enlargement of the liver) or splenomegaly (enlargement of the spleen).

Genetic profile

The genetic profile of ZLS has been a subject of controversy since the early 2000s both in terms of the causative

KEY TERMS

Anonychia—The absence of fingernails and toenails.

Dysmorphic—Referring to a malformed or misshapen body part.

Genetic heterogeneity—The production of apparently identical genetic disorders by different genetic mechanisms or by different genes at different positions on the chromosomes.

Gingival—Pertaining to the gums. Gingival fibromatosis refers to an overgrowth of the tissue of the gums.

Hepatomegaly—Enlargement of the liver.

Hyperextension—The movement or extension of joints, bones, or muscles beyond the normal range of motion.

Hypertrichosis—An abnormal amount of hair growth over the body. It may be generalized over the entire body or localized to certain areas of the body.

Macrotia—Abnormally large ears.

Malocclusion—Misalignment or incorrect relation between the teeth in the upper and lower jaws as the jaws close.

Organelle—A specialized subunit within a cell.

Phalanges (singular, phalanx)—The bones that make up the fingers of the hand and the toes of the foot. There are 56 phalanges in the human body.

Philtrum—The vertical groove in the center of the upper lip.

Scoliosis—Abnormal curvature of the spine, usually defined as greater than 10 degrees to the right or left as the doctor faces the patient.

Splenomegaly—Enlargement of the spleen.

Xerostomia—The medical term for dry mouth. It is most often a side effect of medications but is also found in some genetic syndromes.

gene and its pattern of inheritance. In 2003, a team of Bulgarian researchers suggested that the gene that causes ZLS is located on either chromosome 3 or chromosome 8. In 2007, a group of researchers in Boston identified a position for the ZLS gene on the short arm of chromosome 3 at 3p14.3, but did not name a specific candidate gene.

Most recently, an international group of researchers based in Europe and Australia reported that mutations

in two genes, *KCNH1* and *ATP6V1B2*, are responsible for Zimmermann-Laband syndrome. *KCNH1* is located on the long arm of chromosome 1 at 1q32.2. The *KCNH1* gene has been linked to Temple-Baraitser syndrome, another rare genetic disorder characterized by absent or malformed nails, intellectual disability, and various deformities of the facial features. Mutations in this gene accounted for a large proportion of the cases of ZLS that the researchers studied. The *ATP6V1B2* gene codes for a protein that governs the acidity of the organelles within cells. It has been linked to several syndromes characterized by deafness, malformations of the skeleton, and intellectual disability. The *ATP6V1B2* gene is located on the short arm of chromosome 8 at 8p21.3. Mutations in this gene were responsible for two cases of ZLS. The researchers concluded that ZLS is a genetically heterogeneous disorder; that is, a single genetic disorder that can be caused by different genetic mechanisms or by different genes at different locations on the chromosomes.

Genetic heterogeneity also accounts for disagreements among geneticists as to the inheritance pattern of ZLS. While some maintain that ZLS is inherited in an autosomal dominant pattern, others have reported cases of ZLS that indicate an autosomal recessive pattern of inheritance. It is possible that the genetic mutations identified as causing ZLS as of 2015 follow different inheritance patterns, but further research is needed to confirm this possibility.

Demographics

ZLS is a very rare disorder, with only 44 cases worldwide reported between 1928 and 2011. An additional four cases were identified between 2011 and 2015. The syndrome affects males and females in equal numbers.

It was thought at first that ZLS was largely limited to people of East Indian origin living in either India or the Caribbean, but additional cases have been reported in families of European and Japanese origin. Although the disorder is very rare, it seems likely that all racial and ethnic groups are affected.

Signs and symptoms

The signs and symptoms of Zimmermann-Laband syndrome vary somewhat in severity from patient to patient; in addition, some patients diagnosed with the syndrome have additional physical abnormalities.

The signs and symptoms typical of ZLS are as follows:

- **Mouth and gums:** Gingival fibromatosis severe enough to interfere with chewing as well as the eruption of the child's permanent teeth; recurrent gum infections;

QUESTIONS TO ASK YOUR DOCTOR

- Does my child have ZLS?
- If so, on what do you base the diagnosis?
- Should we consider genetic testing to confirm the diagnosis?
- Will my child require special education as well as specialized dental treatment?
- How can I help my child cope with the social complications caused by his or her unusual facial features?

failure of teeth to close properly (malocclusion); drooling; speech problems; sores at the corner of the mouth; premature loss of teeth; and dry mouth (xerostomia). In some cases the gums may become overgrown to the point of covering the teeth completely and protruding from the child's mouth.

- **Facial features:** Abnormally narrow face; unusually large and soft ears (macrotia) with long earlobes; large lips and unusually wide mouth; enlarged nose with a bulbous tip; abnormally large philtrum (the groove in the middle of the upper lip).
- **Skin:** Hypertrichosis, which may appear over most of the body or only on limited areas of skin. The body hair in patients with ZLS is typically long, soft, and downy.
- **Hands and feet:** Abnormally long phalanges in the fingers and toes, with large swellings at the tips of the fingers and toes. The joints are often unusually flexible (hyperextensive), and the nails are either malformed or absent.
- **Spine and skeleton:** Scoliosis (sideways curvature of the spine) occurs in about half of patients with ZLS. Other abnormalities include misshapen vertebrae, abnormally shaped ribs, and poor muscle tone.
- **Nervous system:** About half of children with ZLS display moderate to severe intellectual disability. The disorder also carries an increased risk of epilepsy in later childhood.
- **Internal organs:** About half of patients with ZLS have an enlarged spleen (splenomegaly) and enlarged liver (hepatomegaly).

Other symptoms that have been reported in some patients with ZLS include:

- Vision disorders, including extreme nearsightedness, cataracts, and cross eyes (strabismus).

- Abnormalities in the structure of the heart, including unusually thick walls in the lower chambers of the heart (ventricular hypertrophy); dilated cardiomyopathy, a condition in which the heart becomes enlarged and cannot pump blood efficiently; and an abnormally dilated aortic arch.
- Kidney stones.
- Hearing loss.
- In males, an unusually long penis.

Diagnosis

As of 2015, the diagnosis of ZLS was based on observation of the infant's hands and feet at birth, and on the identification of gingival fibromatosis, characteristic facial features, hypertrichosis, intellectual disability, and skeletal abnormalities as the child grows older. Molecular genetic testing has become available only recently due to delayed discovery of the genes responsible for the syndrome. As of mid-2015, there was one laboratory in Quebec offering sequence analysis of the entire coding region of the *ATP6V1B2* gene; there were no laboratories offering tests of the *KCNH1* gene.

Treatment and management

There is no cure for Zimmermann-Laband syndrome, but early diagnosis and treatment are critical to lower the risk of later complications. Treatment is symptomatic. Gingival fibromatosis usually requires specialized treatment by a team of pediatric dentists, oral surgeons, and orthodontists to prevent the development of malocclusion, speech difficulties, drooling, and premature loss of teeth associated with gum overgrowth. In some cases the excess gum tissue may require repeated surgeries, as the symptom returns in about 20% of cases. Speech therapy is often needed if the fibromatosis has not been corrected at an early stage.

Hypertrichosis associated with ZLS and other genetic syndromes cannot be cured but must be treated by various cosmetic methods of hair removal. These may include shaving, waxing, electrolysis, laser hair removal, and chemical depilatories.

Children diagnosed with ZLS should be followed from early childhood for signs of intellectual disability, and monitored for indications of seizure activity. Those with scoliosis and other abnormalities of the spine and joints should receive physical therapy and may require referral to an orthopedic surgeon to correct severe deformities. Most children will need some type of psychotherapy or counseling in order to cope with the unusual appearance of their hands, feet, and facial features.

Prognosis

Zimmermann-Laband syndrome is not a life-threatening disorder. As far as is known, patients diagnosed with ZLS can expect normal lifespans. Patients do, however, vary in the severity of their facial dysmorphism, their mental capacity, their spinal and skeletal abnormalities, and their hypertrichosis; those with milder symptoms generally have fewer problems with social and educational adjustment.

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ORGANIZATIONS

- American Academy of Oral and Maxillofacial Pathology, 214 N. Hale St., Wheaton, IL 60187, (630) 510-4552 or (888) 552-2667, (630) 510-4501, info@aaomp.org, <http://www.aaomp.org/index.php>
- American College of Oral and Maxillofacial Surgeons (ACOMS), 2025 M St. NW, Suite 800, Washington, DC 20036, (202) 367-1182, (202) 367-2182, <http://www.acoms.org/general/?type=CONTACT><http://www.acoms.org>
- National Organization for Rare Disorders (NORD), 55 Kenosia Ave., Danbury, CT 06810, (203) 744-0100, (203) 798-2291, <http://rarediseases.org>
- Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS), 6701 Democracy Blvd., Suite 1001, MSC 4874, Bethesda, MD 20892, (301) 402-4336, (301) 480-9655, ordr@nih.gov, <https://rarediseases.info.nih.gov>

Rebecca J. Frey, PhD

Zinner syndrome

Definition

Zinner syndrome is a congenital syndrome in males classified by the presence of a cyst in the seminal vesicle with an ipsilateral (on the same side as the cyst) renal agenesis (kidney not forming correctly in utero) and ejaculatory duct obstruction. The association between seminal vesicle cyst and ipsilateral renal agenesis was identified in 1914. The later finding of the affiliated ejaculatory duct obstruction completed the triad of Zinner syndrome.

Description

The development of the kidney begins in the growing fetus roughly between 4 and 7 weeks, starting with a mesonephric duct. Embryologically speaking, the mesonephric duct gives rise to the uterine bud. This uterine bud develops toward the center of the metanephric bud to ultimately form the kidney. When this does not occur properly in the developing fetus, it is possible for the kidney and/or the ejaculatory ducts to form incorrectly, leading to a malformed kidney and a buildup of fluid, known as a cyst, in the seminal vesicle. These are the two common coinciding features of Zinner syndrome, where ipsilateral agenesis is present in roughly 70%–80% of patients and infertility is present in 37% of cases.

If there is a diagnosis of seminal vesicle cyst with ipsilateral renal agenesis, the syndrome is classified as a structural congenital anomaly. In the case of Zinner syndrome, the signs and symptoms of renal agenesis do not often present, since the normal kidney can carry out the functions necessary for the entire body. Seminal vesicle obstruction and ejaculatory duct blockage will present itself when a male becomes sexually active, depending on the size of the cyst. A link between the kidney and the male reproductive system is evident in the embryology of the mesonephric duct, which develops into parts of the bladder, urethra, seminal vesicle, vas deferens, and epididymis, among others. If the developing or embryologically changing mesonephric duct is compromised early in the pregnancy, a change in the ultimate structure and function of one or more reproductive and/or excretory parts will likely result. For example, if the distal portion of the duct is not developed correctly, the ejaculatory duct and seminal vesicle will be affected in such a way that fluid blockage will lead to cyst formation. This improper development of the distal portion of the mesonephric duct will also result in abnormal budding of the ureter, ultimately causing agenesis of the kidney itself. Also, depending on the size of the cysts formed early in development and/or the region of malformation

KEY TERMS

Agenesis—Lack or failure of development.

Congenital—Existing since birth.

Cyst—A closed sac having a distinct membrane and developing abnormally in a cavity or structure of the body.

Embryology—The study of the growing embryo.

Epididymis—A system of ducts emerging posteriorly from the testes that holds sperm during maturation and that forms a tangled mass before uniting into a single coiled duct that is continuous with the vas deferens.

Ipsilateral—Situated or appearing on or affecting the same side of the body.

Laparoscopic—Visual examination of the abdomen by means of a laparoscope.

Mesonephric duct—A duct that in the male gives rise to the reproductive system.

Metanephric bud—An embryological precursor to renal organs.

Renal—As related to the kidney.

Seminal vesicle—Either of a pair of glandular pouches that lie on either side of the male reproductive tract and in human males secrete a sugar- and protein-containing fluid into the ejaculatory duct.

Stenosis—A narrowing or constriction of the diameter of a bodily passage or orifice.

of the duct, infertility may result. A variation of the changes in these structures is determined by the structure or timing of the malformation.

Genetic profile

Much like other congenital anomalies, the genetic link to Zinner syndrome is currently unknown. At some point during the development of the embryo a malformation may occur, leading to a congenital anomaly. Some anomalies are often symptom free and are incidental findings during examination. Other congenital anomalies that affect major organs or organ systems oftentimes present themselves with signs and symptoms during early development, although sometimes they present later in life.

Congenital anomalies are fairly common within the population today. The World Health Organization (WHO) reports that approximately half of all known congenital anomalies cannot be linked to a specific cause

such as a specific gene mutation (missense, frameshift, point, etc.). The WHO does, however, state that socioeconomic or demographic factors may be an influence in the incidence of congenital anomalies. These include, but are not limited to, countries and areas with low income and lower access to nutrition and medical support during pregnancy. Age of pregnancy is also a contributing factor to many congenital birth defects.

Demographics

As of 2015, only about 100 cases of Zinner syndrome had been recorded. It is possible that the asymptomatic nature of the syndrome is the reason behind the low numbers of recorded cases to date. Due to the anatomical orientation of the anomaly, only males are affected.

Signs and symptoms

Although oftentimes asymptomatic, Zinner syndrome may present itself with pain in the lower abdominal region and pain in the perineal region, both made worse with ejaculation; a disruption in the flow of urine; pain while urinating; blood in the urine; blood in the semen; and infertility.

Infertility is reportedly common in 37% of cases of Zinner syndrome. The presentation of symptoms is highly associated with the size and exact location of the cysts inside the seminal vesicle, as a cyst of less than 5 cm is oftentimes asymptomatic and is an incidental finding of a routine prostate exam. Cysts between 5 cm and 12 cm are referred to as moderate, and cysts 12 cm and larger are often referred to as severe, as they can cause urinary or stool blockage. Inflammation of the anatomy surrounding the cyst (including, but not limited to, the ipsilateral epididymis and prostate) may also be involved, presenting with a deep, dull, diffuse ache in the lower abdomen. Due to the anatomy affected by the anomaly, signs and symptoms do not typically show until a male is sexually active, as pain during ejaculation is a major finding.

Diagnosis

Upon initial examination of a male suspected to have Zinner syndrome, a digital rectal examination will show a large, soft mass posterior to the prostate indicative of a cyst in the region of the seminal vesicle. If a mass is palpated, many tests are then utilized for diagnosing Zinner syndrome while ruling out other pelvic, renal, prostate, or reproductive syndromes. Further abdominopelvic palpation and observation will reveal normal-sized testes and no kidney findings with normal neurological evaluation. Urinalysis may show blood in the urine otherwise

QUESTIONS TO ASK YOUR DOCTOR

- Will I always have pain during intercourse? If so, how can this be treated?
- What is the best way to check for infertility?
- What are my options for reproduction if I am indeed infertile?
- What is the state of my kidney, and do I have proper kidney function? If my kidney function is altered, what can I do for treatment?
- Are there support groups for coping with infertility?
- How often should I be examined for progression of my disorder?
- How large is my cyst, and what is my best treatment option?

within normal limits. Blood tests are typically within normal limits as well, although, depending on the blockage, inflammatory markers such as ESR/SED rate may be increased. Sperm count will likely be low.

The diagnosis of Zinner syndrome is often concluded via diagnostic imaging. A CT will show a high intensity zone of a mass with easily distinguishable borders of water or near-water attenuation located slightly superior to the prostate gland. An MRI exam will be able to identify if ipsilateral renal agenesis is present with or without stenosis of the vas deferens, and is also necessary for differentiating seminal vesicle cysts from other pelvic cysts, such as cysts in the prostate gland or Müllerian ducts. Other methods of diagnostic testing include intravenous urography or rectal ultrasonography. An ultrasound will reveal a pelvic mass with a thick and irregular wall that does not echo.

Due to the nature of the disorder, diagnosis is often made between the ages of 20–50 years, when males are more sexually active and/or trying to reproduce.

Treatment and management

Conservative treatment of a mild to moderately symptomatic Zinner syndrome may be appropriate and successful. This may include a short-term course of oral antibiotics and a 6-month course of alpha-blockers for decreasing pain, inflammation, and prostate-related symptoms. Fine needle aspiration may also be an option for conservative removal of the cyst without major surgery.

Treatment of a seminal vesicle cyst that is moderately to severely symptomatic includes robotic laparoscopic removal of the cyst itself. Recent studies have shown this to be the method of choice in the removal of a cyst, as the recovery time is low and the prognosis is good.

Management of Zinner syndrome should include routine observations for prevention of life-threatening diagnoses associated with this disorder including squamous cell carcinoma of the seminal vesicle with which the cyst is associated.

Prognosis

The prognosis for Zinner syndrome is very good. As of 2015, there had only been one case noted in the literature where Zinner syndrome progressed into cancer. With proper treatment and management of the condition, patients should expect to live a full life.

Resources

BOOKS

- Jones, Kenneth Lyons, et al., eds. *Smith's Recognizable Patterns of Human Malformation*. 8th ed. Philadelphia: Elsevier, 2021.
- Yu, Alan S. L., et al., eds. *Brenner and Rector's The Kidney*. 11th ed. Philadelphia: Elsevier, 2020.

PERIODICALS

- Di Paola, Valerio, Riccardo Gigli, Angelo Totaro, and Riccardo Manfredi. "Zinner Syndrome: Two Cases and Review of the Literature." *BMJ Case Reports* 14, no. 6 (June 17, 2021). DOI: 10.1136/Bcr-2021-243002.

WEBSITES

- "Zinner syndrome." Radiopaedia. <https://radiopaedia.org/articles/zinner-syndrome-1?lang=us> (accessed June 27, 2021).

ORGANIZATIONS

- RESOLVE: The National Infertility Association, 7918 Jones Branch Dr., Suite 300, McLean, VA 22102, (703) 556-7172, (703) 506-3266, <http://www.resolve.org>

Taryn Terry DC, MSACN, BA

Zygote

Definition

The zygote is the single cell that is formed when the sperm cell fertilizes the egg cell. The zygote divides multiple times, producing identical copies of itself. The cells produced by the division of the zygote form the developing embryo, fetus, and baby. The zygote is the first step in the formation of a new person.



Illustration of a human zygote. (Sebastian Kaulitzkil/Shutterstock)

Description

When the sperm fuses with the egg, a cascade of events begins. Additional sperm are prevented from fertilizing the egg. The membranes of the egg and sperm combine, producing one single cell. The egg and sperm prepare to fuse their genetic material (DNA/chromosomes). Finally, the genetic material combines to produce the zygote with one complete set of chromosomes.

Most cells in the human body have two pairs of 23 chromosomes; that is, 46 chromosomes total. One set of 23 chromosomes is inherited from the mother, and the complementary set is inherited from the father. When the egg and sperm are formed, the two sets of chromosomes divide evenly, from 46 to 23 chromosomes to produce eggs and sperm with 23 chromosomes each. This ensures that when the egg and sperm fuse during conception, the original number of chromosomes (46) is restored.

The reduction of each parent cell from 46 to 23 chromosomes ensures that each parent contributes half of his or her genetic material to form the zygote and the offspring shares 50% of his or her genes with each parent. Duplication of the single zygote occurs through a complete division of the single ball of cells. This begins the process of forming the fetus and eventually the baby. The first division produces two identical cells, the second produces four cells, the third produces eight cells, etc. After many cell divisions, the cells begin to specialize and differentiate (form particular tissues and organs).

Fertilization usually occurs in the fallopian tube, and the first few cell divisions occur as the developing embryo moves to the uterus. The first division occurs about 30 hours after fertilization. As the zygote divides, some of the cells formed will develop into the placenta. Approximately six days after fertilization, the ball of cells attaches to the uterine wall.

Sex determination

Men and women each have 22 pairs of non-sex chromosomes and two sex chromosomes. Men's sex chromosomes are X and Y. A mature sperm cell that has undergone the chromosome division process from 46 to 23 chromosomes produces a cell that is either X or Y. Women's sex chromosomes are X and X. The eggs that women produce have only X chromosomes. Therefore, the sperm determines whether the zygote is XY or XX, which is the initial step on the biological path to becoming a male or female.

Developmental periods

The term “embryo” refers to the developing baby between the second week after conception and the eighth week after conception. Doctors use the term “fetus” from the ninth week after conception to birth. A pregnancy is broken down into three trimesters. The first trimester begins with the first day of the woman's last menstrual period and each trimester is three calendar months.

Twins

Twins may arise in two ways. Identical twins are called “monozygotic” because both individuals are formed from the same zygote. As the zygote divides to form the baby, two separate individuals form instead of one. Fraternal twins are called “dizygotic” because each individual develops from a different zygote. Two eggs are ovulated, and a separate sperm fertilizes each egg. Therefore, identical twins have exactly the same DNA in each cell and fraternal twins share the same amount of DNA as brothers and sisters. Sometimes it is impossible to tell monozygotic twins from dizygotic twins based on the placenta and the fetal membranes. If a person wants to determine whether twins are monozygotic or dizygotic, DNA studies of blood cells will provide a definitive answer.

Abnormalities

The zygote normally contains two complete sets of 23 chromosomes, and two copies of every gene. If the egg or sperm that fuse to form the zygote is abnormal, the zygote will also be abnormal. For example, Down syndrome is caused by an extra chromosome number 21

from the egg or sperm cell. Since the cells formed by division of the zygote are identical to the zygote, any abnormality in the zygote will be in every cell of the baby.

Abnormalities can also arise when the zygote begins to divide. This type of abnormality is usually severe, eventually leading to a miscarriage. If an abnormality occurs after the zygote has divided one or more times, the baby will have some normal cells and some abnormal cells. This situation is referred to as “mosaicism” and may be used to describe the person’s condition.

Molar pregnancies

Molar pregnancies can occur in one of two ways. Sometimes the original cell that duplicates and divides to form the fetus is completely of paternal origin. The chromosomes in a sperm duplicate themselves, then proceed to divide as if they were a normal zygote. These pregnancies are completely abnormal and miscarry. Another type of molar pregnancy occurs when two sperm fertilize one egg. The zygote is triploidy and has 69 chromosomes instead of 46. Although some fetal parts can be seen, these pregnancies normally miscarry in the first or second trimester.

Birth defects

The term “birth defect” describes many different types of abnormalities, including physical malformations. Abnormalities of anatomical structures may be significant or insignificant; minor variations in structure are common. Approximately 3% of newborns have major malformations. The causes are: chromosome abnormalities (6%–7%), inherited genetic conditions (7%–8%), environmental factors (7%–10%), and multifactorial causes (20%–25%). The cause of the remaining 50%–60% of malformations is unknown. Multifactorial refers to causes with both genetic and environmental components. Environmental factors include exposures to drugs, chemicals, or other substances that affect the development of the fetus while he/she is in the uterus. Substances that cause birth defects are referred to as teratogens.

Artificial reproductive technology

Couples may pursue assisted reproductive technologies for a number of reasons. If a couple has artificial insemination, the sperm is inserted into the uterus when the woman is ovulating. Fertilization then occurs as it would normally. If a couple has in vitro fertilization (IVF), the egg and sperm are mixed outside the body in the laboratory. The zygote forms in a petri dish if fertilization occurs. After a number of cell divisions, the developing embryo is placed in the woman’s uterus. If the

KEY TERMS

Chromosome—A microscopic thread-like structure found within each cell of the body and consisting of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

Gene—A building block of inheritance, which contains the instructions for the production of a particular protein, and is made up of a molecular sequence found on a section of DNA. Each gene is found on a precise location on a chromosome.

Teratogen—Any drug, chemical, maternal disease, or exposure that can cause physical or functional defects in an exposed embryo or fetus.

sperm are incapable of fusing with the egg themselves, the sperm may be injected into the egg. This additional step to the IVF procedure is called intracytoplasmic sperm injection (ICSI).

Preimplantation diagnosis is possible for a number of genetic diseases. Couples may pursue this if they are at a significant risk for having a child with a disease that could be diagnosed prior to becoming pregnant through preimplantation diagnosis. The procedure is like that of in vitro fertilization, with an additional step. After fertilization occurs and the zygote has begun to divide, a single cell is removed. Removing the cell does not harm the other cells. The cell that is removed is tested for the genetic disease for which the couple is at risk. Multiple developing embryos are tested. Only the embryos that do not have the condition are placed in the woman’s uterus to complete development.

The development of a person from the zygote is a fascinating and amazing process. It is a difficult area to study because scientists cannot manipulate human embryos to observe the effects, and the development of the fetus cannot be directly observed. Researchers still have many unanswered questions. Following a doctor’s recommendations from prior to the pregnancy throughout pregnancy (such as folic acid intake and avoidance of alcohol and other drugs) increases the chances that the development of a zygote into a full-term infant will be normal. However, there are many babies born with severe birth defects or genetic diseases despite the parents’ efforts at doing everything in their power to prevent a problem. Most birth defects and genetic disorders occur because of an event out of the control of the parents.

Resources

BOOKS

Armstrong, Francisco, ed. *Human Reproductive Biology*. Hayle Medical, 2019.

Carlson, Bruce M. *Human Embryology & Developmental Biology*, 6th ed. Philadelphia: Elsevier, 2018.

PERIODICALS

Cheng, Rui, et al. "Genome-wide analysis of alternative splicing differences between oocyte and zygote." *Biology of Reproduction*, vol. 102, no. 5, 2020, p. 999+.

Navarro-Costa, Paulo, and Rui Gonçalo Martinho. "The emerging role of transcriptional regulation in the oocyte-to-zygote transition." *PLoS Genetics*, vol. 16, no. 3, 2020, p. e1008602.

WEBSITES

"Fetal development." MedlinePlus Medical Encyclopedia. June 30, 2019. <https://medlineplus.gov/ency/article/002398.htm> (accessed June 3, 2021).

"Fetal development: The 1st trimester." Mayo Clinic. June 30, 2020. <https://www.mayoclinic.org/healthy-lifestyle>

/pregnancy-week-by-week/in-depth/prenatal-care/art-20045302 (accessed June 3, 2021).

"Is the probability of having twins determined by genetics?" MedlinePlus Genetics. September 17, 2020. <https://medlineplus.gov/genetics/understanding/traits/twins/> (accessed June 3, 2021).

ORGANIZATIONS

American Congress of Obstetricians and Gynecologists, PO Box 70620, 409 12th St., SW, Washington, DC 20024, (800) 673-8444 or (202) 638-5577, <http://www.acog.org>

Reproductive Facts from the American Society for Reproductive Medicine, 1209 Montgomery Highway, Birmingham, AL 35216, (205) 978-5000, (205) 978-5005, asrm@asrm.org, <http://www.reproductivefacts.org>

RESOLVE: The National Infertility Association, 7918 Jones Branch Dr., Suite 300, McLean, VA 22102, (703) 556-7172, (703) 506-3266, <http://www.resolve.org>

Michelle Queneau Bosworth, MS, CGC

CHROMOSOME MAP

A chromosome map indicates the relative positions of the genes that code for certain characteristics. The basic format for writing a gene position is the chromosome number, arm, band, sub-band, and sub-sub-band, if known. An example is 3p22.5.

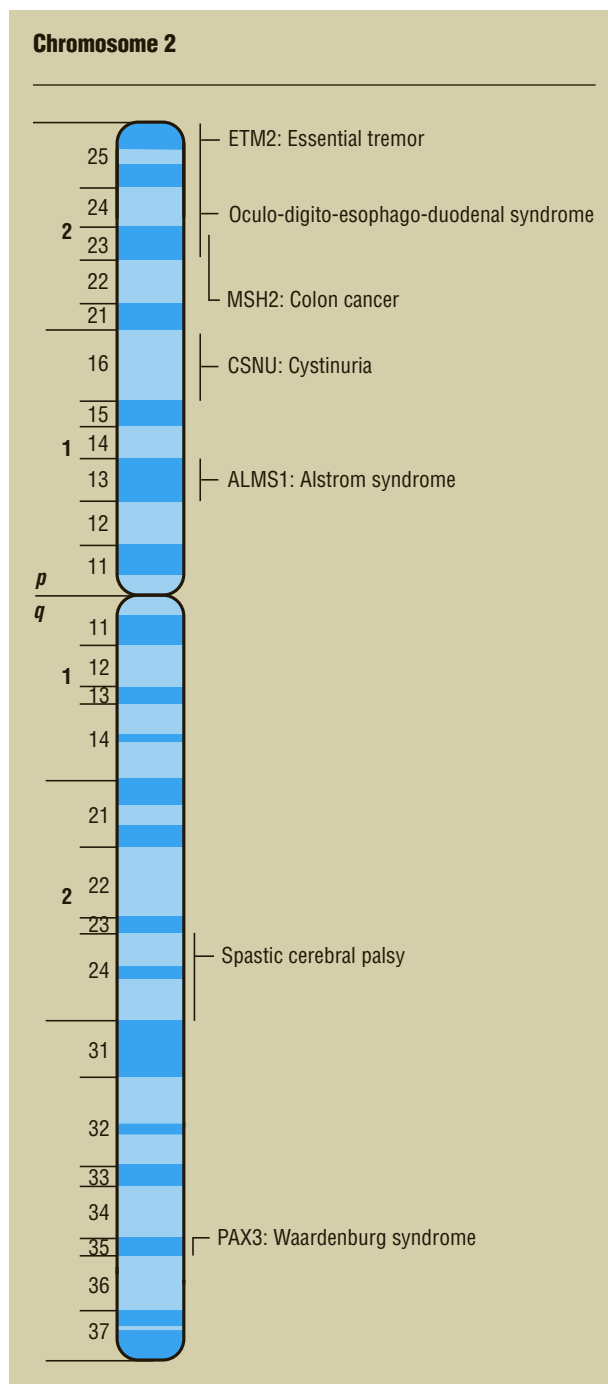
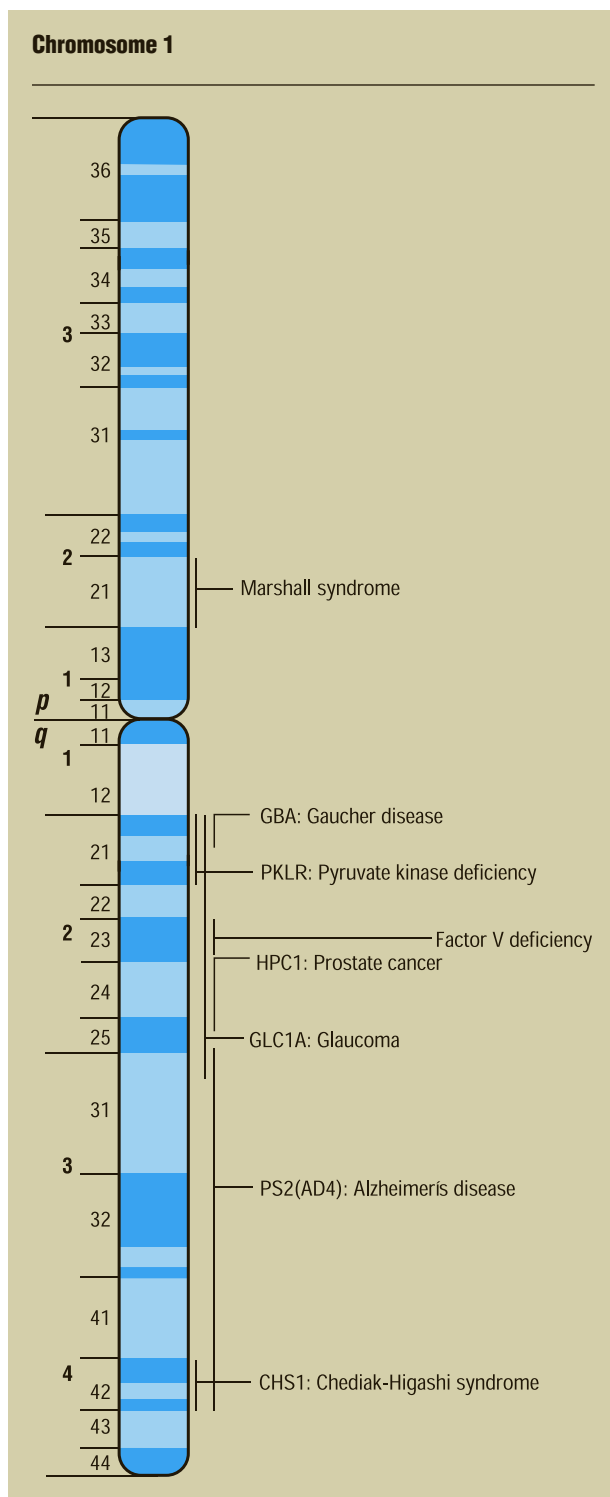
The chromosome number refers to one of the 22 autosomal chromosomes (numbered 1–22) or one of the two sex-determining chromosomes, X and Y. In the example, the gene is on chromosome 3.

Each chromosome has two arms, which are separated by a centromere, the pinched-in area at or above the middle of the chromosome. The short arm, labeled p, is above the centromere, and the long arm, q, is below it. In the case of the example gene, it is found on the short arm (p) of chromosome 3, or 3p.

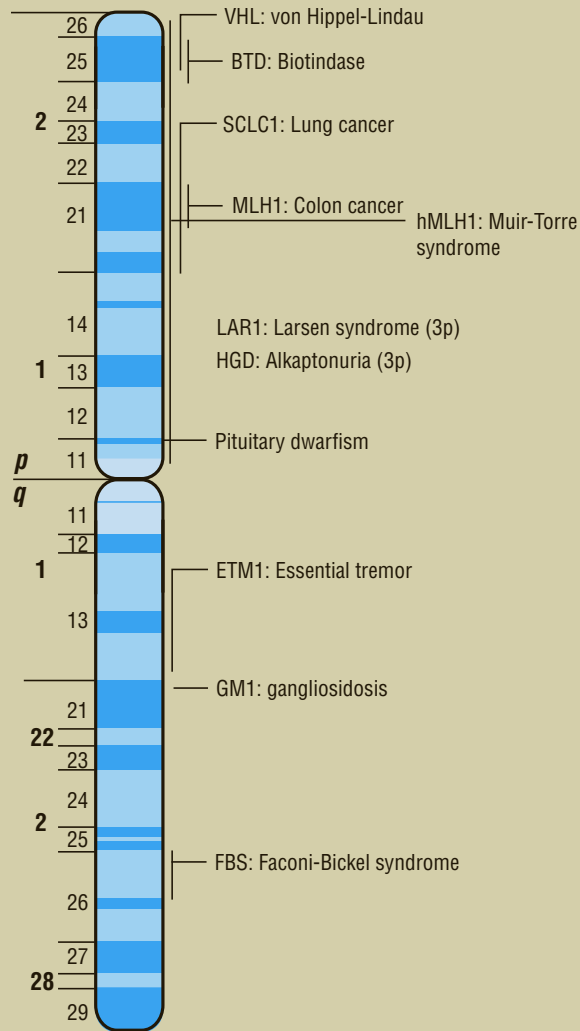
The arms are further divided into cytogenetic bands (regions) numbered 1, 2, 3, etc. The numbers start at the

centromere and increase toward the end of the arm, known as the telomere. These bands can only be seen when stained and viewed under a microscope. Sub-bands, which are numbered the same way as bands, may be visible within bands at greater magnifications. Therefore, the exact location of the example gene is the short arm (p) of chromosome 3, band 2, sub-band region 2, and a sub-sub band 5.

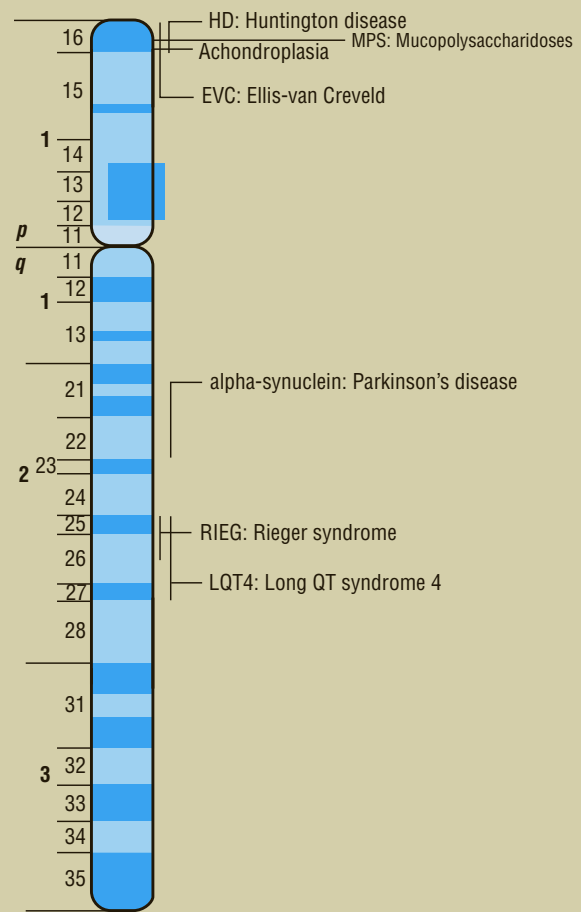
The following 24 illustrations demonstrate the approximate gene location for several of the genes relating to disorders mentioned in this encyclopedia. Disorders known to be related to a specific chromosome but not necessarily at an exact location have been placed below the chromosome. These chromosome maps are in no way complete; rather, they provide an introduction to understanding relative size differences of human chromosomes and where geneticists have located the genes associated with the source of certain genetic disorders.

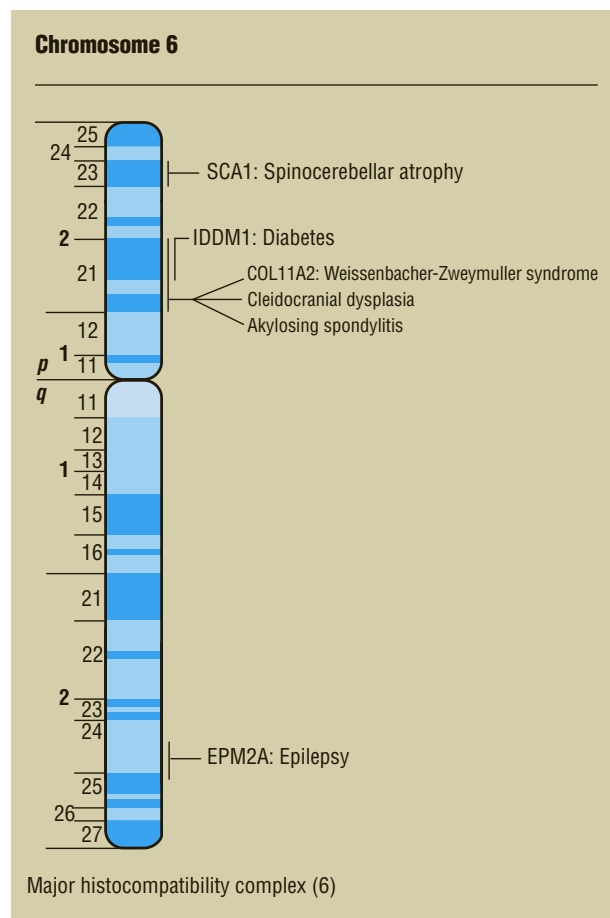
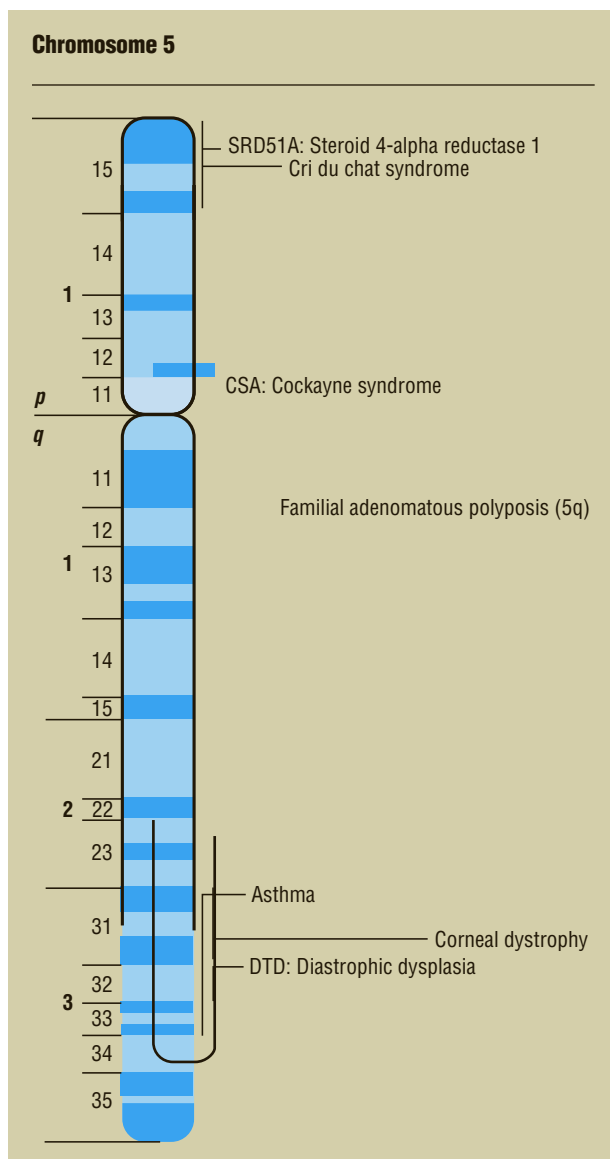


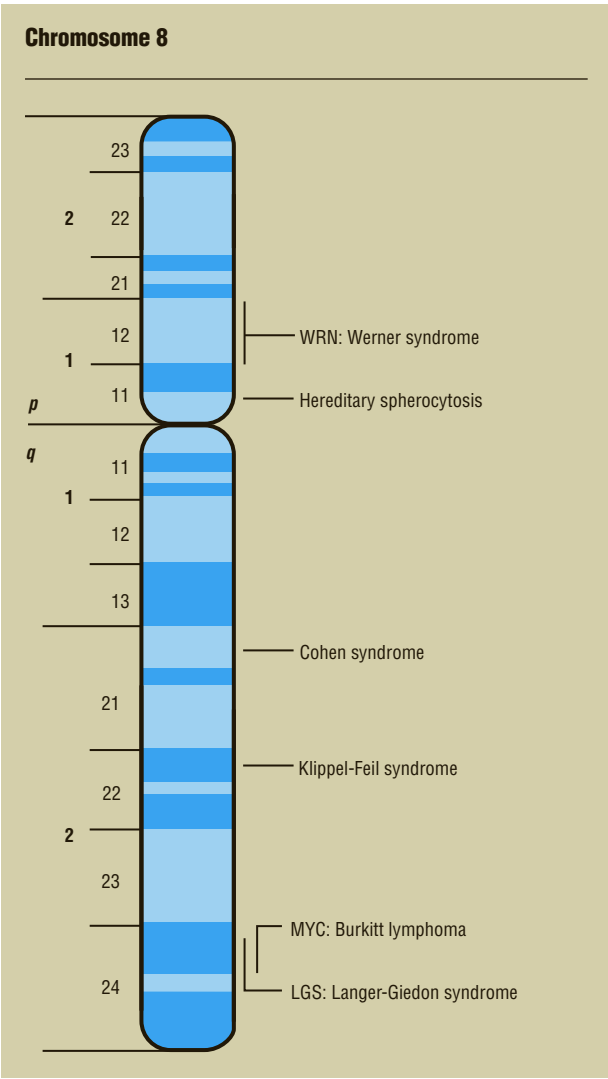
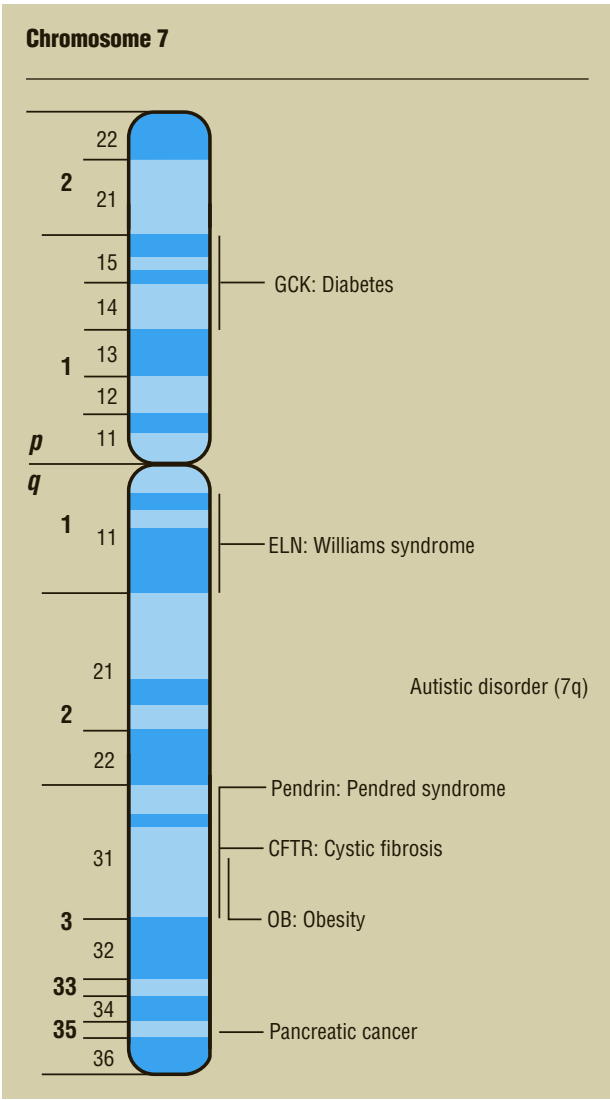
Chromosome 3



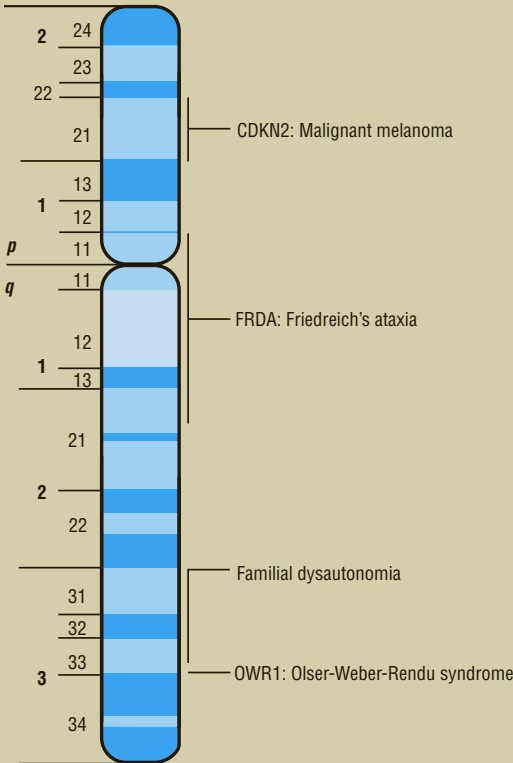
Chromosome 4





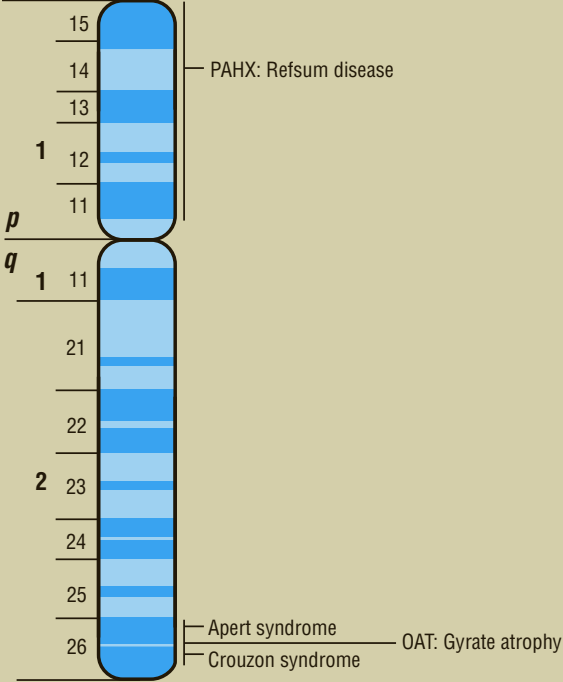


Chromosome 9

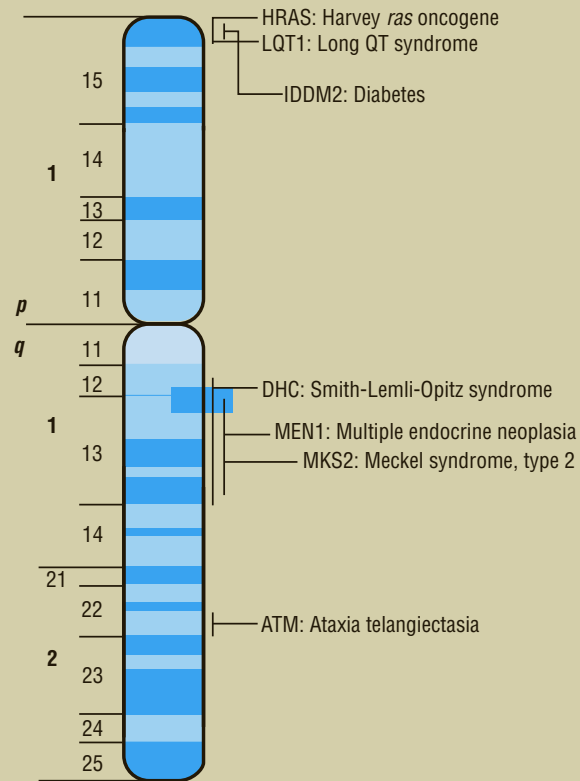


Distal arthrogryposis syndrome (9)

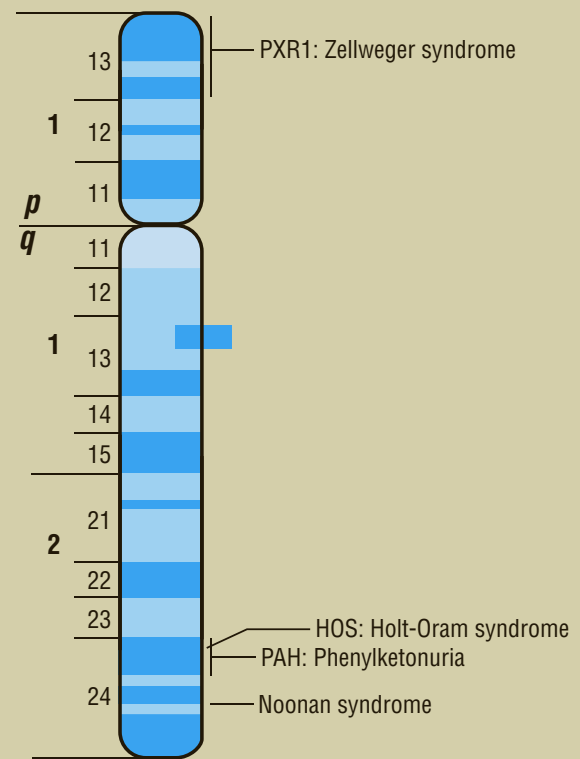
Chromosome 10

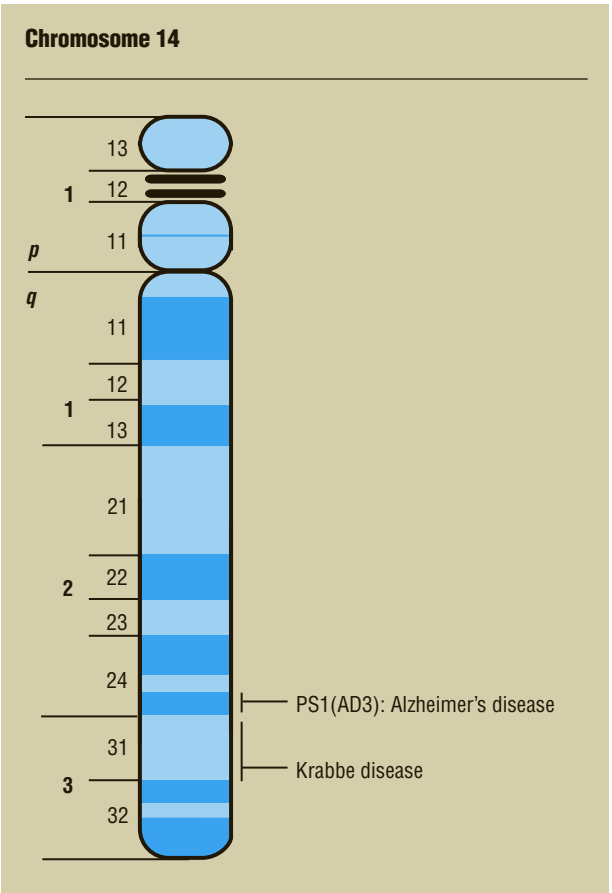
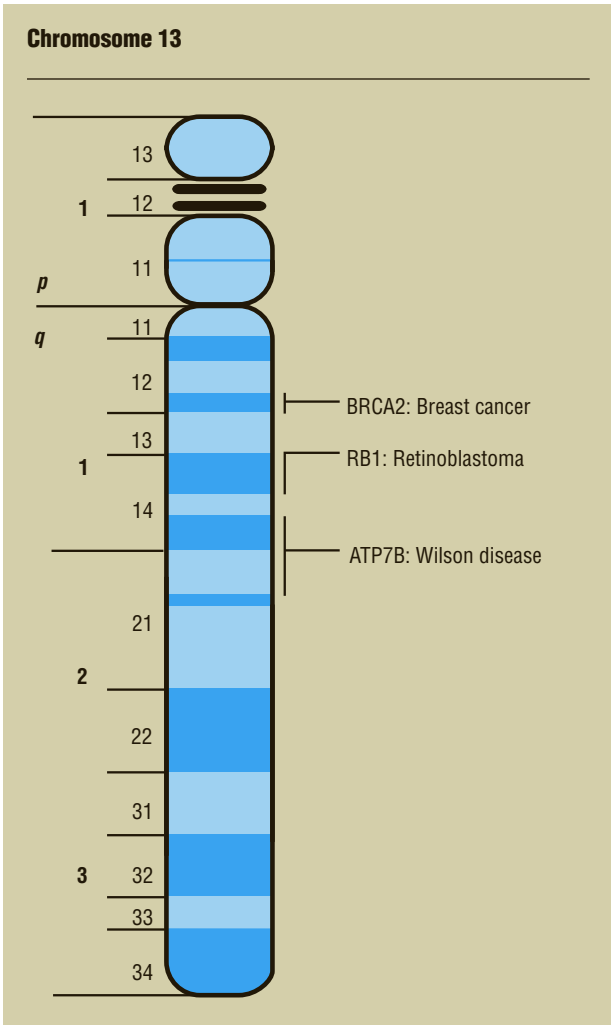


Chromosome 11

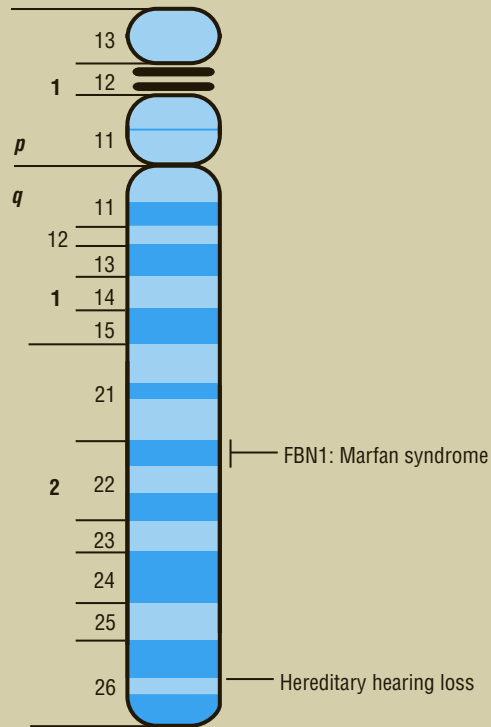


Chromosome 12



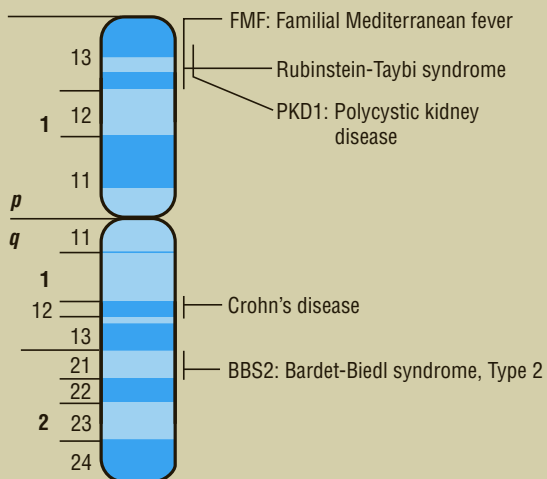


Chromosome 15



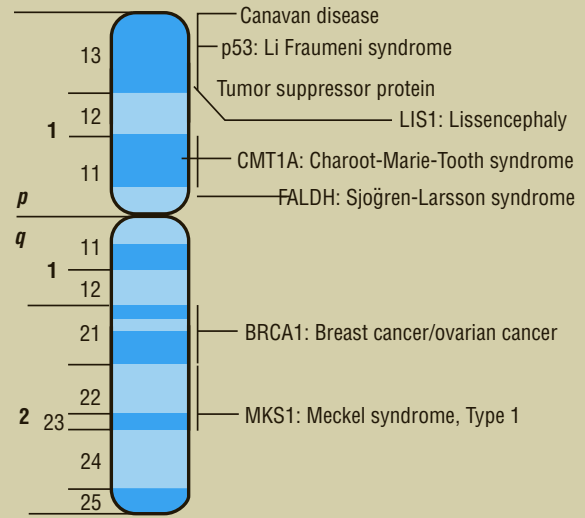
Prader-Willi syndrome (15q)

Chromosome 16



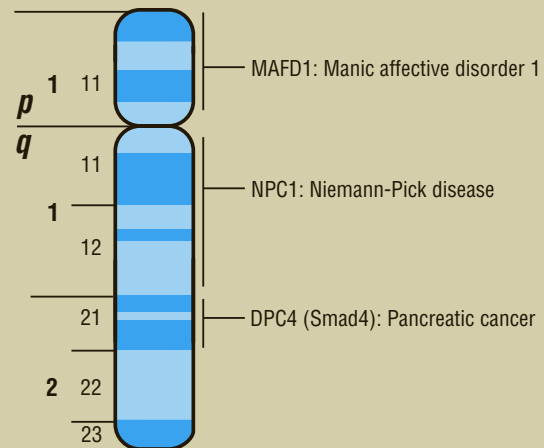
ABCC6: Pseudoaxanthoma elasticum (16)

Chromosome 17

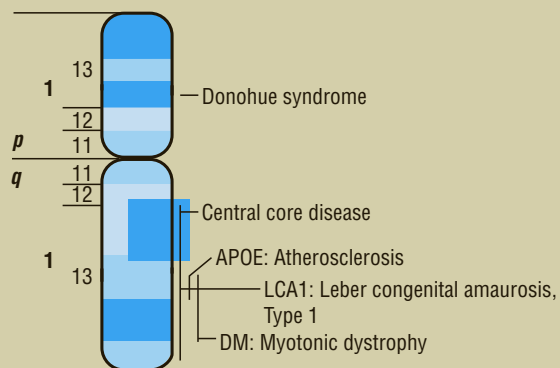


SOX9: Campomelic dysplasia

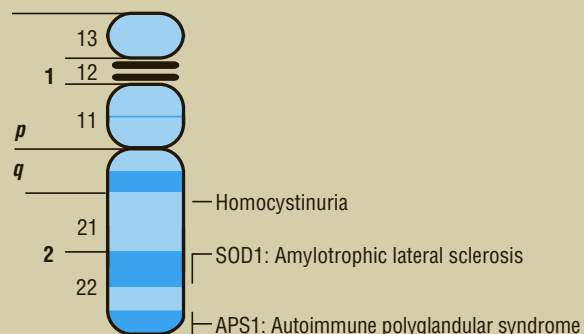
Chromosome 18



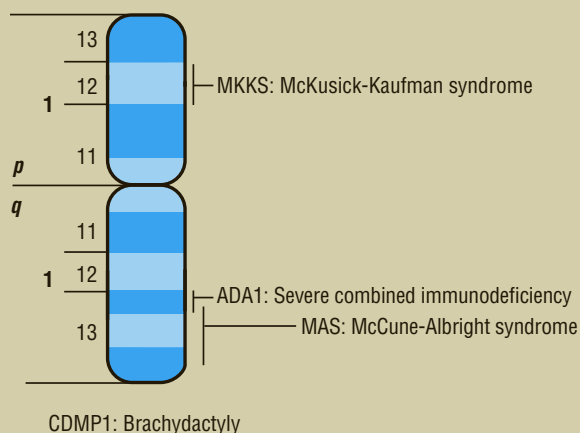
Chromosome 19



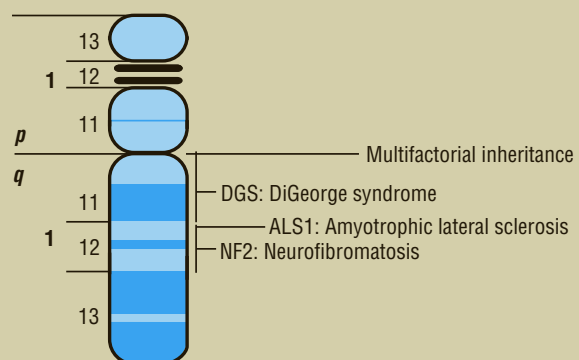
Chromosome 21

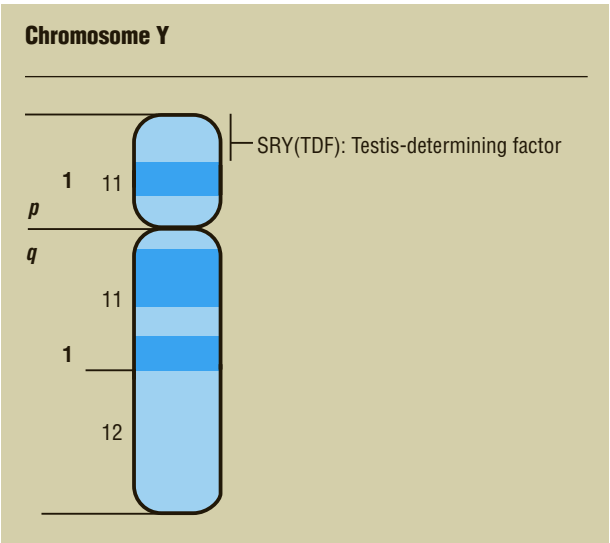
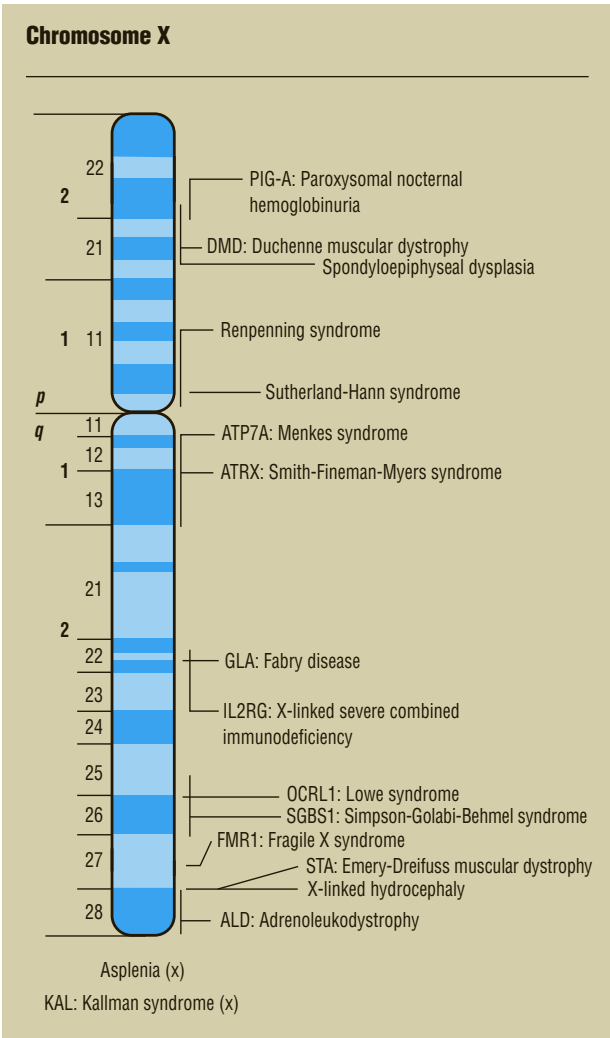


Chromosome 20



Chromosome 22





ORGANIZATIONS

The following is an alphabetical compilation of relevant organizations listed in the **Resources** sections of the main body entries. Although the list is comprehensive, it is by no means exhaustive. It is a starting point for gathering further information. Many of the organizations listed have links to additional related websites. E-mail addresses and web addresses listed were provided by the associations; Gale is not responsible for the accuracy of the addresses or the contents of the websites.

A

4p– Support Group

Website: <http://www.4p-supportgroup.org>

5p– Society

PO Box 268
Lakewood, CA 90714-0268
Phone: (888) 970-0777
Fax: (562) 920-5240
Website: <http://www.fivepminus.org>

“22q and You” Center, The Children’s Hospital of Philadelphia

3401 Civic Center Boulevard
Philadelphia, PA 19104
Phone: (215) 590-23800
Phone: (800) 879-2467
E-mail: genetics@email.chop.edu
Website: <http://www.chop.edu/centers-programs/22q-and-you-center>

A–T Children’s Project

5300 W. Hillsboro Blvd., Suite 105
Coconut Creek, FL 33073
Phone: (800) 543-5728
Fax: (954) 481-6611
E-mail: info@atcp.org
Website: <http://www.communityatcp.org>

A–T Ease Foundation

217 Thompson Street, Suite 404
New York, NY 10012
Phone: (212) 529-0622
Fax: (212) 505-8031
E-mail: info@ateasefoundation.org
Website: <http://www.ateasefoundation.org>

AABB [formerly American Association of Blood Banks]

4550 Montgomery Avenue, Suite 700,
North Tower
Bethesda, MD 20814

Phone: (301) 907-6977
Fax: (301) 907-6895
E-mail: aabb@aabb.org
Website: <http://www.aabb.org/home>

AboutFace

51 Wolseley St.
Toronto, ON, Canada, M5T 1A4
Phone: (416) 597-2229
Toll free: (800) 665-3223
Fax: (416) 597-8494
E-mail: info@aboutface.ca
Website: <https://www.aboutface.ca>

Accord Alliance

3324 E. Ray Road, #578
Higley, AZ 08889
Phone: (602) 492-4144
Website: <http://www.accordalliance.org>

Acid Maltase Deficiency Association (AMDA)

PO Box 700248
San Antonio, TX 78270
Phone: (210) 494-6144
Fax: (210) 490-7161
Website: <http://www.amda-pompe.org>

Adams Oliver Syndrome Support Group

14 College View, Connah’s Quay
Deeside, UK, CH5 4BY
Phone: 01244 816209
E-mail: sandy.ivins@btinternet.com

ADNP Research Project. University of Antwerp

Centrum Medische Genetica, Prins
Boudewijnlaan 43
Edegem, 2950
Phone: +32 (0)3 275 97 56
Website: <http://www.adnpgene.com>

Aicardi Syndrome Foundation

P.O. Box 3202
St. Charles, IL 60174
Phone: (630) 397-9728

E-mail: research@aicardisyndrome.foundation.org
Website: <https://aicardisyndrome.foundation.org>

Al-Anon/Alateen

1600 Corporate Landing Parkway
Virginia Beach, VA 23454-5617
Phone: (757) 563-1600
Phone: (757) 563-1655
E-mail: wso@al-anon.org
Website: <http://www.al-anon.alateen.org>

Alagille Syndrome Alliance

P.O. Box 22
Collierville, TN 38027
Phone: (901) 286-8869
E-mail: alagille@alagille.org
Website: <https://www.alagille.org>

Alcoholics Anonymous World Services, Inc

475 Riverside Drive at West 120th Street
New York, NY 10115
Phone: (212) 870-3400
Website: <http://www.aa.org>

Alexander Graham Bell Association for the Deaf and Hard of Hearing

3417 Volta Pl. NW
Washington, DC 20007
Phone: (202) 337-5220
Fax: (202) 337-8314
E-mail: info@agbell.org
Website: <https://www.agbell.org>

Alkaptonuria Society (AKU)

66 Devonshire Rd.
Cambridge, UK, CB1 2BL
Phone: +44 (0) 1223 322897
Website: <http://www.akusociety.org>

Allergy and Asthma Network.

Mothers of Asthmatics, Inc
8229 Boone Boulevard, Suite 260
Vienna, VA 22182
Phone: (800) 878-4403

Fax: (703) 288-5271
 Website: <http://www.allergyasthma-network.org/main>

Alliance of Genetic Support Groups
 4301 Connecticut Ave. NW, Suite 404
 Washington, DC 20008
 Phone: (202) 966-5557
 Fax: (202) 966-8553
 Website: <http://www.geneticalliance.org>

Alliance of Genome Resources
 E-mail: help@alliancegenome.org
 Website: <https://www.alliancegenome.org>

Alpha-1 Foundation
 3300 Ponce de Leon Boulevard
 Coral Gables, FL 33134
 Phone: (305) 567-9888
 Phone: (877) 2-CURE-A1 or (877) 228-7321
 Fax: (305) 567-1317
 E-mail: info@alpha-1foundation.org
 Website: <http://www.alpha1portal.org>

Alport Syndrome Foundation
 P.O. Box 4130
 Scottsdale, AZ 85261-4130
 Phone: (480) 800-3510
 E-mail: info@alportsyndrome.org
 Website: <http://alportsyndrome.org>

ALS Association
 1300 Wilson Boulevard, Suite 600
 Arlington, VA 22209
 Phone: (800) 782-4747
 Website: <https://www.als.org>

ALS Therapy Development Institute
 480 Arsenal Street, Suite 201
 Watertown, MA 02472
 Phone: (617) 441-7200
 Website: <https://www.als.net>

Alström Syndrome International
 14 Whitney Farm Road
 Mount Desert, ME 04660
 Phone: (800) 371-3628
 E-mail: info@alstrom.org
 Website: <https://www.alstrom.org>

Alzheimer's Association
 225 North Michigan Avenue, Floor 17
 Chicago, IL 60601-7633
 Phone: (312) 335-8700
 Phone: (800) 272-3900
 Phone: (866) 699-1246
 E-mail: info@alz.org
 Website: <https://www.alz.org>

Alzheimer's Disease Information and Referral Center
 National Institute on Aging, NIA
 Information Center, 31 Center Drive,
 MSC 2292

Bethesda, MD 20892
 Phone: (800) 438-4380
 Toll free: (301) 496-1752
 E-mail: adear@nia.nih.gov
 Website: <https://www.nia.nih.gov/alzheimers>

Alzheimer's Disease International
 64 Great Suffolk St.
 London SE1 0BL, UK,
 Phone: +44 20 79810880
 Fax: +44 20 79282357
 E-mail: info@alz.co.uk
 Website: <http://www.alz.co.uk>

AMD Alliance International
 Sixth Floor, City Gate East, Toll House
 Hill
 Nottingham, United Kingdom
 Phone: 44 115-935-2100
 E-mail: info@amdalliance.org
 Website: <http://www.amdalliance.org>

**American Academy of Allergy,
 Asthma & Immunology**
 555 E. Wells St., Ste. 1100
 Milwaukee, WI 53202-3823
 Phone: (414) 272-6071
 Website: <https://www.aaaai.org>

American Academy of Child and Adolescent Psychiatry (AACAP)
 3615 Wisconsin Ave. NW
 Washington, DC 20016-3007
 Phone: (202) 966-7300
 Fax: (202) 966-2891
 Website: <http://www.aacap.org>

American Academy of Dermatology (AAD)
 P.O. Box 1968
 Des Plaines, IL 60017
 Toll free: (888) 462-DERM (3376)
 Phone: (847) 240-1280
 Fax: (847) 240-1859
 E-mail: mrc@aad.org
 Website: <https://www.aad.org>

American Academy of Family Physicians (AAFP)
 11400 Tomahawk Creek Pkwy.
 Leawood, KS 66211-2680
 Phone: (913) 906-6000 or (800) 274-2237
 Fax: (913) 906-6075
 Website: <http://www.aafp.org>

American Academy of Ophthalmology (AAO)
 P.O. Box 7424
 San Francisco, CA 94120-7424
 Phone: (415) 561-8500
 Fax: (415) 561-8533
 Website: <https://www.aao.org>

American Academy of Oral and Maxillofacial Pathology
 P.O. Box 539
 Winfield, IL 60190
 Phone: (630) 510-4552 or (888) 552-2667
 Fax: (630) 510-4501
 E-mail: info@aaomp.org
 Website: <https://aaomp.org>

American Academy of Orthopaedic Surgeons
 PO Box 2058
 Des Plaines, IL 60017
 Phone: (800) 824-2263
 Website: <http://www.aaos.org>

American Academy of Otolaryngology—Head and Neck Surgery
 1650 Diagonal Rd.
 Alexandria, VA 22314
 Phone: (703) 836-4444
 Website: <http://www.entnet.org>

American Academy of Pediatrics (AAP)
 345 Park Boulevard
 Itasca, IL 60143
 Toll free: (800) 433-9016
 Fax: (847) 434-8000
 Website: <https://www.aap.org>

American Association for Clinical Chemistry
 1850 K St. NW, Suite. 625
 Washington, DC 20006-2213
 Phone: (202) 857-0717 or (800) 892-1400
 Fax: (202) 887-5093
 Website: <https://www.aacc.org>

American Association for Klinefelter Syndrome Information and Support (AAKSIS)
 c/o Roberta Rappaport, 3796 Ogden Ln.
 Mundelein, IL 60060
 Phone: (888) 466-5747
 E-mail: aaksis@sbcglobal.net
 Website: <http://www.aaksis.org>

American Association for Pediatric Ophthalmology and Strabismus
 655 Beach St.
 San Francisco, CA 94109-1336
 Phone: (415) 561-8505
 Fax: (415) 561-8531
 E-mail: aapos@aao.org
 Website: <https://aapos.org/home>

American Association of Kidney Patients (AAKP)
 14440 Bruce B. Downs Blvd.
 Tampa, FL 33613
 Toll free: (800) 749-AAKP
 Fax: (813) 636-8122

E-mail: info@aakp.org
 Website: <https://aakp.org>

American Association of the Deaf-Blind

PO Box 8064
 Silver Spring, MD 20907-8064
 Phone: (301) 563-9064
 E-mail: aadb-info@aadb.org
 Website: <http://www.aadb.org>

American Association of Tissue Banks (AATB)

8200 Greensboro Drive, Suite 404
 McLean, VA 22102
 Phone: (703) 229-1020
 E-mail: aatb@aatb.org
 Website: <https://www.aatb.org>

American Association on Intellectual and Developmental Disabilities (AAIDD)

501 3rd St. NW, Suite 200
 Washington, DC 20001
 Phone: (202) 387-1968
 Fax: (202) 387-2193
 Website: <http://www.aamr.org>

American Autoimmune Related Diseases Association

22100 Gratiot Ave.
 Eastpointe, MI 48021
 Phone: (586) 776-3900
 Fax: (586) 776-3903
 Website: <http://www.aarda.org>

American Board of Genetic Counseling (ABGC)

4000 College Boulevard, Suite 220
 Overland Park, KS 66211
 Phone: (913) 222-8661
 Fax: (913) 222-8606
 E-mail: info@abgc.net
 Website: <http://www.abgc.net>

American Brain Tumor Association

8550 W. Bryn Mawr Ave., Suite 550
 Chicago, IL 60631
 Phone: (773) 577-8750
 Toll free: (800) 886-2282
 Fax: 773-577-8738
 E-mail: info@abta.org
 Website: <https://www.abta.org>

American Cancer Society (ACS)

250 Williams Street NW
 Atlanta, GA 30303
 Toll free: (800) 227-2345
 Website: <https://www.cancer.org>

American Childhood Cancer Organization

10920 Connecticut Avenue, Suite A
 Kensington, MD 20895
 Phone: (301) 962-3520 or (855) 858-2226

Fax: (301) 962-3521
 Website: <http://www.acco.org>

American Cleft Palate-Craniofacial Association

1504 East Franklin Street, Suite 102
 Chapel Hill, NC 27514-2820
 Phone: (919) 933-9044 or (800) 242-5338
 Fax: (919) 933-9604
 E-mail: info@acpa-cpf.org
 Website: <http://www.cleftline.org>

American Cleft Palate Foundation

1504 E. Franklin St., Suite 102
 Chapel Hill, NC 27514-2820
 Phone: (919) 933-9044
 Fax: (919) 933-9604
 E-mail: info@acpa-cpf.org
 Website: <https://acpa-cpf.org/acpa-family-services/>

American College of Gastroenterology

6400 Goldsboro Rd., Ste. 200
 Bethesda, MD 20817
 Phone: (301) 263-9000
 E-mail: info@acg.gi.org
 Website: <https://gi.org>

American College of Laboratory Animal Medicine (ACLAM)

c/o Dr. Melvin W. Balk, 96 Chester Street
 Chester, NH 03036
 Phone: (603) 887-2467
 Fax: (603) 887-0096
 E-mail: mel.balk@aclam.org
 Website: <https://www.aclam.org/>

American College of Medical Genetics and Genomics (ACMG)

7101 Wisconsin Ave, Suite 1101
 Bethesda, MD 20814
 Phone: (301) 718-9603
 Fax: (301) 718-9604
 E-mail: acmg@acmg.net
 Website: <https://www.acmg.net/>

American College of Obstetricians and Gynecologists (ACOG)

409 12th Street, SW
 Washington, D.C. 20024-2188
 Toll free: (800) 673-8444
 Phone: (202) 638-5577
 Website: <https://www.acog.org>

American College of Oral and Maxillofacial Surgeons (ACOMS)

2025 M St. NW, Suite 800
 Washington, DC 20036
 Phone: (202) 367-1182
 Fax: (202) 367-2182
 E-mail: info@acoms.org
 Website: <http://www.acoms.org>

American College of Radiology (ACR)

1891 Preston White Dr.
 Reston, VA 20191
 Phone: (703) 648-8900
 E-mail: info@acr.org
 Website: <http://www.acr.org>

American College of Rheumatology

2200 Lake Boulevard NE
 Atlanta, GA 30319
 Phone: (404) 633-3777
 Website: <https://www.rheumatology.org>

American College of Surgeons

633 N. St. Clair St.
 Chicago, IL 60611-3211
 Phone: (312) 202-5000 or (800) 621-4111
 Fax: (312) 202-5001
 E-mail: postmaster@facs.org
 Website: <http://www.facs.org>

American Council of the Blind

1703 N Beauregard St, Suite 420
 Arlington, VA 22311
 Phone: (202) 467-5081
 Toll free: (800) 424-8666
 Fax: (703) 465-5085
 E-mail: info@acb.org
 Website: <https://www.acb.org>

American Diabetes Association

2451 Crystal Drive, Suite 900
 Alexandria, VA 22202
 Phone: (800) 342-2383
 E-mail: askada@diabetes.org
 Website: <https://www.diabetes.org>

American Epilepsy Society

135 South LaSalle Street, Suite 2850
 Chicago, IL 60603
 Phone: (312) 883-3800
 Fax: (312) 896-5784
 E-mail: info@aesnet.org
 Website: <https://www.aesnet.org>

American Foundation for the Blind

1401 South Clark Street, Suite 730
 Arlington, VA 22202
 Phone: (212) 502-7600
 Website: <https://www.afb.org>

American Hair Loss Council

30 South Main
 Shenandoah, PA 17976
 Website: <http://www.ahlc.org>

American Heart Association (AHA)

7272 Greenville Ave.
 Dallas, TX 75231
 Phone: (800) 242-8721
 Website: <https://www.heart.org>

American Hemochromatosis Society, Inc.

P.O. Box 950871
 Lake Mary, FL 32795

Phone: (407) 829-4488
E-mail: mail@americanhs.org
Website: <http://www.americanhs.org>

American Kidney Fund
11921 Rockville Pike, Suite 300
Rockville, MD 20852
Phone: (899) 638-8299
Website: <http://www.kidneyfund.org>

American Liver Foundation
P.O. Box 299
West Orange, NJ 07052
Phone: (800) 465-4837
Website: <https://liverfoundation.org>

American Lung Association
55 W. Wacker Dr., Suite 1150
Chicago, IL 60601
Phone: (800) 586-4872
E-mail: Info@Lung.org
Website: <https://www.lung.org>

American Macular Degeneration Foundation
P.O. Box 515
Northampton, MA 01061-0515
Phone: (413) 268-7660 or (888) 622-8527
Website: <http://www.macular.org>

American Medical Association (AMA)
AMA Plaza, 330 N. Wabash Ave.
Chicago, IL 60611-5885
Phone: (800) 621-8335
Website: <http://www.ama-assn.org/ama>

American Optometric Association (AOA)
243 N. Lindbergh Boulevard
St. Louis, MO 63141-7881
Phone: (314) 991-4100
Toll free: (800) 365-2219
Fax: (314) 991-4101
Website: <https://www.aoa.org>

American Parkinson Disease Association
135 Parkinson Ave.
Staten Island, NY 10305
Phone: (800) 223-2732 or (718) 981-8001
Fax: (718) 981-4399
E-mail: apda@apdaparkinson.org
Website: <http://www.apdaparkinson.org>

American Pediatric Surgical Association
1061 E. Main St., Suite 300
East Dundee, IL 60118
Phone: (309) 733-7874
E-mail: info@apsaped surg.org
Website: <https://apsaped surg.org>

American Porphyria Foundation (APF)
4915 St. Elmo Avenue, Suite 200
Bethesda, MD 20814

Phone: (301) 347-7166
Toll free: (866) APF-3635
E-mail: info@porphyriafoundation.org
Website: <https://porphyriafoundation.org>

American Pregnancy Association
Toll free: (800) 672-2296
E-mail: <https://americanpregnancy.org/contact>
Website: <https://americanpregnancy.org>

American Psychiatric Association
800 Maine Avenue, SW, Suite 900
Washington, DC 20024
Toll free: (888) 357-7924
Phone: (202) 559-3900
E-mail: apa@psych.org
Website: <https://www.psychiatry.org>

American Psychological Association
750 First Street NE
Washington, DC 20002-4242
Toll free: (800) 374-2721
Phone: (202) 336-5500
Phone: TTY: (202) 336-6123
Website: <https://www.apa.org>

American SIDS Institute
528 Raven Way
Naples, FL 34110
Phone: (239) 431-5425
Fax: (239) 431-5536
Website: <http://sids.org>

American Society for Deaf Children
PO Box 23
Woodbine, MD 21797
Toll free: (800) 942-2732
E-mail: info@deafchildren.org
Website: <https://deafchildren.org>

American Society for Dermatologic Surgery
5550 Meadowbrook Dr., Suite 120
Rolling Meadows, IL 60008
Phone: (847) 956-0900
Website: <https://www.asds.net>

American Society for Reproductive Medicine (ASRM)
J. Benjamin Younger Office of Public Affairs, 726 7th Street SE
Washington, DC 20003
Phone: (202) 863-4985
E-mail: asrm@asrm.org
Website: <https://www.reproductivefacts.org> and <https://www.asrm.org>

American Society for Surgery of the Hand (ASSH)
822 W. Washington Blvd.
Chicago, IL 60607
Phone: (312) 880-1900
E-mail: info@assh.org
Website: <https://www.assh.org>

American Society of Clinical Oncology (ASCO)
2318 Mill Road, Suite 800
Alexandria, VA 22314
Toll free: (888) 282-2552
Phone: (703) 299-0158
Fax: (703) 299-0255
E-mail: customerservice@asco.org
Website: <https://www.asco.org>

American Society of Colon & Rectal Surgeons
85 W. Algonquin Rd., Suite 550
Arlington Heights, IL 60005
Phone: (847) 290-9184
Fax: (847) 290-9203
E-mail: ascrs@fascrs.org
Website: <http://www.fascrs.org>

American Society of Hematology (ASH)
2021 L Street NW, Suite 900
Washington, DC 20036
Toll free: (866) 828-1231
Phone: (202) 776-0544
Fax: (202) 776-0545
E-mail: <https://www.hematology.org/contact-us>
Website: <https://www.hematology.org>

American Society of Human Genetics (ASHG)
6120 Executive Boulevard, Suite 500
Rockville, MD 20852
Phone: (301) 634-7300
E-mail: society@ashg.org
Website: <https://www.ashg.org>

American Society of Hypertension (ASH)
45 Main St., Suite 712
Brooklyn, NY 11201
Phone: (212) 696-9099
E-mail: ash@ash-us.org
Website: <http://www.ash-us.org>

American Society of Nephrology (ASN)
1510 H St. NW, Suite 800
Washington, DC 20005
Phone: (202) 640-4660
Fax: (202) 637-9793
E-mail: email@asn-online.org
Website: <http://asn-online.org>

American Syringomyelia & Chiari Alliance Project
PO Box 1586
Longview, TX 75606-1586
Phone: (903) 236-7079
Phone: (800) ASAP-282
Phone: (903) 757-7456
E-mail: Info@ASAP.org
Website: <http://asap.org>

American Thyroid Association (ATA)
2000 Duke Street, Suite 300

Alexandria, VA 22314
Website: <https://www.thyroid.org>

American Type Culture Collection (ATCC)

10801 University Blvd.
Manassas, VA 20110
Toll free: (800) 638-6597
Phone: (703) 365-2700
E-mail: <https://www.atcc.org/en/support/contact-us>
Website: <https://www.atcc.org/en>

American Urological Association (AUA)

1000 Corporate Boulevard
Linthicum, MD 21090
Toll free: (866) 746-4282
Phone: (410) 689-3700
Fax: (410) 689-3800
E-mail: aua@AUAnet.org
Website: <https://www.auanet.org/>

Amyloidosis Foundation

7151 N. Main Street, Suite 2
Clarkston, MI 48346
Phone: (248)922-9610
E-mail: info@amyloidosis.org
Website: <http://www.amyloidosis.org>

Amyloidosis Support Groups

232 Orchard Drive
Wood Dale, IL 60191
Phone: (630) 350-7539 or (866) 404-7539
E-mail: info@amyloidosisupport.com
Website: <http://amyloidosisupport.org>

Angelman Syndrome Foundation

414 Plaza Dr., Suite 209
Westmont, IL 60559
Phone: (800) IF-ANGEL or (630) 734-9267
Fax: (630) 655-0391
E-mail: info@angelman.org
Website: <http://www.angelman.org>

Apert International

PO Box 2571
Columbia, SC 29202
Phone: (803)732-2372
E-mail: info@apert-international.org
Website: <http://www.apert-international.org>

Aplastic Anemia and MDS International Foundation

4330 East West Highway, Suite 230
Bethesda, MD 20814
Phone: (800) 747-2820 or (301) 279-7202
E-mail: help@aamds.org
Website: <http://www.aamds.org>

The Arc

1825 K St. NW, Suite 1200
Washington, DC 20006

Toll free: (800) 433-5255
Phone: (202) 534-3700
Fax: (202) 534-3731
E-mail: <https://thearc.org/about-us/contact-us>
Website: <https://thearc.org>

Arthritis Foundation

1355 Peachtree St., NE, Suite 600
Atlanta, GA 30309
Toll free: (800) 283-7800
Website: <http://www.arthritis.org>

Arthritis Research Institute of America

300 South Duncan Avenue, Suite 188
Clearwater, FL33755
Phone: (727) 461-4054
E-mail: info@awlife.org
Website: <http://www.preventarthritits.org>

Arthrogryposis Multiplex Congenita Support

PO Box 6291
Spartanburg, SC 29304
Website: <http://www.amcsupport.org>

Asperger Autism Spectrum Education Network (ASPEN)

9 Aspen Circle
Edison, NJ 08820
Phone: (732) 321-0880
Website: <http://aspennj.org>

Asperger/Autism Network

51 Water St., Suite 206
Watertown, MA 02472
Phone: (617) 393-3824
E-mail: info@aane.org
Website: <http://www.aane.org>

Association for Frontotemporal Degeneration

Radnor Station Building 2, Suite 320,
290 King of Prussia Rd.
Radnor, PA 19087
Phone: (267) 514-7221 or (866) 507-7222
Website: <http://www.theaftd.org>

Association for Glycogen Storage Disease

PO Box 896
Durant, IA 52747
Phone: (563) 514-4022
E-mail: info@agsdus.org
Website: <http://www.agsdus.org>

Association for Science in Autism Treatment

PO Box 1447
Hoboken, NJ 07030
E-mail: info@asatonline.org
Website: <https://asatonline.org>

Association for the Bladder Exstrophy Community

6737 W. Washington St., Suite 3265

West Allis, WI 53214
Website: <http://www.bladderexstrophy.com>

Asthma and Allergy Foundation of America (AAFA)

8201 Corporate Drive Suite 1000
Landover, MD 20785
Phone: (800) 727-8462
Website: <http://www.aafa.org>

Attention Deficit Disorder Association

P.O. Box 103
Denver, PA 17517
Phone: (800) 939-1019
Website: <http://www.add.org>

Autism Research Institute

4182 Adams Ave.
San Diego, CA 92116
Phone: (866) 366-3661
Website: <http://www.autism.com>

Autism Society

6110 Executive Boulevard, Suite 305
Rockville, MD 20852
Toll free: (800) 328-8476
Website: <https://www.autism-society.org>

Autism Speaks

1060 State Road, 2nd Floor
Princeton, NJ 08540
Phone: (212) 252-8584
Phone: (646) 385-8500
Fax: (609) 430-9163 or (609) 430-9505
E-mail: help@autismspeaks.org
Website: <https://www.autismspeaks.org>

AVENUES (National Support Group for Arthrogryposis Multiplex Congenita)

E-mail: info@avenuesforamc.com
Website: <http://www.avenuesforamc.com>

AXYS

PO Box 872
Pine, CO 80470
Phone: (888) 999-9428
E-mail: info@genetic.org
Website: <http://www.genetic.org>

B

Bachmann-Strauss Dystonia & Parkinson Foundation

PO Box 38016
Albany, NY 12203
Website: <http://www.dystonia-parkinsons.org>

Bardet Biedl Syndrome Family Association

E-mail: darla.mansker@bardetbiedl.org
 Website: <http://www.bardetbiedl.org>

Barth Syndrome Foundation

2005 Palmer Avenue, #1033
 Larchmont, NY 10538
 Phone: (914) 303-6323
 Website: <https://www.barthsyndrome.org/home>

Barth Syndrome Foundation of Canada

162 Guelph Street, Suite 115
 Georgetown, ON Canada L7G 5X7
 Phone: (905) 873-2391
 Phone: (888) 732-9458
 Website: <http://www.barthsyndrome.ca/home>

Basal Cell Carcinoma Nevus Syndrome Life Support Network (BCCNS)

PO Box 321
 Burton, OH 44021
 Phone: (440) 834-0011
 Toll free: (866) 834-1895
 Fax: (440) 834-0132
 E-mail: info@bccns.org
 Website: <http://www.gorlinsyndrome.org>

Battens Disease Support and Research Association

1175 Dublin Rd.
 Columbus, OH 43215
 Phone: (800) 448-4570
 Fax: (866) 648-8718
 Website: <http://www.bdsra.org>

Bicuspid Aortic Foundation

30100 Town Center Drive, Suite O-299
 Laguna Niguel, CA 92677
 Phone: (949) 371-9223
 E-mail: contactus@bicuspidfoundation.com
 Website: <http://bicuspidfoundation.com>

Birth Defect Research for Children

976 Lake Baldwin Lane, Suite 104
 Orlando, FL 32814
 Phone: (407) 895-0802
 E-mail: staff@birthdefects.org
 Website: <https://birthdefects.org>

BlackInGenetics

E-mail: <https://www.blackingenetics.com/contact>
 Website: <http://www.blackingenetics.com>

Boston University Amyloidosis Center

Boston University School of Medicine,
 72 East Concord Street, K-503

Boston, MA 02118
 Phone: (617) 358-4750
 Fax: (617) 358-4735
 E-mail: amyloid@bmc.org
 Website: <http://www.bu.edu/amyloid>

Breastcancer.org

7 East Lancaster Avenue, 3rd Floor
 Ardmore, PA 19003
 Website: <http://www.breastcancer.org>

Broad Institute

415 Main Street
 Cambridge, MA 02142
 Phone: (617) 714-7000
 E-mail: <https://www.broadinstitute.org/contact>
 Website: <https://www.broadinstitute.org/>

**C3: Colorectal Cancer Coalition**

1414 Prince St., Suite 204
 Alexandria, VA 22314
 Phone: (703) 548-1225 or (877) 427-2111
 Website: <http://fightcolorectalcancer.org>

CADASIL Association

10 Schalks Crossing Rd., Suite 501A-133
 Plainsboro, NJ 08536
 Phone: (307) 215-9840
 Website: <http://cadasilassociation.org/home>

Cain Foundation for Branchio-otorenal (BOR) Syndrome

PO Box 306
 Jannali, 2226
 Website: <http://www.thecainfoundation.com>

Canadian Association for Porphyria

13604 108 Ave. NW
 Edmonton, Alberta, Canada, T5M 2C8
 Phone: (866) 476-2801
 E-mail: porphyria@cpf-inc.ca
 Website: <http://www.cpf-inc.ca>

Canadian Association of Genetic Counsellors (CAGC)

P.O. Box 52083
 Oakville, ON, L6J 7N5, Canada
 Phone: (905) 847-1363
 Fax: (905) 847-3855
 E-mail: CAGCOffice@cagc-accg.ca
 Website: <http://cagc-accg.ca>

Canadian Cancer Society (CCS)

Suite 200, 10 Alcorn Ave.
 Toronto, Canada, ON M4V 3B1
 Phone: (416) 961-7223
 Fax: (416) 961-4189
 E-mail: ccs@cancer.ca
 Website: <http://www.cancer.ca>

Canadian Hemophilia Society

301-666 Sherbrooke St. W
 Montreal, Quebec, Canada, H3A 1E72
 Phone: (514) 848-0503
 Fax: (514) 848-9661
 E-mail: chs@hemophilia.ca
 Website: <http://www.hemophilia.ca/english/index.html>

Canadian Immunodeficiencies Patient Organization (CIPO)

8516-18 Ave. SW
 Edmonton, AB Canada, T6X 0R7
 E-mail: info@cipo.ca
 Website: <http://www.cipo.ca>

Canadian Liver Foundation (CLF)

3100 Steeles Ave. E, Suite 801
 Markham, ON Canada, L3R 8T3
 Phone: (416) 491-3353 or (800) 563-5483
 Fax: (905) 752-1540
 E-mail: clf@liver.ca
 Website: <http://www.liver.ca>

Canadian National Institute for the Blind (CNIB)

1929 Bayview Ave.
 Toronto, ON, Canada M4G 3E8
 Phone: (800) 563-2642
 E-mail: info@cnib.ca
 Website: <http://cnib.ca/en/Pages/default.aspx>

Canadian PKU and Allied Disorders

260 Adelaide St. E, No. 180
 Toronto, ON Canada, M5A 1N1
 Phone: (877) 226-7581
 E-mail: info@canpku.org
 Website: <http://www.canpku.org>

Canadian MPS Society for Mucopolysaccharide & Related Diseases

#218-2055 Commercial Dr.
 Vancouver, BC Canada, V5N 0C7
 Phone: (604) 924-5130
 Toll free: (800) 667-1846
 E-mail: info@mpsociety.ca
 Website: <https://www.mpsociety.ca>

Canavan Foundation

600 West 111th Street, 8A
 New York, NY 10025-1813
 Phone: (866) 907-1847
 E-mail: info@canavanfoundation.org
 Website: <https://www.canavanfoundation.org>

Cancernet. National Cancer Institute, National Institutes of Health

NCI Public Inquiries Office, Building 31, Room 10A03, 31 Center Dr., MSC 2580
 Bethesda, MD 20892-2580

CardioFacioCutaneous Support Network

157 Alder Ave.
McKee City, NJ 08232
Phone: (609) 646-5606

CARES Foundation

2414 Morris Ave., Suite 110
Union, NJ 07083
Phone: (908) 364-0272
Toll free: (866) 227-3737
Fax: (908) 686-2019
E-mail: contact@caresfoundation.org
Website: <https://caresfoundation.org>

Celiac Disease Foundation

20350 Ventura Boulevard, Suite 240
Woodland Hills, CA 91364
Phone: (818) 716-1513
Fax: (818) 267-5577
E-mail: cdf@celiac.org
Website: <http://celiac.org>

Celiac Support Association

PO Box 31700
Omaha, NE 68131-0700
Phone: (402) 558-1347 or (877) 272-4272
Website: <http://www.csaceliacs.org>

Center for Ehlers-Danlos Syndrome Alliance

4805 Hospital Drive
Cass City, MI 48726
Phone: (989) 872-3372
Fax: (989) 912-2203
Website: <https://www.cedsa.org>

Center for Gene Therapy

Nationwide Children's Hospital, 700
Children's Dr.
Columbus, OH 43205
Phone: (614) 722-2000 or (800) 792-8401
Website: <http://www.nationwidechildrens.org/center-for-gene-therapy>

Center for Loss in Multiple Birth, Inc. (CLIMB)

P.O. Box 91377
Anchorage, AK 99509
Phone: (907) 222-5321
E-mail: climb@climb-support.org
Website: <http://www.climb-support.org>

Center for Study of Multiple Birth

333 E. Superior Street, Suite 464
Chicago, IL 60611
Phone: (312) 695-1677
Fax: (312) 908-8777
E-mail: lgk395@northwestern.edu
Website: <http://www.multiplebirth.com>

Centers for Disease Control and Prevention (CDC)

Toll free: (800) 232-4636
Phone: TTY: (888) 232-6348
E-mail: <https://www.cdc.gov/dcs/ContactUs/Form>
Website: <https://www.cdc.gov>

Cerebral Palsy International Research Foundation (CPIRF)

3 Columbus Circle, 15th Floor
New York, NY, United States 10019
Phone: (212) 520-1686
E-mail: info@yourcpf.org
Website: <https://www.yourcpf.org/>

CFC International

183 Brown Rd.
Vestal, NY 13850
Phone: (607) 772-9666
Fax: (607) 748-0409
E-mail: info@cfcysndrome.org
Website: <http://www.cfcysndrome.org>

Charcot-Marie-Tooth Association

P.O. Box 105
Glenolden, PA 19036
Toll free: (800) 606-2682
E-mail: info@cmtausa.org
Website: <https://www.cmtausa.org>

CHARGE Family Support Group

82 Gwendolen Ave.
London, UK, E13 0RD
Phone: 020-8552-6961
Website: <http://www.widerworld.co.uk/charge>

CHARGE Syndrome Foundation

2004 Parkade Blvd.
Columbia, MO 65202-3121
Phone: (800) 442-7604
Website: <http://www.chargesyndrome.org>

Chediak-Higashi Syndrome Association

One South Road, Oyster Bay
New York, NY 11771
Phone: (516) 922-4022 or (800) 789-9477
Fax: (516) 922-4022
E-mail: hpsnet@worldnet.att.net
Website: <http://www.chediak-higashi.org>

Children and Adults with Attention/Hyperactivity Deficit Disorder {CHADD}

4221 Forbes Boulevard, Suite 270
Lanham, MD 20706
Website: <http://www.chadd.org>

Children Living with Inherited Metabolic Diseases (CLIMB)

Climb Building, 176 Nantwich Rd.

Crewe, UK, CW2 6BG
Phone: 0845 241 2173
E-mail: info.svcs@climb.org.uk
Website: <http://www.climb.org.uk>

Children's Brittle Bone Foundation (CBBF)

7701 95th St.
Pleasant Prairie, WI 53158
Phone: (773) 236-2223
Fax: (262) 947-0724
E-mail: webmaster@cbbf.org
Website: <http://www.cbbf.org/home-page>

Children's Cardiomyopathy Foundation (CCF)

24 West Railroad Avenue, Suite 408
Tenaflly, NJ 07670
Toll free: (866) 808-CURE (2873)
E-mail: info@childrenscardiomyopathy.org
Website: <https://www.childrenscardiomyopathy.org/pages/childrens-cardiomyopathy-foundation>

Children's Craniofacial Association (CCA)

13140 Coit Rd., Suite 517
Dallas, TX 75240
Toll free: (800) 535-3643
E-mail: contactCCA@ccakids.com
Website: <https://ccakids.org>

Children's Gaucher Research Fund

8110 Warren Court
Granite Bay, CA 95746
Phone: (916) 797-3700
Fax: (916) 737-3707
Website: <https://www.childrensgaucher.org>

Children's Mitochondrial Disease Network

Mayfield House, 30 Heber Walk,
Chester Way
Northwich, Cheshire UK, CW9 5JB
Phone: +44(0) 01606 43946
Website: <http://www.emdn-mitonet.co.uk>

Children's PKU Network

3306 Bumann Rd.
Encinitas, CA 92024
Phone: (858) 756-0079
Fax: (858) 756-1059
E-mail: pkunetwork@aol.com
Website: <http://www.pkunetwork.org>

Children's Tumor Foundation

120 Wall St., 16th Floor
New York, NY 10005-3904
Phone: (212) 344-6633
Toll free: (800) 323-7938
Fax: (212) 747-0004

E-mail: info@ctf.org
 Website: <http://www.ctf.org>
 Website: <http://www.ctf.org>

Choroideremia Research Foundation
 23 E. Brundeth St.
 Springfield, MA 01109
 Phone: (413) 781-2274
 Website: <http://curechm.org>

Chromosome 18 Clinical Research Center. Department of Pediatrics, University of Texas Health Science Center
 7703 Floyd Curl Drive
 San Antonio, TX 78229
 Phone: (210) 567-7000
 Website: <https://wp.uthscsa.edu/chrome-18/>

Chromosome 18 Registry & Research Society
 7155 Oakridge Drive
 San Antonio, TX 78229
 Phone: (210) 657-4968
 E-mail: office@chromosome18.org
 Website: <https://www.chromosome18.org>

Chromosome 22 Central
 1129 Carolina Gardens Ave.
 Fuquay-Varina, NC 27526
 Phone: (919) 762-7979
 E-mail: usinfo@c22c.org or c22central@gmail.com
 Website: <http://www.c22c.org>

Chromosome Disorder Outreach
 PO Box 724
 Boca Raton, FL 33429-0724
 Phone: (561) 395-4252
 E-mail: info@chromodisorder.org
 Website: <https://chromodisorder.org>

Ciliopathy Alliance
 91 Royal College St.
 London, UK, NW1 0SE
 Website: <http://www.ciliopathyalliance.org>

Cincinnati Children's Hospital Medical Center, Molecular Genetics Laboratory
 3333 Burnet Ave., NRB 1042
 Cincinnati, OH 45229
 Phone: (513) 636-4474
 Fax: (513) 636-4373
 E-mail: moleculargenetics@cchmc.org
 Website: <http://www.cincinnatichildrens.org/service/d/diagnostic-labs/molecular-genetics/default>

CJD Aware!
 2527 South Carrollton Avenue
 New Orleans, LA 70118
 E-mail: info@cjdaware.com

Website: <http://www.cjdaware.com/index.html>

Cleft Lip and Palate Foundation of Smiles
 2044 Michael Avenue SW
 Wyoming, MI 49509
 Phone: (616) 329-1335
 Website: <http://www.cleftsmile.org>

Clinic for Special Children
 535 Bunker Hill Rd.
 Strasburg, PA 17579
 Phone: (717) 687-9407
 Fax: (717) 687-9237
 E-mail: queries@clinicforspecialchildren.org
 Website: <https://clinicforspecialchildren.org>

Coffin-Lowry Syndrome Foundation (CLSF)
 675 Kalmia Pl. NW
 Issaquah, WA 98027
 Phone: (425) 427-0939 after 5 pm PST
 Website: <http://clsf.info>

Cohen Syndrome Association
 Website: <http://cohen-syndrome.org>

College of American Pathologists (CAP)
 325 Waukegan Road
 Northfield, IL 60093-2750
 Toll free: (800) 323-4040
 Phone: (847) 832-7000
 Fax: (847) 832-8000
 E-mail: <https://www.cap.org/contact-and-support/contact-us>
 Website: <https://www.cap.org/>

Colorectal Cancer Alliance
 1025 Vermont Ave. NW, Suite 1066
 Washington, DC 20005
 Toll free: (877) 422-2030
 Phone: (202) 628-0123
 Website: <https://www.ccalliance.org>

Colorectal Cancer Network
 Website: <http://www.colorectal-cancer.net>

Compassionate Friends
 48660 Pontiac Trail, #930808
 Wixom, MI 48393
 Phone: (877) 969-0010
 Fax: (630) 990-0246
 Website: <https://www.compassionatefriends.org>

Congenital Heart Information Network (C.H.I.N.)
 PO Box 3397
 Margate City, NJ 08402
 Phone: (609) 823-4507
 Website: <http://tchin.org>

Cooley's Anemia Foundation
 330 Seventh Avenue, #200
 New York, NY 10001
 Phone: (212) 279-8090
 Website: <https://www.thalassemia.org>

Corneal Dystrophy Foundation
 6066 McAbee Rd.
 San Jose, CA 95120
 Phone: (866) 807-8965
 E-mail: execdir@cornealdystrophyfoundation.org
 Website: <http://www.cornealdystrophyfoundation.org>

Cornelia de Lange Syndrome Foundation, Inc
 30, Tower Lane, #400
 Avon, CT 06001
 Phone: (860) 676-8166
 Toll free: (800) 223-8355. (800) 753-2357
 Fax: (860) 676-8337
 E-mail: info@cdlsusa.org
 Website: <http://www.cdlsusa.org>

Cortical Foundation
 PO Box 340894
 Austin, TX 78734
 Phone: (512) 256-3855
 E-mail: info@cortfoundation.org
 Website: <http://cortfoundation.org/cms>

Costello Kids
 90 Parkfield Rd. N
 New Moston, Manchester, UK, M40 3RQ
 Website: <http://www.costellokids.com>

Craniofacial Foundation of America
 975 E. Third St.
 Chattanooga, TN 37403
 Phone: (423) 778-9176 or (800) 418-3223
 Fax: (423) 778-8172
 Website: <http://www.craniofacialfoundation.org>

Craniosynostosis and Positional Plagiocephaly Support (CAPPS)
 208 NY-109 #205
 Farmingdale, NY 11735
 Phone: (888) 572-5526
 E-mail: info@CAPPSKIDS.org
 Website: <https://www.cappskids.org>

Creutzfeldt-Jakob Disease Foundation, Inc.
 3634 W. Market Street, Suite 110
 Akron, OH 44333
 Toll free: (800) 659-1991
 Fax: (234) 466-7077
 E-mail: help@cjd.foundation.org
 Website: <https://cjd.foundation.org>

Cristine M. Trahms Program for Phenylketonuria

PKU Clinic, Box 357920, University of Washington
Seattle, WA 98195-7920
Phone: (206) 598-1800 or (877) 685-3015
E-mail: pku@u.washington.edu
Website: <http://depts.washington.edu/pku>

Crohn's & Colitis Foundation

733 Third Ave., Suite 510
New York, NY 10017
Phone: (800) 932-2423
E-mail: info@crohnscolitisfoundation.org
Website: <https://www.crohnscolitisfoundation.org>

Cure SMA

925 Busse Rd.
Elk Grove Village, IL 60007
Phone: (800) 886-1762
E-mail: info@curesma.org
Website: <https://www.curesma.org>

Cystic Fibrosis Foundation

4550 Montgomery Avenue, Suite 1100 N
Bethesda, MD 20814
Phone: (301) 951-4422
Phone: (800) FIGHT CF (344-4823)
E-mail: info@cff.org
Website: <https://www.cff.org>

Cystinosis Foundation

58 Miramonte Dr.
Moraga, CA 94556
Phone: (888) 631-1588
Toll free: (925) 631-1588
Website: <http://cystinosis.com>

Cystinosis Research Network

302 Whytegate Court
Lake Forest, IL 60045
Phone: (847) 735-0471
Toll free: (866) 276-3369
Fax: (847) 235-2273
E-mail: info@cystinosis.org
Website: <https://cystinosis.org>

D**Dandy-Walker Syndrome Network**

5030 142nd Path West
Apple Valley, MN 55124 USA
Phone: (612) 423-4008
Website: <http://www.kumc.edu/gec/support/dandy.htm>

Depression and Bipolar Support Alliance

55 East Jackson Boulevard, Suite 490
Chicago, IL 60604
Toll free: (800) 826-3632

Fax: (312) 642-7243

Website: <http://www.dbsalliance.org/site/PageServer?pagename=home>

Desmoid Tumor Research Foundation (DTRF)

PO Box 273
Suffern, NY 10901
E-mail: marlene@dtmf.org
Website: <http://www.dtmf.org>

Developmental Delay Resources (DDR)

5801 Beacon Street
Pittsburgh, PA 15217
Phone: (800) 497-0944
Fax: (412) 422-1374
E-mail: devdelay@mindspring.com
Website: <http://www.devdelay.org>

Diamond Blackfan Anemia Foundation (DBAF)

PO Box 1092
West Seneca, New York 14224
Phone: (716) 674-2818
E-mail: dbafoundation@juno.com
Website: <https://dbafoundation.org>

Diamond Blackfan Anemia Registry, The Feinstein Institutes for Medical Research

350 Community Drive
Manhasset, NY 11030
Toll free: (888) 884-DBAR (3227)
Fax: (516) 562-1599
E-mail: <https://www.dbar.org/contact>
Website: <https://www.dbar.org>

Down Syndrome Education USA

1451 Quail St., Suite 110
Newport Beach, CA 92660-2747
Phone: (949) 757-1877
E-mail: info@dseusa.org
Website: <http://www.dseusa.org/en-us>

Dysautonomia Foundation

315 W. 39th St., Suite 701
New York, NY 10018
Phone: (212) 279-1066
Fax: (212) 279-2066
E-mail: info@famdys.org
Website: <http://www.familialdysautonomia.org>

Dystonia Medical Research Foundation

One East Wacker Drive, Suite 1730
Chicago, IL 60601-1980
Phone: (312) 755-0198
Toll free: (800) 377-3978
Fax: (312) 803-0138
E-mail: dystonia@dystonia-foundation.org
Website: <https://dystonia-foundation.org>

Dystrophic Epidermolysis Bullosa Research Association (DEBRA) of America

75 Broad St., Suite 300
New York, NY 10004
Phone: (212) 868-1573 or (855) CURE-4-EB
Fax: (212) 868-9296
E-mail: staff@debra.org
Website: <http://www.debra.org>

E**Ectodermal Dysplasia Society**

Unit 1 Maida Vale Business Centre
Cheltenham, Gloucestershire UK, GL53 7ER
Phone: +44 (0) 1242 261332
E-mail: info@edsociety.co.uk
Website: <https://edsociety.co.uk>

Ehlers-Danlos Society

1732 1st Avenue #20373
New York, NY 10128
Phone: (410) 670-7577
Website: <https://www.ehlers-danlos.com>

Ellis-van Crevelde Foundation

Farthingdale Farm, Hackmans Lane
Purleigh, Chelmsford UK, CM3 6RW
Phone: 01-621-829675
Website: <http://patient.info/support/Ellis-van-Crevelde-Foundation.htm>

Endocrine Society

2055 L St. NW, Suite 600
Washington, DC 20036
Phone: (202) 971-3636
Toll free: (888) 363-6274
Fax: (202) 736-9705
E-mail: info@endocrine.org
Website: <https://www.endocrine.org>

Epidermolysis Bullosa Medical Research Foundation

2757 Anchor Ave.
Los Angeles, CA 90064
Website: <http://www.ebkids.org>

Epilepsy and Brain Mapping, Huntington Hospital

100 W. California Boulevard
Pasadena, CA 91105
Phone: (626) 397-5000
Website: <https://www.huntingtonhospital.org/our-services/neurology/epilepsy-and-brain-mapping/>

Epilepsy Foundation

3540 Crain Highway, Suite 675
Bowie, MD 20716
Toll free: (800) 332-1000
Phone: (301) 459-3700

Fax: 301-577-2684
E-mail: ContactUs@efa.org
Website: <http://www.epilepsy.com>

**Eunice Kennedy Shriver National
Institute of Child Health and
Human Development**

PO Box 3006
Rockville, MD 20847
Phone: (800) 370-2943
Fax: (866) 760-5947
E-mail: NICHDInformationResourceCenter@mail.nih.gov
Website: <https://www.nichd.nih.gov>

EURORDIS—Rare Diseases Europe

96, rue Didot
Paris, France, 75014
Phone: +33 (1) 56.53.52.10
Fax: +33 (1) 56.53.52.15
E-mail: eurordis@eurordis.org
Website: <https://www.eurordis.org>

F

**FACES: The National Craniofacial
Association**

PO Box 11082
Chattanooga, TN 37401
Toll free: (800) 332-2373
E-mail: info@faces-cranio.org
Website: <https://www.faces-cranio.org>

**Facing Our Risk of Cancer
Empowered (FORCE)**

16057 Tampa Palms Boulevard W,
PMB #373
Tampa, FL 33647
Phone: (954) 827-2200
E-mail: info@facingourrisk.org
Website: <http://www.facingourrisk.org>

Family Equality

475 Park Avenue, Suite 2100
New York, NY 10016
Phone: (646) 880-3005
Website: <https://www.familyequality.org>

Fanconi Anemia Research Fund

360 E. 10th Avenue, Suite 201
Eugene, OR 97401
Phone: (888) 326-2664
Website: <http://www.fanconi.org>

**Fatty Oxidation Disorders (FOD)
Family Support Group**

PO Box 54
Okemos, MI 48805-0054
Phone: (517) 381-1940
Fax: (866) 290-5206
E-mail: deb@fodsupport.org
E-mail: fodgroup@gmail.com
Website: <https://www.fodsupport.org>

**Federal Trade Commission
Consumer Information**

600 Pennsylvania Avenue, NW
Washington, D.C. 20580
Toll free: To file a complaint: (877)
FTC-HELP
Phone: (202) 326-2222
Website: <https://www.consumer.ftc.gov>

**Federation of Esophageal Atresia and
Tracheo-Esophageal Fistula
Support Groups**

Sommerrainstrasse 61
Stuttgart, Germany, 70374
Website: <http://www.we-are-eat.org>

**Fetal Alcohol Spectrum Disorders
Center for Excellence (FASD)**

SAMHSA FASD Center for Excellence,
2101 Gaither Road, Suite 600
Rockville, MD Canada, 20850
Phone: (866) 786-7327
E-mail: Jon.dunbar@samhsa.hhs.gov
Website: <http://fasdcenter.samhsa.gov>

Fetal Health Foundation

9786 S. Holland St.
Littleton, CO 80127
Phone: (303) 932-0553 or (877) 789-
HOPE
E-mail: info@fetalhealthfoundation.org
Website: <http://www.fetalhealthfoundation.org>

Fight SMA

8016 Staples Mill Rd.
Richmond, VA 23228-2713
Phone: (703) 299-1144
E-mail: web@fightasma.org
Website: <http://fightasma.org>

**FINDbase: Genome Variation Allele
Frequencies Worldwide**

University of Patras School of Health
Sciences, Department of Pharmacy,
University Campus, Rion
Patras, Greece, GR-265 04
Phone: [no telephone numbers given]
E-mail: permed@upatras.gr
Website: <https://www.findbase.org/#/>

**Food and Drug Administration
(FDA)**

10903 New Hampshire Ave.
Silver Spring, MD 20993
Fax: (888) INFO-FDA (463-6332)
Website: <http://www.fda.gov/AboutFDA/Contact-FDA/default.htm>
Website: <http://www.fda.gov/default.htm>

Foundation Fighting Blindness

6925 Oakland Mills Road, #701
Columbia, MD 21045
Toll free: (800) 683-5555

Phone: TDD: (800) 683-5551
E-mail: info@FightBlindness.org
Website: <https://www.fightingblindness.org>

**Foundation Fighting Blindness
(Canada)**

890 Yonge St., 12th Floor
Toronto, ON, Canada M4W 3P4
Phone: (416) 360-4200 or (800) 461-
3331
Fax: (416) 360-0060
E-mail: info@ffb.ca
Website: <http://www.ffb.ca>

Foundation for Faces of Children

258 Harvard Street, #367
Brookline, MA 02446-2904
Phone: (617) 355-8299
E-mail: info@facesofchildren.org
Website: <http://www.facesofchildren.org>

**Foundation for Ichthyosis & Related
Skin Types (FIRST)**

PO Box 1067
Lansdale, PA 19446
Toll free: (800) 545-3286
Phone: (215) 997-9400
E-mail: info@firstskinfoundation.org
Website: <https://www.firstskinfoundation.org>

**Foundation for Osteoporosis
Research and Education**

300 27th Street
Oakland, CA 94612
Phone: (888) 266-3015
Website: <http://www.fore.org>

**Foundation for Peripheral
Neuropathy**

485 Half Day Rd., Suite 350
Buffalo Grove, IL 60089
Phone: (877) 883-9942
Fax: (847) 883-9960
Website: <https://www.foundationforpn.org>

**Foundation of the American
Academy of Ophthalmology**

PO Box 7424
San Francisco, CA 94120-7424
Phone: (415) 561-8500
Website: <http://www.aao.org>

**Fragile X Research Foundation
(FRAXA)**

10 Prince Place, Suite 203
Newburyport, MA 01950
Phone: (978) 462-1866
E-mail: info@fraxa.org
Website: <http://www.fraxa.org>

Friedreich's Ataxia Research Alliance

533 W. Uwchlan Avenue

Downingtown, PA 19335
 Phone: (484) 879-6160
 Fax: (484) 872-1402
 E-mail: info@cureFA.org
 Website: <https://cureFA.org>

FSH Society
 450 Bedford Street
 Lexington, MA 02420
 Phone: (781) 301-6060
 E-mail: info@fshsociety.org
 Website: <http://www.fshsociety.org>

FTD Support Forum
 Website: <http://ftdsupportforum.com>

G

GAVI, Global Vaccine Alliance
 Global Health Campus Chemin du
 Pommier 40 1218
 Le Grand-Saconnex, Switzerland,
 Toll free: +41 22 909 6500
 Fax: +41 22 909 6550
 E-mail: info@gavi.org

Genetic Alliance
 26400 Woodfield Road, #189
 Damascus, MD 20872
 Phone: (202) 966-5557
 Fax: (202) 966-8553
 E-mail: info@geneticalliance.org
 Website: <http://www.geneticalliance.org>

**Genetic and Rare Diseases
 Information Center (GARD)**
 P.O. Box 8126
 Gaithersburg, MD 20898-8126
 Toll free: (888) 205-2311
 Phone: TTY: (888) 205-3223
 Fax: (301) 251-4911
 E-mail: [https://ncats.force.com/
 gccinquiries/GccInquiryFormEn](https://ncats.force.com/gccinquiries/GccInquiryFormEn)
 Website: <https://rarediseases.info.nih.gov>

**The Genetic Disease Foundation,
 Mount Sinai School of Medicine**
 One Gustavo L. Levy Place, Box 1497
 New York, NY 10029
 E-mail: info@geneticdiseasefoundation.org
 Website: <http://www.geneticdiseasefoundation.org>

**Genetic Science Learning Center,
 University of Utah**
 383 Colorow Dr.
 Salt Lake City, UT 84108
 Phone: (801) 585-3470
 Website: <http://learn.genetics.utah.edu>

Genetics Society of America
 6120 Executive Boulevard Suite 550

Rockville, MD 20852
 Phone: (240) 880-2000
 Website: <https://genetics-gsa.org>

Gilda's Club
 195 West Houston Street
 New York, NY 10014
 Phone: (212) 647-9700
 Fax: (212) 647-1151
 Website: <http://www.gildasclubnyc.org>

Glaucoma Foundation
 80 Maiden Lane, Suite 700
 New York, NY 10038
 Phone: (212) 285-0080
 E-mail: info@glaucomafoundation.org
 Website: <http://www.glaucomafoundation.org>

**Global and Regional Asperger's
 Syndrome Partnership (GRASP)**
 369 Lexington Avenue, 2nd Floor
 New York, NY 10017
 Toll free: (888) 474-7277
 E-mail: info@grasp.org
 Website: <https://grasp.org>

Global Initiative for Asthma (GINA)
 Website: <http://www.ginasthma.com>

Gluten Intolerance Group
 31214 124th Ave. SE
 Auburn, WA 98092
 Phone: (253) 833-6655
 Fax: (253) 833-6675
 E-mail: customerservice@gluten.net
 Website: <https://www.gluten.org>

Grace Wilsey Foundation
 E-mail: matt@gracewilsey.org
 Website: <https://gracewilsey.org>

**Greenberg Center for Skeletal
 Dysplasias**
 Johns Hopkins Hospital, 600 N. Wolfe St.
 Baltimore, MD 21287
 Phone: (410) 614-0977
 Fax: (410) 502-2475
 Website: [https://igm.jhmi.edu/content/
 greenberg-center-skeletal-
 dysplasias-welcome](https://igm.jhmi.edu/content/greenberg-center-skeletal-dysplasias-welcome)

**GTEx Consortium, National Human
 Genome Research Institute**
 E-mail: GTExInfo@mail.nih.gov
 Website: [https://commonfund.nih.gov/
 GTEx/index](https://commonfund.nih.gov/GTEx/index)

H

HCU Network America
 15 S. Mallory Ave.
 Batavia, Illinois 60510
 Phone: 630-360-2087

E-mail: info@hcunetworkamerica.org
 Website: <https://hcunetworkamerica.org>

Hearing Health Foundation
 363 Seventh Ave., 10th Floor
 New York, NY 10001-3904
 Phone: (212) 257-6140 or (866) 454-3924
 E-mail: info@hhf.org
 Website: <http://hearinghealthfoundation.org>

Hearing Loss Association of America
 6116 Executive Boulevard, Suite 320
 Rockville, MD 20852
 Phone: (301) 657-2248
 Fax: (301) 913-9413
 Website: <http://www.hearingloss.org>

Helen Keller Services for the Blind
 141 Middle Neck Rd.
 Sands Point, NY 11050
 Phone: (516) 944-8900
 Fax: (516) 944-7302
 E-mail: info@helenkeller.org
 Website: <https://www.helenkeller.org>

Helping Hands Foundation
 E-mail: info@HelpingHandsGroup.org
 Website: <http://helpinghandsgroup.org>

Hemophilia Federation of America
 820 First St. NE, Suite 720
 Washington, DC 20002
 Phone: (202) 675-6984 or (800) 230-9797
 Fax: (972) 616-6211
 Website: <http://www.hemophiliafed.org>

Henrietta Lacks Commission
 1100 Confroy Drive
 South Boston, VA 24592
 E-mail: [https://henrietalacks
 commission.com/#contact](https://henrietalackscommission.com/#contact)
 Website: <https://henrietalackscommission.com/>

Hereditary Colon Cancer Foundation
 3519 NE 15th Avenue
 Portland City, OR, 97212
 Phone: (334) 740-8657
 E-mail: info@HCCtakesGuts.org
 Website: <http://www.hcctakesguts.org>

Hereditary Neuropathy Foundation
 1641 Third Avenue, #28K
 New York, NY 10128
 Phone: (646) 429-0981
 Fax: (917) 591-2758
 E-mail: info@hnf-cure.org
 Website: <http://www.hnf-cure.org>

**Hermansky-Pudlak Syndrome
 Network**
 1 South Rd.
 Oyster Bay, NY 11771-1905
 Phone: (800) 789-9HPS

Fax: (516) 624-0640
E-mail: info@hpsnetwork.org
Website: <https://www.hpsnetwork.org>

HHT Foundation International

PO Box 329
Monkton, MD 21111
Phone: (410) 357-9932
Fax: (410) 357-0655
E-mail: hhtinfo@curehht.org
Website: <http://curehht.org>

**Hide & Seek Foundation for
Lysosomal Storage Research**

6475 East Pacific Coast Highway, Suite 466
Long Beach, CA 90803
Phone: (877) 621-1122
Fax: (866) 215-8850
E-mail: info@hideandseek.org
Website: <http://www.hideandseek.org>

Hope for Hypothalamic Hamartomas

PO Box 721
Waddell, AZ 85355
E-mail: admin@hopeforhh.org
Website: <http://hopeforhh.org>

Hope for NKH

8904 232nd Street East
Graham, WA 98338
Phone: (253) 219-7535 or (989) 845-4253
E-mail: hopeforhkh@gmail.com
Website: <http://hopeforhkh.org>

HPP-Choose Hope

2140 W. Greenview Dr., Suite 10
Middleton, WI 53562
Phone: (888) 348-4673
E-mail: info@hppchoosehope.com
Website: <http://www.choosehope.org>

Human Genome Editing Initiative

500 Fifth Street NW
Washington, D.C. 20001
Phone: (202) 334-2000
Website: <https://www.nationalacademies.org/our-work/human-gene-editing-initiative>

Human Growth Foundation (HGF)

997 Glen Cove Ave., Suite 5
Glen Head, NY 11545
Phone: (800) 451-6434
Fax: (516) 671-4055
E-mail: hgf1@hgfound.org
Website: <https://www.hgfound.org>

Hunter's Hope Foundation

6368 W. Quaker St., PO Box 643
Orchard Park, NY 14127
Phone: (716) 667-1200
E-mail: info@huntershope.org
Website: <http://www.huntershope.org>

Huntington's Disease Society of America

505 Eighth Avenue, Suite 902
New York, NY 10018
Phone: (800) 345-HDSA
E-mail: hdsainfo@hdsa.org
Website: <http://hdsa.org>

Hydrocephalus Association

4340 East West Hwy., Suite 905
Bethesda, MD 20814-4447
Phone: (301) 202-3811 or (888) 598-3789
Fax: (301) 202-3813
E-mail: info@hydroassoc.org
Website: <https://www.hydroassoc.org>

Hypertrophic Cardiomyopathy Association (HCMA)

1450 Western Ave., Suite 101
Albany, NY 12203
Phone: (973) 983-7429
Fax: (973) 983-7870
E-mail: support@4hcm.org
Website: <https://www.4hcm.org>

Hypospadias and Epispadias Association

PO Box 1617
Kyle, TX 78640
E-mail: heainfo1@gmail.com
Website: <http://heainfo.org>



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Website: <http://icahn.mssm.edu/departments-and-institutes/genomics>

Illumina, Inc.

5200 Illumina Way
San Diego, CA 92122
Phone: (858) 202-4500
Fax: (858) 202-4766
Website: <https://www.illumina.com/>

Immune Deficiency Foundation

110 West Rd., Suite 300
Towson, MD 21204
Phone: (800) 296-4433
Fax: (410) 321-9165
Website: <https://primaryimmune.org>

IMPACC (Intestinal Multiple Polyposis and Colorectal Cancer)

PO Box 11
Conyngham, PA 18219
Phone: (570) 788-3712

E-mail: impacc@epix.net

Incontinentia Pigmenti International Foundation (IPIF)

78 Saint Moritz Dr.
Erial, NJ 08081
Phone: (212) 452-1231
Fax: (212) 452-1231
E-mail: ipif@ipif.org
Website: <http://www.ipif.org>

Institute of Human Genetics, University Hospital Cologne

Building 47 (Women's Hospital), 9th Floor, Kerpener Str. 34
Cologne, Germany, 50931
Phone: +49 221 478-86837
Fax: +49 221 478-86812
E-mail: mvz-humangenetik@uk-koeln.de
Website: <https://humangenetik.uk-koeln.de/en/>

International 22q11.2 Deletion Syndrome Foundation, Inc.

P.O. Box 532
Matawan, NJ 07747
Phone: (877) 739-1849
E-mail: info@22q.org
Website: <http://www.22q.org>

International Advocate for Glycoprotein Storage Diseases (ISMRD)

20880 Canyon View Dr.
Saratoga, CA 95070
E-mail: info@ismrd.org
Website: <http://www.ismrd.org>

International Center for Fabry Disease, Department of Genetics and Genomic Sciences, Icahn School of Medicine

1 Gustave L. Levy Place
New York, NY 10029-5674
Phone: (212) 241-6500
E-mail: fabry.disease@mssm.edu
Website: <https://icahn.mssm.edu/research/fabry/what-is>

International Essential Tremor Foundation

PO Box 14005
Lenexa, KS 66285-4005
Phone: (888) 387-3667
Fax: (913) 341-1296
E-mail: info@essentialtremor.org
Website: <http://www.essentialtremor.org>

International Foundation for Functional Gastrointestinal Disorders (IFFGD)

700 W. Virginia St., No. 201
Milwaukee, WI 53204
Phone: (888) 964-2001 or (414) 964-1799

Fax: (414) 964-7176
E-mail: iffgd@iffgd.org
Website: <http://www.iffgd.org>

International Foundation for Optic Nerve Disease (IFOND)

PO Box 777
Cornwall, NY 12518
Phone: (675) 206-7250
E-mail: IFONDORG@gmail.com
Website: <http://www.ifond.org>

International League Against Epilepsy (ILAE)

2221 Justin Road, Suite 119-352
Flower Mound, TX 75028
Phone: (860) 586-7547
Website: <https://www.ilae.org>

International Prader-Willi Syndrome Organization

1779 Massachusetts Avenue, NW, Suite 500
Washington, D.C.
Phone: (203) 744-0100
Website: <https://rarediseases.org/>

International Progeria Registry, Progeria Research Foundation

PO Box 3453
Peabody, MA 01961
Phone: (978) 535-2594
Fax: (978) 535-5849
E-mail: info@progeriaresearch.org
Website: http://www.progeriaresearch.org/patient_registry.html

International Registry of Werner Syndrome, Department of Pathology, School of Medicine, University of Washington

Box 357470, Health Sciences Center, Room K-543, 1959 NE Pacific St.
Seattle, WA 98195
Phone: (206) 543-5088
E-mail: picard@u.washington.edu
Website: <http://www.wernersyndrome.org/registry/registry.html>

International Rett Syndrome Foundation

4600 Devitt Dr.
Cincinnati, OH 45246
Phone: (800) 818-7388
E-mail: admin@rettsyndrome.org
Website: <http://www.rettsyndrome.org>

International Society for Prenatal Diagnosis (ISPD)

154 Hansen Road, Suite 201
Charlottesville, VA 22911
Phone: (434) 979-4773
Fax: (434) 977-1856
E-mail: info@ispdhome.org
Website: <http://ispdhome.org>

Intersex Society of North America

979 Golf Course Dr., No. 282
Rohnert Park, CA 94928
Website: <http://www.isna.org>

Iron Disorders Institute

PO Box 4891
Greenville, SC 29608
Website: <https://irondisorders.org>

ISMARD: The International Advocate for Glycoprotein Storage Diseases

20880 Canyon View Dr.
Saratoga, CA 95070
E-mail: info@ismrd.org
Website: <http://www.ismrd.org>

Jain Foundation

9725 Third Ave. NE, Suite 204
Seattle, WA 98115
Phone: (425) 882-1492
E-mail: patients@jain-foundation.org
Website: <http://www.jain-foundation.org>

Jeffrey Modell Foundation

780 Third Ave.
New York, NY 10017
Fax: (212) 764-4180
E-mail: info@jmfworld.org
Website: <http://www.info4pi.org>

Johns Hopkins University

3400 N. Charles Street
Baltimore, MD 21218
Phone: (410) 516-8000
Website: <https://www.jhu.edu/>

Joshua Frase Foundation

PO Box 2041
Ponte Vedra Beach, FL 32004
Phone: (904) 607-1358
Fax: (904) 273-9818
E-mail: info@joshuafrase.org

Joubert Syndrome and Related Disorders Foundation

9 Dorenfeld Court
Petaluma, CA
E-mail: president@jsrdf.org
Website: <https://www.jsrdf.org>

Juvenile Diabetes Research Foundation International (JDRF)

26 Broadway
New York, NY 10004
Phone: (212) 785-9500 or (800) 533-2873
Fax: (212) 785-9595
E-mail: info@jdrf.org
Website: <http://www.jdrf.org>

K

Kabuki Syndrome Network

8060 Struthers
Regina, SK, Canada S4Y 1J3
Phone: (306) 543-8715
Website: <http://kabukisyndrome.com>

Kathryn and Alan C. Greenberg Center for Skeletal Dysplasias, McKusick-Nathans Institute of Genetic Medicine. Johns Hopkins University

600 N. Wolfe St.
Baltimore, MD 21287
Phone: (410) 614-0977
Fax: (410) 502-2475
Website: <https://igm.jhmi.edu/content/greenberg-center-skeletal-dysplasias-welcome>

Kennedy's Disease Association

PO Box 1105
Coarsegold, CA 93614
Phone: (559)-658-5950
E-mail: info@kennedysdisease.org
Website: <http://www.kennedysdisease.org>

Kidney and Urology Foundation of America

104 W. 40th St., Suite 500
New York, NY 10018
Phone: (800) 633-6628
Website: <http://www.kidneyurology.org>

Kids with Heart National Association for Children's Heart Disorders

1578 Careful Dr.
Green Bay, WI 54304
Website: <http://kidswithheart.org>

Klippel-Trenaunay Syndrome Support Group

Phone: (513) 722-7724
E-mail: support@k-t.org
Website: <http://k-t.org>

L

Learning Disabilities Association of America

4156 Library Road
Pittsburgh, PA 15234-1349
Phone: (412) 341-1515
Fax: (412) 344-0224
E-mail: info@LDAAmerica.org
Website: <http://ldaamerica.org>

Let's Face It

72 Victoria Ave.
Westgate on Sea, Kent UK, CT8 8BH
Phone: 01843 833724

E-mail: chrisletsfaceit@aol.com
 Website: <http://www.lets-face-it.org.uk>

Leukemia & Lymphoma Society
 1311 Mamaroneck Ave., Suite 310
 White Plains, NY 10605
 Phone: (914) 949-5213
 Fax: (914) 949-6691
 Website: <http://www.lls.org>

Li-Fraumeni Syndrome Association
 PO Box 6458
 Holliston, MA 01746
 Phone: (855) 239-LFSA
 Website: <http://www.lfsassociation.org>

**Limb Study, Department of
 Bioengineering and Therapeutic
 Sciences, University of California,
 San Francisco**
 Rock Hall, 1550 Fourth St., Room
 RH584C
 San Francisco, CA 94158
 Phone: (415) 476-1838
 Fax: (415) 502-0720
 E-mail: bts.limbstudy@ucsf.edu
 Website: <http://pharm.ucsf.edu/limb-study>

Lissencephaly Network
 716 Autumn Ridge Lane
 Fort Wayne, IN 46804-6402
 Phone: (219) 432-4310
 Fax: (219) 432-4310
 E-mail: lissencephalyOne@aol.com
 Website: <http://www.lissencephaly.org>

Little People of America (LPA)
 617 Broadway #518
 Sonoma, CA 95476
 Toll free: (888) LPA-2001
 Phone: (714) 368-3689
 Fax: (707) 721-1896
 E-mail: info@lpaonline.org
 Website: <https://www.lpaonline.org>

**LND Net (Lesch-Nyhan Disease
 support group)**
 Website: <http://lndnet.ning.com>

Lowe Syndrome Association
 7025 CR 46A Ste. 1071 #434
 Lake Mary, FL 32746-4753
 Phone: (216) 630-7723
 E-mail: info@lowesyndrome.org
 Website: <https://lowesyndrome.org>

Lupus Foundation of America
 2121 K St. NW, Suite 200
 Washington, DC 20037
 Phone: (202) 349-1155 or (800) 558-0121
 Fax: (202) 349-1156
 E-mail: info@lupus.org
 Website: <http://www.lupus.org>

Lynch Syndrome International (LSI)
 PO Box 19
 Madison, CT 06443
 Phone: (203) 779-5034
 Website: <http://www.lynchcancers.com>



MAB Community Services
 200 Ivy St.
 Brookline, MA 02446
 Phone: (617) 738-5110
 Website: <http://www.mabcommunity.org>

The MAGIC Foundation
 4200 Cantera Drive, #106
 Warrenville, IL 60555
 Phone: (630) 836-8200
 Toll free: (800) 362-4423
 Fax: (630) 836-8181
 E-mail: contactus@magicfoundation.org
 Website: <https://www.magicfoundation.org>

**Malignant Hyperthermia Association
 of the United States**
 PO Box 1069
 Sherburne, NY 13460
 Phone: (607) 674-7901
 Fax: (607) 674-7910
 E-mail: fay@mhaus.org
 Website: <https://www.mhaus.org>

March of Dimes
 1550 Crystal Dr, Suite 1300
 Arlington, VA 22202
 Phone: (888) 663-4637
 Website: <https://www.marchofdimes.org>

Marfan Foundation
 22 Manhasset Ave.
 Port Washington, NY 11050
 Phone: (516) 883-8712
 Toll free: (800) 8-MARFAN
 Fax: (516) 883-8040
 Website: <https://www.marfan.org>

Melanoma Institute Australia
 40 Rocklands Road
 Wollstonecraft, NSW, Australia, 2065
 Phone: +61 2 9911 7200
 Fax: +61 79547290
 E-mail: info@melanoma.org.au
 Website: <https://www.melanoma.org.au/>

Melanoma Network of Canada
 482 South Service Road E. Unit 110
 Oakville, Ontario, Canada, L6J 2X6
 Toll free: (877) 560-8035
 E-mail: info@melanomaneetwork.ca

Website: <https://www.melanoma-network.ca/>

Mental Health America
 500 Montgomery Street, Suite 820
 Alexandria, VA 22314
 Phone: (703) 684-7722
 Toll free: (800) 969-6642
 Fax: (703) 684-5968
 Website: <https://www.mhanational.org>

MHE Coalition
 6783 York Rd. #104
 Parma Heights, OH 44130
 Phone: (845) 258-6058
 Website: <http://www.mhecoalition.org>

MHE Research Foundation
 8019 Harbor View Terrace
 Brooklyn, NY 11209
 Phone: (917) 848-7774
 Website: <http://www.mheresearchfoundation.org>

**The Michael J. Fox Foundation for
 Parkinson's Research**
 Grand Central Station, P.O. Box 4777
 New York, NY 10163-4777
 Phone: (800) 708-7644
 Website: <https://www.michaeljfox.org>

**Minority Genetic Professionals
 Network of the Western States
 Regional Genetics Network**
 Hawaii Department of Health Genetics
 Program, 741 Sunset Avenue
 Honolulu, HI 96816
 Phone: (808) 733-9039
 Website: <https://minoritygenetics.org>

MitoAction
 PO Box 310
 Novi, MI 48376
 Toll free: (888) 648-6228
 E-mail: info@mitoaction.org
 Website: <https://www.mitoaction.org>

MitoCanada
 30052-478 Dundas Street West
 Oakville, Ontario, Canada, L6H 7L8
 Toll free: (877) 708-MITO (6486)
 E-mail: info@mitocanada.org
 Website: <https://mitocanada.org/>

Moebius Syndrome Foundation
 PO Box 147, EH32
 Pilot Grove, MO 65276
 Phone: (660) 834-3406
 E-mail: vicki@moebiussyndrome.com
 Website: <http://www.moebiussyndrome.com/index.cfm>

**MotherToBaby: A Service of the
 Organization of Teratology
 Information Specialists (OTIS)**
 5034A Thoroughbred Lane

Brentwood, TN 37027
Phone: (866) 626-OTIS
E-mail: contactus@otispregnancy.org
Website: <http://www.mothertobaby.org>

Mowat-Wilson Syndrome Foundation
4009 Tyler William Ln.
Las Vegas, NV 89130-2628
Phone: (702) 658-5391
E-mail: <https://mowat-wilson.org/about/contact/>
Website: <http://www.mowat-wilson.org>

MSS Research Foundation
Oeverbiesstraat 20
The Hague, NL The Netherlands, 2548 WP
Phone: 31703356956
E-mail: info@marshallsmith.org
Website: <http://www.marshallsmith.org>

Multiple Sclerosis Association of America
706 Haddonfield Road
Cherry Hill, NJ 08002
Phone: (800) 532-7667
Website: <http://www.msaa.org>

Multiple Sclerosis Foundation
6350 North Andrews Ave.
Ft. Lauderdale, FL 33309-2130
Phone: (954) 776-6805 or (888) 673-6287
Website: <http://www.msfocus.org>

Multiple Sclerosis International Federation
Skyline House, 200 Union Street
London SE1 0LX, UK,
Phone: +44 (0) 20 7620 1911
Website: <http://www.msif.org>

Multiples of America
2000 Mallory Lane, Suite 130-600
Franklin, TN 37067-8231
Phone: (248) 231-4480
E-mail: info@multiplesofamerica.org
Website: <http://www.nomotc.org>

Muscular Dystrophy Association (MDA)
161 N. Clark, Suite 3550
Chicago, IL 60601
Phone: (800) 572-1717
E-mail: ResourceCenter@mdausa.org
Website: <https://www.mda.org>

Muscular Dystrophy Canada
40 Eglinton Avenue East, Unit 500
Toronto, ON, Canada, M4P 3A2
Toll free: (800) 567-2873
E-mail: info@muscle.ca
Website: <https://muscle.ca>

Muscular Dystrophy Family Foundation
PO Box 776

Carmel, IN 46032
Phone: (317) 615-9140
Website: <http://www.mdff.org>

Muscular Dystrophy UK
Phone: (800) 652-6352
E-mail: info@musculardystrophyuk.org
Website: <https://www.musculardystrophyuk.org>

My Face
333 E. 30th St., Lobby Unit
New York, NY 10016
Phone: (212) 263-6656
Fax: (212) 263-7534
E-mail: info@myface.org
Website: <http://myface.org>

Myasthenia Gravis Foundation of America
355 Lexington Ave., 15th Floor
New York, NY 10017
Phone: (800) 541-5454
Fax: (212) 370-9047
Website: <http://www.myasthenia.org>

Myotonic Dystrophy Family Registry (MDFR)
Phone: (602) 435-7496
E-mail: Coordinator@myotonicregistry.org
E-mail: myotonicregistry.patientcrossroads.org

Myotonic Dystrophy Foundation
1004A O'Reilly Ave.
San Francisco, CA 94129
Phone: (866) 968-6642
E-mail: info@myotonic.org
Website: <http://www.myotonic.org>

Narcolepsy Network
46 Union Drive, #A212
North Kingstown, RI 02852
Phone: (888) 292-6522
Toll free: (401) 667-2523
Fax: (401) 633-6567
E-mail: NarNet@narcolepsynetwork.org
Website: <http://www.narcolepsynetwork.org>

National Adrenal Diseases Foundation
PO Box 566
Lake Zurich, IL 60047
Phone: (847) 726-9010
E-mail: nadfsupport@nadf.us
Website: <https://www.nadf.us>

National Alliance on Mental Illness (NAMI)
4301 Wilson Boulevard, Suite 300
Arlington, VA 22203
Phone: (703) 524-7600
Toll free: (888) 999-6264
E-mail: <https://www.nami.org/Contact-Us>
Website: <https://www.nami.org>

National Alopecia Areata Foundation (NAAF)
65 Mitchell Blvd., Suite 200-B
San Rafael, CA 94903
Phone: (415) 472-3780
Fax: (415) 480-1800
E-mail: info@naaf.org
Website: <https://www.naaf.org>

National Association of the Deaf
8630 Fenton St., No. 820
Silver Spring, MD 20910
Phone: (301) 328-1443
Phone: TTY: (301) 810-3182
Fax: (301) 587-1791
E-mail: nad.info@nad.org
Website: <https://www.nad.org>

National Asthma Education and Prevention Program (NAEPP). School Asthma Education Subcommittee
Website: http://www.nhlbi.nih.gov/health/dci/Diseases/Asthma/Asthma_WhatIs.html

National Ataxia Foundation (NAF)
600 Highway 169 South, Suite 1725
Minneapolis, MN 55426
Phone: (763) 553-0020
Fax: (763) 553-0167
E-mail: naf@ataxia.org
Website: <https://www.ataxia.org>

National Birth Defects Prevention Network
1321 Upland Dr., Suite 1561
Houston, TX 77043
E-mail: nbdpn@nbdpn.org
Website: <https://www.nbdpn.org>

National Blood Clot Alliance
P.O. Box 825687
Philadelphia, PA 19182-5687
Phone: (703) 935-8845
Toll free: (877) 466-2568
E-mail: info@stoptheclot.org
Website: <http://www.stoptheclot.org>

National Brain Tumor Society
55 Chapel Street, Suite 200
Newton, MA 02458
Phone: (617) 924-9997
Fax: (617) 924-9998
E-mail: <https://braintumor.org/our-mission/contact-us>
Website: <http://braintumor.org>

National Cancer Institute (NCI)

Phone: (800) 422-6237
E-mail: NCIinfo@nih.gov
Website: <https://www.cancer.gov>

National Center for Biotechnology Information

National Library of Medicine, 8600 Rockville Pike
Bethesda, MD 20894
Website: <https://www.ncbi.nlm.nih.gov>

National Center for Environmental Health

Centers for Disease Control and Prevention, Mail Stop F-29, 4770 Buford Highway NE
Atlanta, GA 30341-3724
Website: <http://www.cdc.gov/asthma>

National Center for Posttraumatic Stress Disorder

Phone: (802) 296-6300
E-mail: ncptsd@va.gov
Website: <http://www.ptsd.va.gov>

National Center on Birth Defects and Developmental Disabilities, Division of Birth Defects and Developmental Disabilities

Mail-Stop E87, 1600 Clifton Rd.
Atlanta, GA 30333
Website: <http://www.cdc.gov/ncbddd/birthdefects/Anencephaly.html>

National Comprehensive Cancer Network (NCCN)

275 Commerce Dr., Suite 300
Fort Washington, PA 19034
Phone: (215) 690-0300
Fax: (215) 690-0280
Website: <http://www.nccn.org>

National Council on Alcoholism and Drug Dependence (NCADD)

217 Broadway, Suite 712
New York, NY 10017
Phone: (212) 269-7797
Phone: (212) 269-7510
E-mail: national@ncadd.org
Website: <http://ncadd.org>

National Diabetes Education Program. Centers for Disease Control and Prevention

1600 Clifton Road
Atlanta, GA 30333
Phone: (800) 232-4636
Website: <http://www.cdc.gov/diabetes/ndep/index.htm>

National Diabetes Information Clearinghouse. National Institute of Diabetes and Digestive and Kidney Diseases

Website: <https://www.niddk.nih.gov/health-information/diabetes>

National Down Syndrome Congress

30 Mansell Court, Suite 108
Roswell, GA 30076
Phone: (770) 604-9500
Toll free: (800) 232-6372
Fax: (770) 604-9898
E-mail: info@ndsccenter.org
Website: <http://www.ndsccenter.org>

National Down Syndrome Society (NDSS)

666 Broadway, 8th Floor
New York, NY 10012
Phone: (800) 221-4602
E-mail: info@ndss.org
Website: <http://www.ndss.org>

National Eye Institute (NEI)

31 Center Drive MSC 2510
Bethesda, MD 20892-2510
Phone: (301) 496-5248
E-mail: 2020@nei.nih.gov
Website: <https://www.nei.nih.gov>

National Federation of the Blind

200 East Wells Street
Baltimore, MD 21230
Phone: (410) 659-9314
Fax: (410) 685-5653
E-mail: nfb@nfb.org
Website: <https://nfb.org>

National Foundation for Celiac Awareness (NFCA)

PO Box 544
Ambler, PA 19002-0544
Phone: (215) 325-1306 or (844) 856-6692
Fax: (215) 643-1707
E-mail: info@celiaccentral.org
Website: <http://www.celiaccentral.org>

National Foundation for Ectodermal Dysplasias (NFED)

6 Executive Dr., Ste. 2
Fairview Heights, IL 62208-1360
Phone: (618) 566-2020
E-mail: info@nfed.org
Website: <https://www.nfed.org>

National Fragile X Foundation

1861 International Drive Suite 200
McLean, VA 22102
Phone: (800) 688-8765
Website: <https://fragilex.org>

National Gaucher Foundation

5410 Edson Lane #220
Rockville, MD 20852
Phone: (800) 504-3189
Website: <https://www.gaucherdisease.org>

National Genetics and Genomics Education Centre. c/o National School of Healthcare Science

St Chad's House, 213 Hagley Rd.
Birmingham B16 9RG, UK,
E-mail: enquiries@geneticseducation.nhs.uk
Website: <http://www.geneticseducation.nhs.uk>

National Heart, Blood, and Lung Institute (NHLBI)

Building 31, 31 Center Drive
Bethesda, MD 20892
Phone: (877) 645-2448
Website: <https://www.nhlbi.nih.gov>

National Hemophilia Foundation

7 Penn Plaza, Suite 1204
New York, NY 10001
Phone: (212) 328-3700
Fax: (212) 328-3777
E-mail: info@hemophilia.org
Website: <https://www.hemophilia.org>

National Human Genome Research Institute (NHGRI)

Building 31, Room 4B09, 31 Center Drive, MSC 2152, 9000 Rockville Pike
Bethesda, MD 20892-2152
Phone: (301) 402-0911
Fax: (301) 402-2218
E-mail: <https://www.genome.gov/about-nhgri/Contact>
Website: <https://www.genome.gov>

National Hydrocephalus Foundation

12413 Centralia Rd.
Lakewood, CA 90715-1653
Phone: (562) 924-6666
E-mail: info@nhfonline.org
Website: <https://nhfonline.org>

National Information Center for Metabolic Diseases (NICMD)

Climb Building, 176 Nantwich Rd.
Crewe, UK, CW2 6BG
Phone: (0800) 652-3181
Website: <http://www.climb.org.uk>

National Institute of Allergy and Infectious Diseases (NIAID)

5601 Fishers Lane, MSC 9806
Bethesda, MD 20892
Phone: (301) 496-5717 or (866) 284-4107
Fax: (301) 402-3573
E-mail: ocpostoffice@niaid.nih.gov
Website: <http://www.niaid.nih.gov>

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Science Communications and Outreach Branch, National Institute of

Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bldg. 31, Room 4C02, 31 Center Dr. MSC 2350
Bethesda, MD 20892-2350
Phone: (301) 496-8190
Fax: (301) 718-2814
E-mail: NIAMSinfo@mail.nih.gov
Website: <https://www.niams.nih.gov>

National Institute of Child Health and Human Development (NICHD)
Patient Recruitment and Public Liaison Office, Building 61, 10 Cloister Court
Bethesda, MD 20892-4754
Phone: (800) 411-1222
E-mail: prpl@mail.cc.nih.gov
Website: <https://www.nichd.nih.gov/Pages/index.aspx>

National Institute of Dental and Craniofacial Research, National Institutes of Health
31 Center Dr., MSC 2290
Bethesda, MD 20892
Phone: (866) 232-4528
Fax: (301) 480-4098
E-mail: nidcrinfo@mail.nih.gov
Website: <http://www.nidcr.nih.gov>

National Institute of Dental and Craniofacial Research
Bethesda, MD 20892-2190
Phone: (866) 232-4528
Fax: (301) 480-4098
E-mail: nidcrinfo@mail.nih.gov
Website: <http://www.nidcr.nih.gov>

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Toll free: (800) 860-8747
Phone: TTY: (866) 569-1162
E-mail: healthinfo@nidk.nih.gov
Website: <https://www.niddk.nih.gov>

National Institute of Mental Health (NIMH)
6001 Executive Boulevard, Room 6200, MSC 9663
Bethesda, MD 20892-9663
Toll free: (866) 615-6464
Phone: TTY: (301) 443-8431
Phone: TTY: (866) 415-8051
E-mail: nimhinfo@nih.gov
Website: <https://www.nimh.nih.gov>

National Institute of Neurological Disorders and Stroke (NINDS)
NIH Neurological Institute, P.O. Box 5801
Bethesda, MD 20824
Toll free: (800) 352-9424
E-mail: https://www.ninds.nih.gov/Contact_Us

Website: <http://www.ninds.nih.gov>
Website: <http://www.ninds.nih.gov>

National Institute on Aging NIA Information Center
31 Center Drive, MSC 2292
Bethesda, MD 20892
Phone: (800) 222-2225
E-mail: niaic@nia.nih.gov
Website: <http://www.nia.nih.gov>

National Institute on Alcohol Abuse and Alcoholism (NIAAA)
5635 Fishers Lane, Room 2015
Bethesda, MD 20892-9304
Phone: (301) 443-2860
Phone: (888)-696-4222 (888-MY-NIAAA)
Website: <http://www.niaaa.nih.gov>

National Institute on Deafness and Other Communication Disorders
31 Center Dr., MSC 2320
Bethesda, MD 20892-2320
Toll free: (800) 241-1044
Phone: TTY: (800) 241-1055
E-mail: nidcdinfo@nidcd.nih.gov
Website: <https://www.nidcd.nih.gov>

National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892
Phone: (301) 496-4000
Phone: TTY: (301) 402-9612
E-mail: <https://www.nih.gov/about-nih/ask-nih>
Website: <https://www.nih.gov>

National Kidney Foundation
30 East 33rd St.
New York, NY 10016
Toll free: (800) 622-9010
Fax: (212) 689-9261
E-mail: info@kidney.org
Website: <https://www.kidney.org>

National Marfan Foundation
22 Manhasset Avenue
Port Washington, NY 11050
Phone: (516) 883-8712 or (800) 8-MARFAN
Fax: (516) 883-8040
E-mail: staff@marfan.org
Website: <https://www.marfan.org>

National MPS Society
PO Box 14686
Durham, NC 27709-4686
Phone: (919) 806-0101
Toll free: (877) MPS-1001
E-mail: <https://mpssociety.org/contact>
Website: <https://mpssociety.org>

National Multiple Sclerosis Society
733 Third Avenue 6th Floor
New York, NY . . , 10017-3288

Phone: (800) 344-4867
Website: <http://www.nationalmssociety.org>

National Newborn Screening and Genetics Resource Center (NNSGRC)
3907 Galacia Dr.
Austin, TX 78759
Phone: (512) 921-1400
E-mail: therell@uthscsa.edu
E-mail: fodgroup@gmail.com
Website: <http://genes-r-us.uthscsa.edu>

National Niemann-Pick Disease Foundation
Inc. P.O. Box 49, 401 Madison Avenue, Suite B
Fort Atkinson, WI 53538
Phone: (877) 287-3672
Fax: (920) 563-0931
E-mail: nnpdf@nnpdf.org
Website: <https://www.nnpdf.org>

National Organization for Albinism and Hypopigmentation (NOAH)
PO Box 959
East Hampstead, NH 03826-0959
Phone: (603) 887-2310 or (800) 473-2310
Fax: (800) 648-2310
E-mail: info@albinism.org
Website: <http://www.albinism.org>

National Organization for Disorders of the Corpus Callosum (NODCC)
PMB 363, 18032-C Lemon Drive
Yorba Linda, CA 92886
Phone: (714) 747-0063
E-mail: info@nodcc.org
Website: <https://nodcc.org>

National Organization for Rare Disorders (NORD)
55 Kenosia Avenue
Danbury, CT 06810
Phone: (203) 744-0100
Fax: (203) 263-9938
E-mail: <https://rarediseases.org/contact-us>
Website: <https://rarediseases.org>

National Organization on Fetal Alcohol Syndrome (NOFAS)
1200 Eton Court, NW, Third Floor
Washington, D.C. 20007
Phone: (202) 785-4585
E-mail: Information@nofas.org
Website: <https://www.nofas.org>

National Osteoporosis Foundation
251 18th Street S, Suite 630
Arlington, VA 20036
Phone: (800) 231-4222
Fax: (202) 223-2237
Website: <http://nof.org>

National Ovarian Cancer Coalition
12221 Merit Drive, Suite 1950
Dallas, TX 75251
Phone: (888) 682-7426
Fax: (214) 273-4201
Website: <http://www.ovarian.org>

National Pancreas Foundation
3 Bethesda Metro Center, Suite 700
Bethesda, MD 20814
Phone: (301) 961-1508 or (866) 726-2737
Fax: (301) 657-9776
E-mail: info@pancreasfoundation.org
Website: <http://pancreasfoundation.org>

National Parkinson Foundation
200 SE 1st Street, Suite 800
Miami, FL 33136
Phone: (800) 473-4636
Fax: (305) 537-9901
E-mail: contact@parkinson.org
Website: <http://www.parkinson.org>

National PKU Alliance
PO Box 501
Tomahawk, WI 54487
Fax: (715) 435-7670
Website: <http://www.npkua.org>

National Registry for Ichthyosis and Related Disorders. University of Washington Dermatology Department
Box 356524, 1959 NE Pacific, Rm. BB1353
Seattle, WA 98195
Phone: (206) 616-3179 or (800) 595-1265
Website: <http://www.skinregistry.org>

National Registry of Myotonic Dystrophy and FSHD Patients and Family Members
601 Elmwood Ave., Box 673
Rochester, NY 14642
Phone: (888) 925-4302
Fax: (585) 273-1255
E-mail: dystrophy_registry@urmc.rochester.edu

National Scoliosis Foundation
5 Cabot Place
Stoughton, MA 02072
Phone: (781) 341-6333
E-mail: nsf@scoliosis.org
Website: <http://www.scoliosis.org>

National Sleep Foundation
1010 N. Glebe Road, Suite 310
Arlington, VA 22201
Phone: (703) 243-1697
E-mail: nsf@sleepfoundation.org
Website: <http://www.sleepfoundation.org>

National Society of Genetic Counselors (NSGC)
330 North Wabash Ave., Suite 2000
Chicago, IL 60611
Phone: (312) 321-6834
E-mail: nsgc@nsgc.org
Website: <https://www.nsgc.org>

National Tay-Sachs and Allied Diseases Association (NTSAD)
2001 Beacon St., Suite 204
Boston, MA 02135
Phone: (617) 277-4463
E-mail: info@ntsad.org
Website: <https://www.ntsad.org>

National Urea Cycle Disorders Foundation (NUCDF)
75 S. Grand Ave.
Pasadena, CA 91105
Phone: (626) 578-0833
E-mail: info@nucdf.org
Website: <http://www.nucdf.org>

NBIA Disorders Association
2082 Monaco Court
El Cajon, CA 92019-4235
Phone: (619) 588-2315
E-mail: info@NBIAdisorders.org
Website: <http://www.NBIAdisorders.org>

Nemours Children's Health System
10140 Centurion Pkwy. N.
Jacksonville, FL 32256
Fax: (904) 697-4100
Website: <http://www.nemours.org/welcome.html>

NephCure Kidney International
150 S. Warner Rd., Suite 402
King of Prussia, PA 19406
Phone: (866) 637-4287
E-mail: info@nephcure.org
Website: <http://nephcure.org>

Neurofibromatosis Network
213 S. Wheaton Ave.
Wheaton, IL 60187
Phone: (630) 510-1115
Toll free: (800) 942-6825
Fax: (630) 510-8508
E-mail: admin@nfnetwork.org
Website: <http://www.nfinc.org>

Nevus Network, The Congenital Nevus Support Group
PO Box 1981
Woodbridge, VA 22193
Phone: (703) 492-0253
Website: <http://www.nevusnetwork.org>

Nevus Outreach
361 Southwest Drive, #353
Jonesboro, AR 72404
Phone: (918) 331-0595

E-mail: <https://www.nevus.org/contact-nevus-outreach>
Website: <https://www.nevus.org>

New England Connection for PKU and Allied Disorders
PO Box 3235
Woburn, MA 01888-2135
Website: <http://www.necpad.org/index.php>

NGLY1.org
Phone: (650) 646-4591
E-mail: info@ngly1.org
Website: <https://www.ngly1.org>

NIAID Primary Immune Deficiency Clinic
NIH, 10 Center Dr., Building 10, Room 12C-103
Bethesda, MD 20892
Phone: (301) 402-1006 or (866) 857-5274
Fax: (301) 451-5680
Website: <http://www.niaid.nih.gov>

NICHD Zebrafish Core
Building 6, Room B140, 6 Center Drive
Bethesda, MD 20892-2759
Phone: (301) 435-5556
E-mail: bfeldman@mail.nih.gov
Website: <https://www.nichd.nih.gov/about/org/dir/other-facilities/cores/zebrafish>

NIH Intramural Sequencing Center (NISC)
Room 5S-16, 5625 Fishers Lane
Rockville, MD 20852
Phone: (301) 451-0282
E-mail: nisc@mail.nih.gov
Website: <https://www.nisc.nih.gov>

NIH Osteoporosis and Related Bone Diseases National Resource Center
Toll free: (800) 624-2663
Phone: (202) 223-0344
Phone: TTY: (202) 466-4315
Fax: (202) 293-2356
E-mail: NIHBoneInfo@mail.nih.gov
Website: <https://www.bones.nih.gov>

NKH Crusaders Foundation
Phone: (781) 249-1835
E-mail: nkh.crusaders@yahoo.com
Website: <http://www.nkhcrusaders.com>

NKH International Family Network
E-mail: admin@nkh-network.org
Website: <http://www.nkh-network.org>

No Stomach for Cancer
PO Box 46070
Madison, WI 53744
Phone: (608) 692-5141

E-mail: info@nostomachforcancer.org
 Website: <http://www.nostomachforcancer.org>

Noonan Syndrome Foundation

Phone: (866) 875-8928
 Fax: (866) 875-1258
 E-mail: info@teamnoonan.org
 Website: <http://www.teamnoonan.org>

Norrie Disease Association

Massachusetts General Hospital, E No.
 6217, 149 13th St.
 Charlestown, MA 02129
 Phone: (617) 726-5718
 E-mail: sims@helix.mgh.harvard.edu
 Website: <http://www.norriedisease.org>

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

PO Box 6
 Flourtown, PA 19031
 Phone: (215) 233-0808
 Fax: (215) 233-3918
 E-mail: naspghan@naspghan.org
 Website: <http://www.naspghan.org>

Norton & Elaine Sarnoff Center for Jewish Genetics

30 S Wells, 216-600
 Chicago, IL 60606
 Phone: (312) 357-4718
 E-mail: <https://www.jewishgenetics.org/cjg/Contact-Us.aspx>
 Website: <https://www.jewishgenetics.org>

O

The Obesity Society

1110 Bonifant Street, Suite 500
 Silver Spring, MD 20910
 Phone: (301) 563-6526 or (800) 974-3084
 Fax: (301) 563-6595
 Website: <http://www.obesity.org>

Office of Public Health Genomics, Centers for Disease Control and Prevention

1600 Clifton Rd., NE, MS E61
 Atlanta, GA 30333
 Phone: (404) 498-0001
 E-mail: genetics@cdc.gov
 Website: <http://www.cdc.gov/genomics/default.htm>

Organic Acidemia Association

9040 Duluth St.
 Golden Valley, MN 55427
 Phone: (763) 559-1797
 Fax: (866) 539-4060
 E-mail: mkstagni@gmail.com
 Website: <https://www.oaanews.org>

Orphanet/INSERM US14 Rare Disease Platform

96, rue Didot
 Paris, France 75014
 Phone: +33(0)156.53.81.37
 Fax: +33(0)156.53.81.38
 E-mail: contact.orphanet@inserm.fr
 Website: <http://www.orpha.net>

Osteogenesis Imperfecta Foundation (OIF)

656 Quince Orchard Rd., Suite 650
 Gaithersburg, MD 20878
 Phone: (301) 947-0083
 Toll free: (844) 889-7579
 Fax: (301) 947-0456
 E-mail: bonelink@oif.org
 Website: <https://oif.org>

Oxalosis and Hyperoxaluria Foundation

201 East 19th St., 12E
 New York, NY 10003
 Phone: (800) OHF-8699
 E-mail: info@ohf.org
 Website: <http://ohf.org>

P

Parent Project Muscular Dystrophy (PPMD)

1012 14th Street, NW, Suite 500
 Washington, D.C. 07601
 Phone: (201) 250-8440
 Toll free: (800) 714-5437
 E-mail: info@parentprojectmd.org
 Website: <http://www.parentprojectmd.org>

Parents of Galactosemic Children

PO Box 1512
 Deerfield Beach, FL 33443
 Phone: (866) 900-7421 (PGC1)
 Website: <http://www.galactosemia.org>

Parkinson's Foundation

1359 Broadway, Suite 1509
 New York, NY 10018
 Toll free: (800) 473-4636
 E-mail: helpline@parkinson.org
 Website: <https://www.parkinson.org>

PCOS Foundation

10901 Katy Freeway
 Houston, TX 77079
 Phone: (713) 487-7267
 E-mail: info@pcosfoundation.org
 Website: <http://www.pcosfoundation.org>

Pediatric Hydrocephalus Foundation

66 Caroline St., 2nd Floor
 Woodbridge, NJ 07095
 Phone: (732) 634-1283

Fax: (847) 589-1250
 Website: <http://www.hydrocephaluskids.org/wordpress>

Phelan-McDermid Syndrome Foundation

8 Sorrento Drive
 Osprey, FL 34229
 Phone: (941) 485-8000
 Website: <http://www.pmsf.org>

Pierre Robin Network

6304 Biscayne
 Quincy, IL 62305
 E-mail: info@pierreroobin.org
 Website: <http://www.pierreroobin.org/index.html>

Pituitary Foundation

86 Colston Street
 Bristol, UK, BS1 5BB
 Phone: 0117 370 1333
 Fax: 0117 933 0910
 E-mail: enquiries@pituitary.org.uk
 Website: <https://www.pituitary.org.uk>

Pituitary Network Association

P.O. Box 1958
 Thousand Oaks, CA 91358
 Phone: (805) 499-9973
 Fax: (805) 480-0633
 E-mail: info@pituitary.org
 Website: <http://pituitary.org>

Pituitary Society. VA Medical Center

8700 Beverly Boulevard, Room 2051
 Los Angeles, CA 90048
 Phone: (310) 988-9486
 Website: <http://www.pituitarysociety.org>

PKS Kids

PO Box 12211
 Green Bay, WI 543017
 E-mail: gpeters@pkskids.net
 Website: <http://www.pkskids.net>

PMD Foundation

1 Greentree Center, 1000 Lincoln Drive
 East, Suite 201
 Marlton, NJ 08053
 Phone: (609) 443-9623
 E-mail: jeffleonard@pmdfoundation.org
 Website: <http://pmdfoundation.org>

Polycystic Kidney Disease Foundation National Headquarters

8330 Ward Pkwy., Suite 510
 Kansas City, MO 64114
 Phone: (800) 753-2873
 E-mail: pkdcure@pkdcure.org
 Website: <http://www.pkdcure.org>

Polygenic Score (PGS) Catalog
c/o European Molecular Biology
Laboratory-Hinxton
Wellcome Genome Campus, Hinxton,
Cambridgeshire, United Kingdom,
CB10 1SD
Phone: +44 (0)1223 494 444
E-mail: info@ebi.ac.uk
Website: <https://www.pgscatalog.org/>

**Ponseti International Association,
University of Iowa Healthcare,
International Office**
118 CMAB
Iowa City, IA 52242
Phone: (319) 467-5107
E-mail: PonsetiIA@gmail.com
Website: <http://www.ponseti.info>

Prader-Willi Syndrome Association
8588 Potter Park Drive, Suite 500
Sarasota, FL 34238
Phone: (800) 926-4797
E-mail: info@pwsausa.org
Website: <http://www.pwsausa.org>

Prevent Blindness
225 West Wacker Dr., Suite 400
Chicago, IL 60606
Toll free: (800) 331-2020
E-mail: info@preventblindness.org
Website: <https://preventblindness.org>

**Primary Ciliary Dyskinesia
Foundation**
61 Lake Meadow Drive
Rochester, NY 14612
Phone: (844) 287-3723
E-mail: info@pcdfoundation.org
Website: <https://www.pcdfoundation.org>

Progeria Research Foundation
PO Box 3453
Peabody, MA 01961-3453
Phone: (978) 535-2594
Fax: (978) 535-5849
E-mail: info@progeriaresearch.org
Website: <http://www.progeriaresearch.org>

Propionic Acidemia Foundation
1963 McCraren Rd.
Highland Park, IL 60035
Phone: (877) 720-2192
E-mail: paf@pafoundation.com
Website: <http://www.pafoundation.com>

Proteus Syndrome Foundation
6235 Whetstone Dr.
Colorado Springs, CO 80918
Phone: (719) 264-8445
Website: <http://www.Proteus-syndrome.org>

Prune Belly Syndrome Network
PO Box 16071
Philadelphia, PA 19154

Phone: (855) 275-7276
Website: <http://prunebelly.org>

Pull-thru Network
1705 Wintergreen Parkway
Normal, IL 61761
E-mail: pullthrunetwork@gmail.com
Website: <http://www.pullthrunetwork.org>

Pulmonary Hypertension Association
801 Roeder Rd., Suite 1000
Silver Spring, MD 20910
Phone: (800) 748-7274
E-mail: PHA@PHAssociation.org
Website: <http://www.phassociation.org>

PXE International
4301 Connecticut Ave. NW, Suite 404
Washington, DC 20008
Phone: (202) 362-9599
E-mail: info@pxe.org
Website: <http://www.pxe.org>

R

Raynaud's Association
11 Topstone Rd.
Redding, CT 06896
Phone: (800) 280-8055
E-mail: info@raynauds.org
Website: <http://www.raynauds.org>

Reach
Pearl Assurance House, Brook Street
Tavistock, Devon UK, PL19 0BN
Phone: 0845 130 6225 or 020 3478 0100
E-mail: <https://reach.org.uk/contact-us>
Website: <https://reach.org.uk>

**Reproductive Health Technologies
Project**
1634 Eye St. NW, Suite 650
Washington, DC 20006
Phone: (202) 530-4401
Fax: (202) 530-4404
E-mail: info@rhtp.org
Website: <http://www.rhtp.org>

**RESOLVE: The National Infertility
Association**
7918 Jones Branch Drive, Suite 300
McLean, VA 22102
Phone: (703) 556-7172
Fax: (703) 506-3266
E-mail: info@resolve.org
Website: <https://resolve.org/>

Retinitis Pigmentosa International
PO Box 900
Woodland Hills, CA 91365
Phone: (800) 344-4877
E-mail: info@rpinternational.org
Website: <http://www.rpinternational.org>

Retinoblastoma International
18030 Brookhurst Street, P.O. Box 408
Fountain Valley, CA 92708
E-mail: info@retinoblastoma.net
Website: <http://www.retinoblastoma.net>

Rett Syndrome Research Foundation
4600 Devitt Dr.
Cincinnati, OH 45246
Website: <http://www.rsfr.org>

RhizoKids International
50 Cross Creek Lane
Alpine, AL 35014
Website: <http://www.rhizokids.com>

Robinow Syndrome Foundation
PO Box 934
Anoka, MN 55303
Website: <http://www.robinow.org>

**Royal National Institute of Blind
People (RNIB)**
105 Judd Street
London, UK, WC1H 9NE
Phone: 0303 123 9999
E-mail: helpline@rnib.org.uk
Website: <http://www.rnib.org.uk>

S

SADS Foundation
508 E. South Temple, Suite 202
Salt Lake City, UT 84102
Phone: (800) STOP-SAD or (801) 531-0937
Website: <http://www.sads.org>

**Schepens Eye Research Institute of
Massachusetts Eye and Ear**
243 Charles Street
Boston, MA 02114
Phone: (617) 523-7900
Website: <https://masseyeandear.org/research/ophthalmology/seri>

Schizophrenics Anonymous
15920 W. Twelve Mile
Southfield, MI 48076
Phone: (248) 477-1983

Scleroderma Foundation
300 Rosewood Drive Suite 105
Danvers, MA 01923
Phone: (978) 463-5843 or (800) 722or4673
Fax: (978) 463-5809
E-mail: sfinfo@scleroderma.org
Website: <http://www.scleroderma.org>

Scoliosis Research Society
555 E. Wells St., Suite 1100
Milwaukee, WI 53202
Phone: (414) 289-9107

Fax: (414) 276-3349
E-mail: info@srs.org
Website: <http://www.srs.org>

Share-Pregnancy and Infant Loss Support

402 Jackson St.
Saint Charles, MO 63301-3468
Phone: (800) 821-6819
E-mail: info@nationalshare.org
Website: <http://nationalshare.org>

Shriners Hospitals for Children

International Shrine Headquarters, 2900
Rocky Point Drive
Tampa, FL 33607-1460
Phone: (813) 281-0300
Website: <http://www.nbdpn.org>

Sickle Cell Disease Association of America, Inc

3700 Koppers St., Suite 570
Baltimore, MD 21227
Phone: (800) 421-8453
E-mail: scdaa@sicklecelldisease.org
Website: <http://sicklecelldisease.org>

Skin Cancer Foundation

205 Lexington Avenue, 11th Floor
New York, NY 10016
Phone: (212) 725-5176
E-mail: <https://www.skincancer.org/about-us/contact-us>
Website: <https://www.skincancer.org>

Smith-Lemli-Opitz RSH Foundation

Website: <http://www.smithlemliopitz.org>

Society for Assisted Reproductive Technology (SART)

1209 Montgomery Highway
Birmingham, AL 35216-2809
Phone: (205) 978-5000
Fax: (205) 978-5018
E-mail: sart@asrm.org
Website: <https://www.sart.org>

Society for In Vitro Biology

514 Daniels St., Suite 411
Raleigh, NC 27605
Phone: (910) 755-5431
Fax: (910) 755-5432
E-mail: <https://sivb.org/contactus.html>
Website: <https://sivb.org/>

Society for Maternal-Fetal Medicine (SMFM)

409 12th St. SW
Washington, DC 20024
E-mail: smfm@smfm.org
Website: <https://www.smfm.org>

Society of Thoracic Surgeons

633 N. St. Clair St., Fl. 23
Chicago, IL 60611

Phone: (312) 202-5800
Fax: (312) 202-5801
Website: <http://www.sts.org>

Sotos Syndrome Support Association (SSSA)

PO Box 4626
Wheaton, IL 60189
Phone: (888) 246-7772
E-mail: info@sotossyndrome.org
Website: <https://sotossyndrome.org>

Spasmodic Torticollis Dystonia/ST Dystonia

PO Box 28
Mukwonago, WI 53149
Phone: (888) 445-4588
E-mail: info@spasmodictorticollis.org
Website: <http://www.spasmodictorticollis.org>

Spastic Paraplegia Foundation

1605 Goularte Place
Fremont, CA 94539
Phone: (877) 773-4483
Website: <http://www.sp-foundation.org>

Spina Bifida Association

1600 Wilson Blvd, Suite 800
Arlington, VA 22209
Toll free: (800) 621-3141
E-mail: sbaa@sbaa.org
Website: <https://www.spinabifidaassociation.org>

Spondylitis Association of America

PO Box 5872
Sherman Oaks, CA 91413
Phone: (800) 777-8189
Fax: (818) 892-1611
E-mail: info@spondylitis.org
Website: <http://www.spondylitis.org>

Stanford University Center for Marfan Syndrome and Aortic Disorders

300 Pasteur Drive, 3rd Floor
Stanford, CA 94305-5233
Phone: (650) 725-8246
Website: <https://stanfordhealthcare.org/medical-clinics/center-marfan-syndrome-related-aortic-disorders.html>

Stickler Involved People

15 Angelina
Augusta, KS 67010
Phone: (316) 259-5194
E-mail: sip@sticklers.org
Website: <http://stickler.org>

Stickler Syndrome UK

PO Box 3351
Littlehampton, UK, BN16 9GB
Phone: 01903 785771
E-mail: info@stickler.org.uk
Website: <https://stickler.org.uk>

Sturge-Weber Foundation

PO Box 418
Mount Freedom, NJ 07970
Phone: (973) 895-4445 or (800) 627-5482
Fax: (973) 895-4846
E-mail: swf@sturge-weber.org
Website: <http://www.sturge-weber.org/home.html>

Sudden Arrhythmia Death Syndromes (SADS) Foundation

4527 South 2300 East, Suite 104
Salt Lake City, UT 84117-4448
Phone: 801-272-3023
E-mail: <https://www.sads.org/Contact-Us>
Website: <https://www.sads.org>

Support Organization for Trisomy 18, 13, and Related Disorders (SOFT)

2982 S. Union St.
Rochester, NY 14624
E-mail: <https://trisomy.org/contact>
Website: <https://trisomy.org>

T

Texas Heart Institute Heart

MC 3-116, P.O. Box 20345
Houston, TX 77225-0345
Phone: (832) 355-4011
Website: <http://www.texasheart.org/index.cfm>

Thalassemia Foundation of Canada

10 Holland Drive
Bolton, ON, Canada, L7E 1G6
Phone: (416) 242-THAL (8425)
Fax: (416) 242-THAL
E-mail: info@thalassemia.ca
Website: <https://www.thalassemia.ca>

Tourette Association of America

42-40 Bell Blvd.
Bayside, NY 11361
Phone: (718) 224-2999
Fax: (718) 279-9596
Website: <http://www.tsa-usa.org>

Tourette Canada

5945 Airport Rd., Suite 175
Mississauga, ON, Canada, L4V 1R9
Phone: (800) 361-3120
Toll free: (905) 673-2255
Fax: (800) 387-0120
Fax: (905) 673-2638
Website: <http://www.tourette.ca>

Tremor Action Network

PO Box 5013
Pleasanton, CA 94566-0513
Phone: (510) 681-6565

Fax: (925) 369-0485
Website: <http://www.tremoraction.org>

Trichorhinophalangeal Syndrome Association (TRPSA)

6585 Dawn Way E
Inver Grove Heights, MN 55076
Phone: (651) 450-0788
E-mail: TRPSA@comcast.net
Website: http://trpsa.org/trpsa_wp

Tuberous Sclerosis Alliance

801 Roeder Rd., Suite 750
Silver Spring, MD 20910
Phone: (301) 562-9890
Toll free: (800) 225-6872
Fax: (301) 562-9870
E-mail: info@tsalliance.org
Website: <http://www.tsalliance.org>

Turner Syndrome Society of Canada

30 Cleary Ave., Room 9
Ottawa, ON, Canada, K2A 4A1
Phone: (800) 465-6744
E-mail: info@turnersyndrome.ca
Website: <http://www.turnersyndrome.ca>

Turner Syndrome Society of the United States

11250 West Rd., Suite G
Houston, TX 77065
Phone: (800) 365-9944
Toll free: (832) 912-6006
Website: <http://www.turnersyndrome.org>

Twin to Twin Transfusion Foundation

411 Longbeach Pkwy.
Bay Village, OH 44140
Phone: (800) 815-9211
Website: <http://www.ttsfoundation.org>

U

UCLA International Skeletal Dysplasia Registry (ISDR)

615 Charles E. Young Dr. South, Room 410
Los Angeles, CA 90095-7358
Phone: (310) 825-2631
Fax: (310) 206-5266
E-mail: ISDR@mednet.ucla.edu
Website: <https://www.uclahealth.org/ortho/isdr>

U.S. Department of Veterans Affairs

Toll free: (800) 698-2411
Website: <https://www.va.gov>

U.S. Hereditary Angioedema Association

Seven Waterfront Plaza, 500 Ala Moana Blvd., Suite 400
Honolulu, HI 96813

Phone: (866) 798-5598
Website: <http://www.hereditaryangioedema.com>

UCSF Benioff Children's Hospital, San Francisco Craniofacial Center

1825 Fourth St., Fifth Floor, 5C
San Francisco, CA 94158
Phone: (415) 476-2271
Website: <https://www.ucsfbenioffchildrens.org>

UK Biobank Participant Resource Centre

Division of Population Medicine,
Cardiff University, 5th Floor
Neuadd Meirionnydd, Heath Park,
Cardiff, United Kingdom, CF14 4YS
Toll free: 0800 0 276 276
E-mail: ukbiobank@ukbiobank.ac.uk
Website: <https://www.ukbiobank.ac.uk/>

Undiagnosed Diseases Network (UDN) Coordinating Center

c/o Department of Biomedical Informatics, 10 Shattuck Street, Suite 514
Boston, MA 02115
Phone: (844) 746-4836
E-mail: UDN@hms.harvard.edu
Website: <https://undiagnosed.hms.harvard.edu/>

Unique: Rare Chromosome Disorder Support Group

The Stables, Station Road West
Oxted, Surrey UK, RH8 9EE
Phone: +44(0)1883 723356
E-mail: info@rarechromo.org
Website: <https://rarechromo.org>

United Cerebral Palsy (UCP)

1825 K St. NW, Suite 600
Washington, DC 20006
Toll free: (800) 872-5827
Phone: (202) 776-0406
E-mail: info@ucp.org
Website: <https://ucp.org>

United Leukodystrophy Foundation (ULF)

224 N. 2nd St., Suite 2
DeKalb, IL 60115
Toll free: (800) 728-5483
Phone: (815) 748-3211
E-mail: office@ulf.org
Website: <https://ulf.org>

United Mitochondrial Disease Foundation (UMDF)

8085 Saltsburg Road, Suite 201
Pittsburg, PA 15239
Toll free: (888) 317-8633
Fax: (412) 793-6477

E-mail: info@umdf.org
Website: <https://www.umdf.org>

University of Texas Anderson Cancer Center

1515 Holcombe Blvd.
Houston, TX 77030
Phone: (713) 792-2121 or (877) 632-6789
Website: <http://www.mdanderson.org>

Urology Care Foundation

1000 Corporate Blvd.
Linthicum, MD 21090
Toll free: (800) 828-7866
Phone: (410) 689-3700
E-mail: info@UrologyCareFoundation.org
Website: <https://www.urologyhealth.org>

Usher Syndrome Coalition

2 Clock Tower Place, Suite 418
Maynard, MA 01754
Phone: (978) 637-2625
Website: <http://www.usher-syndrome.org>

V

Vestibular Disorders Association

5018 NE 15th Ave.
Portland, OR 97211
Toll free: (800) 837-8428
E-mail: info@vestibular.org
Website: <https://vestibular.org>

VHL Family Alliance

2001 Beacon St., Suite 208
Boston, MA 02135-7787
Phone: (800) 767-4845
E-mail: info@vhl.org
Website: <http://www.vhl.org>

W

Williams Syndrome Association

570 Kirts Blvd., Suite 223
Troy, MI 48084-4156
Phone: (248) 244-2229 or (800) 806-1871
E-mail: info@williams-syndrome.org
Website: <https://williams-syndrome.org>

Williams Syndrome Changing Lives Foundation

PO Box 76021
Saint Petersburg, FL 33734
E-mail: info@wschanginglives.org
Website: <http://www.wschanginglives.org>

Wilson Disease Association

1732 First Ave., No. 20043

New York, NY 10128
Phone: (414) 961-0533 or (866) 961-0533

E-mail: info@wilsonsdisease.org
Website: <http://www.wilsonsdisease.org>

Windows of Hope Project

Walnut Creek, OH 44687
Website: <http://www.wohproject.org>

World Craniofacial Foundation (WCF)

7777 Forest Lane, Suite C-616
Dallas, TX 75230
Toll free: (800) 533-3315
Phone: (972) 566-6669
E-mail: info@worldcf.org
Website: <https://worldcf.org>



Xeroderma Pigmentosum Society

437 Snyderstown Rd.
Caryville, NY 12521
Phone: (518) 851-3466
E-mail: xps@xps.org
Website: <http://www.xps.org>

XLH Network

911 Central Ave., No. 161
Albany, NY 12206
E-mail: info@xlhnetwork.org
Website: <http://www.xlhnetwork.org>

YoungStroke

PO Box 692
Conway, SC 29528

Phone: (843) 655-2835
E-mail: info@youngstroke.org
Website: <http://youngstroke.org>

Zebrafish Information Network (ZFIN)

5291 University of Oregon
Eugene, OR 97403-5291
E-mail: zfinadm@zfin.org
Website: <http://zfin.org>

Zebrafish International Resource Center (ZIRC)

5274 University of Oregon
Eugene, OR 97403-5274
Phone: (541) 346-6028
E-mail: zirc@zebrafish.org
Website: <http://zebrafish.org>

GLOSSARY

The glossary is an alphabetical compilation of terms and definitions listed in the **Key Terms** sections of the main body entries. Although the list is comprehensive, it is by no means exhaustive.

A

AADC INHIBITORS. Drugs that block the amino acid decarboxylase, one type of enzyme that breaks down dopamine. Also called DC inhibitors, they include carbidopa and benserazide.

ABDOMINAL HERNIA. Bulging of an organ or tissue through the muscle of the stomach wall.

ABDUCENS NERVE. Cranial nerve VI; the nerve that extends from the midbrain to the lateral rectus muscle of the eye and controls movement of the eye toward the ear (abduction).

ABDUCTION. Turning away from the body.

ABLATION. A general term for medical techniques for destroying a cancer (or other unwanted tissue) without removing it.

ABSCCESS. A localized collection of pus or infection that is walled off from the rest of the body.

ABSENCE SEIZURE. A type of epileptic seizure characterized by a brief loss of, and return to, consciousness, usually without being followed by a period of confusion or disorientation.

ACANTHOCYTOSIS. The presence of acanthocytes in the blood. Acanthocytes are red blood cells that have the appearance of thorns on their outer surface.

ACANTHOSIS NIGRICANS. A brownish-black hyperpigmentation of the skin, most often found in the folds of the body. It can be caused by genetic disorders as well as by certain malignancies and endocrine disorders.

ACCIDENTAL INCEST. Sexual activity or marriage between persons who are unaware of a close familial relationship between them.

ACCOMMODATION. The ability of the lens to change its focus from distant to near objects. It is achieved through the action of the ciliary muscles that change the shape of the lens.

ACETYLCHOLINESTERASE (ACHE). An enzyme found in nerve tissue.

ACHONDROGENESIS. A genetic disorder of skeletal development with three subtypes, one of which (achondrogenesis type II) is caused by mutations in the same gene as hypochondrogenesis.

ACHONDROPLASIA. An autosomal dominant form of dwarfism caused by a defect in the formation of cartilage at the ends of long bones. Affected individuals typically have short limbs, a large head with a prominent forehead and flattened profile, and a normal-sized trunk.

ACHROMATOPSIA. The inability to distinguish any colors.

ACID MALTASE. The enzyme that regulates the amount of glycogen stored in muscle cells. When too much glycogen is present, acid maltase is released to break it down into waste products.

ACIDOSIS. A condition of decreased alkalinity resulting from abnormally high acid levels (low pH) in the blood and tissues. Usually indicated by sickly sweet breath, headaches, nausea, vomiting, and visual impairments.

ACQUIRED ANGIONEUROTIC EDEMA. Abbreviated AANE, or AAE, this is a nonhereditary form of angio edema that generally begins to show symptoms in, or after, the fourth decade of life.

ACQUIRED IMMUNITY. Also called specific immunity, refers to immune reaction mediated by B-cells and/or T-cells. Includes humoral and cellular immunity.

ACROCENTRIC. A centromere positioned at the top end of a chromosome.

ACROCEPHALOPOLYSYNDACTYLY SYNDROMES. A collection of genetic disorders characterized by a cone-shaped abnormality of the skull and partial fusing of adjacent fingers or toes.

ACROCEPHALY. An abnormal cone shape of the head.

ACROMELIC. The anatomical term used to denote the end of a limb (arm or leg). In the context of Robinow syndrome, it refers to bones of the hands and feet.

ACROOSTEOLYSIS. Loss of bone tissue at the ends of the fingers and/or toes.

ACROPARESTHESIA. Painful burning sensation in hands and feet.

ACROSOME. The cap at the top of the sperm head that releases egg-penetrating enzymes.

ACTA2. The gene that encodes smooth muscle alpha-2 actin; up to 20% of familial thoracic aortic aneurysms and dissections (TAADs) are caused by mutations in the *ACTA2* gene.

ACTIN. A protein that interacts with myosin during the process of muscle contraction.

ACTION POTENTIAL. The wave-like change in the electrical properties of a cell membrane, resulting from the difference in electrical charge between the inside and outside of the membrane.

ACTIVITIES OF DAILY LIVING (ADL). The skills and practices necessary for functioning in daily life and for participating in one's environment; progressively lost with Alzheimer's disease.

ACUPUNCTURE. An alternative health procedure based on ancient Chinese methods, involving insertion of thin needles at specific pressure points in the body.

ACUTE MYELOGENOUS LEUKEMIA (AML). A life-threatening disorder of the bone marrow in which a large number of abnormal white blood cells accumulates in the marrow and reduces the production of normal red and white blood cells and platelets. It is also called acute myeloid leukemia.

ACUTE PHASE REACTANTS. Blood proteins whose concentrations increase or decrease in reaction to the inflammation process.

ACUTE STRESS DISORDER (ASD). An anxiety disorder similar to PTSD but with symptoms occurring immediately after a traumatic event and resolving within a month.

ADDUCTED THUMBS. Thumbs clasped across the palm.

ADDUCTION. Movement toward the body. In Duane retraction syndrome, turning the eye inward toward the nose.

ADENOCARCINOMA. A general term for a type of cancer that originates in glandular tissue or behaves like glandular tissue. About 10% to 15% of cancers of the cervix are adenocarcinomas.

ADENOMA. A benign tumor that develops in glandular tissue. A thyroid adenoma may produce large amounts of thyroid hormone that disrupt the normal thyroid feedback system.

ADENOMATOUS. Derived from glandular structures.

ADENOMATOUS POLYPS (ADENOMAS). A growth in the colon that may become cancerous if not removed.

ADENOSINE DEAMINASE 2 (ADA2). The enzyme produced by the *CECR1* gene and required for blood-vessel and immune-system development and maintenance; *CECR1* gene mutations that result in little or no ADA2 can cause recurrent fevers and strokes in children and other syndromes in children and adults.

ADENOSINE TRIPHOSPHATE (ATP). An organic molecule found in all living organisms, involved in energy production for metabolic processes and RNA synthesis.

ADJUVANT THERAPY. Treatment given to patients who are at risk of having microscopic untreated disease present but have no obvious symptoms.

ADRENAL CRISIS. A life-threatening complication of salt-losing (salt-wasting) congenital adrenal hyperplasia with 21-hydroxylase deficiency.

ADRENAL GLAND. A triangle-shaped endocrine gland, located above each kidney, that synthesizes aldosterone, cortisol, and testosterone from cholesterol. The adrenal glands are responsible for salt and water levels in the body, as well as for protein, fat, and carbohydrate metabolism.

ADRENAL INSUFFICIENCY. Problems with the adrenal glands that can be life threatening if not treated. Symptoms include sluggishness, weakness, weight loss, vomiting, darkening of the skin and mental changes.

ADRENOCORTICOTROPIC HORMONE (ACTH). A pituitary hormone that acts on cells of the adrenal cortex to produce male sex hormones and hormones that control water and mineral balance in the body.

ADVANCED BONE AGE. The bones, on x-ray, appear to be those of an older individual.

ADYSPLASIA. A term referring to the combination of renal agenesis (complete absence of one or both kidneys) and renal dysplasia (developmental anomaly of the kidney).

AFFECTIVE FLATTENING. A loss or lack of emotional expressiveness; sometimes called blunted or restricted affect.

AFFORDABLE CARE ACT (ACA). The Patient Protection and Affordable Care Act ("Obamacare"); signed into law by President Barack Obama in March of 2010, the ACA overhauled the U.S. healthcare system.

AFLATOXIN. A mycotoxin, produced by several species of *Aspergillus* fungi, that is a known carcinogen.

AGANGLIONOSIS. Section of bowel in which the normal enteric nerves are absent.

AGE-ASSOCIATED MEMORY IMPAIRMENT (AAMI). A condition in which an older person suffers some memory loss and takes longer to learn new information; AAMI is distinguished from dementia in that it is not progressive and does not represent a serious decline from the person's previous level of functioning.

AGENESIS. Failure of an organ, tissue, or cell to develop or grow.

AGENESIS OF THE CORPUS CALLOSUM. An absence of the structure in the brain that connects the two hemispheres of the brain.

AGENESIS/HYPOPLASIA OF THE CORPUS CALLOSUM. Birth defect in which the two halves of the brain are not properly separated.

AGNOSIA. Loss of the ability to recognize objects by use of the physical senses.

AGONIST. A chemical or biological agent that binds to a receptor and activates the receptor to produce a biological response.

AGYRIA. The absence of gyri, or convolutions, in the cerebral cortex.

AKATHISIA. Agitated or restless movement, usually affecting the legs and accompanied by a sense of discomfort; a common side effect of neuroleptic medications.

AKINESIA. A loss of the ability to move; freezing in place.

AKINETIC MUTISM. A medical condition in which the patient is unable to move (akinetik) or speak (mutism).

ALBUMINURIA. Abnormally high levels of albumin (the most abundant protein in blood) in the urine. Albuminuria may be visible as white foam in the urine.

ALDOSTERONE. A steroid hormone produced by the adrenal gland that regulates salt and fluid balance in the body and is deficient in congenital adrenal hyperplasia.

ALGORITHM. A set of rules for solving a problem in a finite number of steps.

ALKALINE. Having a basic pH; not acidic.

ALKALINE PHOSPHATASE (ALP). An enzyme that is found in the blood and that helps to break down proteins in the body. ALP can be present in different forms depending on where it was synthesized. ALP can be made in the liver, kidneys, intestines, and bones.

ALKALINIZATION. The process of making a solution more basic, rather than more acidic, by raising the pH.

ALLELE. Any of the alternative versions of a gene that are present in the population.

ALLELIC. Related to the same gene.

ALLELIC VARIANTS. A disease is said to have allelic variants when different mutations in the same allele result in identical, or nearly identical, symptoms. An allele is the combined locations of a gene on the two paired chromosomes that contain this gene.

ALLERGEN. A substance or organism foreign to the body; allergens stimulate the immune system to produce antibodies.

ALLERGY. A condition in which the immune system is hypersensitive to contact with allergens; an abnormal response by the immune system to contact with an allergen; a condition in which contact with an allergen produces symptoms such as inflammation of tissues and production of excess mucus in the respiratory system.

ALOPECIA. Loss of hair or baldness.

ALOPECIA AREATA. A nonscarring hair loss syndrome characterized by smooth, round, or oval hairless areas on the scalp.

ALPHA-FETOPROTEIN (AFP). A chemical substance produced by the fetus and found in the fetal circulation. AFP is also found in abnormally high concentrations in most patients with primary liver cancer.

ALPHA-SYNUCLEIN. A protein that forms aggregates in nerve cells in certain types of dementia.

ALPHA THALASSEMIA. A genetic disorder in which mutations in the *HBA1* and *HBA2* genes on chromosome 16 lead to impaired production of a subtype of hemoglobin known as alpha globin. The severity of the disorder depends on how many of the four alpha globin chains are affected by mutations.

ALTERATION. Change or mutation in a gene, specifically in the DNA that codes for the gene.

ALTERNATE COMPLEMENT PATHWAY. A cascade of enzymatic reactions that produce antibacterial proteins. This pathway helps to ward off infections.

ALX. Genes encoding transcription factors that are required for normal prenatal development of the head and face; mutations in the *ALX1* gene cause frontonasal dysplasia (FND) type 3; mutations in *ALX3* cause FND1; mutations in *ALX4* cause FND2.

ALZHEIMER'S DISEASE (AD). A progressive neurodegenerative disease characterized by loss of function and

death of nerve cells in several areas of the brain, leading to mental deterioration; the most common cause of dementia.

AMASTIA. A birth defect involving the absence of mammary glands.

AMBIGUOUS. Unclear or open to more than one interpretation.

AMELOGENESIS IMPERFECTA. A hereditary dental defect characterized by discoloration of the teeth.

AMENORRHEA. Absence of menstruation, usually defined as missing one or more menstrual periods.

AMINO ACIDS. Organic compounds that form the building blocks of protein. There are 20 types of amino acids (8 are “essential amino acids” that the body cannot make that and must be obtained from food).

AMINOSALICYLATES. Anti-inflammatory medications containing 5-aminosalicylic acid (5-ASA) that are commonly used to treat colitis.

AMNESTIC MILD COGNITIVE IMPAIRMENT (AMCI). An early symptom of Alzheimer’s disease in which there is mild impairment but normal cognitive functioning is still present.

AMNIOCENTESIS. A procedure performed at 16 to 18 weeks of pregnancy in which a needle is inserted through a woman’s abdomen into her uterus to draw out a small sample of the amniotic fluid from around the baby. Either the fluid itself or cells from it can be used for a variety of tests to obtain information about genetic disorders and other medical conditions in the fetus.

AMNION. The thin, protective sac that suspends the fetus in a protective amniotic fluid.

AMNIOTIC FLUID. Fluid contained in a sac within the uterus that surrounds and protects the fetus during its development.

AMNIOTIC SAC. Contains the fetus, which is surrounded by amniotic fluid.

AMNIOTIC SAMPLE. Sample of amniotic fluid, the protective fluid surrounding a fetus in the womb.

AMPLIFICATION. A process by which something is made larger. In clotting, only a very few chemicals are released by the initial injury; they result in a cascade of chemical reactions that produces increasingly larger quantities of different chemicals, resulting in an appropriately sized, strong fibrin clot.

AMYGDALA. Any of the four basal ganglia in each cerebral hemisphere that are involved in triggering fear.

AMYLASE. A digestive enzyme found in saliva or pancreatic fluid that breaks down starch and sugars.

AMYLOID. Any of a group of insoluble abnormal proteins that accumulate in body organs and tissues and interfere with their normal functioning.

AMYLOID PRECURSOR PROTEIN (APP). A protein that forms beta-amyloid in the brain when it is not correctly broken down; mutations in the APP gene can cause early-onset familial Alzheimer’s disease.

AMYLOIDOSIS. Accumulation of amyloid deposits in various organs and tissues in the body such that normal functioning of an organ is compromised.

AMYOPLASIA. The most common form of arthrogryposis multiplex congenita, characterized by sporadic and recurrent contractures of the wrists, elbows, and knees; an abnormal internal rotation of the shoulders; and clubfeet.

AMYOTROPHY. Wasting of the muscles.

ANABOLISM. The energy-using process of building up complex chemical compounds from simpler ones in the body.

ANAGEN. The growth phase of the human hair growth cycle.

ANALOGUE. A drug or other chemical compound that resembles another in structure or constituents but has different effects.

ANALYTE. A chemical compound that is the subject of a laboratory test.

ANAPLASTIC. Undifferentiated, appearing to have an immature cell type.

ANDROGEN INSENSITIVITY SYNDROME. An intersex condition found in people who are chromosomally male (karyotype XY) but have a mutation in the *AR* gene that makes them unable to respond to male sex hormones. As a result, they may have some or all of the physical traits of a female.

ANDROGENS. Steroid hormones that contribute to the development of male sex organs and male secondary sexual characteristics.

ANEMIA. A blood condition in which the level of hemoglobin or the number of red blood cells falls below normal values. Common symptoms include paleness, fatigue, and shortness of breath.

ANENCEPHALY. The absence of a major portion of the brain, upper skull, and scalp during fetal development.

ANESTHESIA. Lack of normal sensation (especially to pain) brought on by medications just prior to surgery or other medical procedures.

ANESTHESIA OF THE SKIN. A loss of feeling or sensation in the skin associated with spine-related injury or disorders.

ANESTHETIC. A drug used to temporarily cause loss of sensation in an area of the body. An anesthetic may either be general, associated with a loss of consciousness, or local, affecting one area only without loss of consciousness. Anesthetics are administered via either inhalation or needle injection.

ANEUPLOIDY. A condition in which an abnormal number of chromosomes exists in the nucleus of a cell. Trisomy 18 and trisomy 13 are examples of aneuploid conditions.

ANEURYSM. An abnormal blood-filled bulge in a blood vessel, and especially an artery, resulting from weakening (as from disease) of the vessel wall.

ANGELMAN SYNDROME (AS). A disorder caused by the deletion or absence of active imprinted genes.

ANGINA. A sensation of chest pain, squeezing, or pressure, usually arising from reduced blood supply to the heart muscle due to obstruction or spasm of the coronary arteries.

ANGIOGENESIS. The medical term for the formation of new blood vessels out of preexisting blood vessels.

ANGIOGRAPHY. A procedure that shows the system of blood vessels and the blood flow in a portion of the body. Requires an injection of dye to help see the vessels.

ANGIOID STREAKS. Gray, orange, or red wavy branching lines in Bruch's membrane.

ANGIOKERATOMA. A skin rash made up of red bumps. The rash most commonly occurs between the navel and the knees.

ANGIOMA. A benign tumor composed of blood vessels or lymph vessels.

ANGIONEUROTIC EDEMA. Recurrent episodes of swelling of the tissues of the body caused by an overactive immune system. This is also called angioedema.

ANGIOTENSINOGEN. A plasma globulin (protein) formed in the liver and directly involved in the regulation of blood pressure.

ANGLE-CLOSURE GLAUCOMA. An increase in the fluid pressure within the eye due to a complete, and sometimes sudden, blockage of the fluid-drainage passages.

ANHEDONIA. The inability to experience satisfaction or pleasure from activities or interests that the person previously enjoyed. It is a common symptom of depression.

ANHIDROSIS. Complete inability to sweat in response to heat.

ANIMAL DISEASE MODEL. A living nonhuman animal used during the research and investigation of human disease. The animal model may or may not be genetically engineered.

ANKYLOSIS. Immobility of a joint due to the formation of new bone at the site of inflammation.

ANOMALOUS. Irregular or different from normal.

ANOMALOUS VENOUS RETURN. Normally, the veins that bring blood containing oxygen from the lungs to the heart (called pulmonary veins) are connected to the left atrium. In this situation, the pulmonary veins are connected to the right atrium.

ANOMALY. A malformation or abnormality in any part of the body.

ANONYCHIA. The absence or abnormal development of the fingernails and toenails.

ANOPHTHALMIA. Congenital absence of the eyes.

ANOSMIA. Impairment or absence of the sense of smell.

ANTERIOR CHAMBER. The fluid-filled front portion of the eye that lies between the iris and the cornea (the transparent front part of the eye that covers the iris and pupil).

ANTERIOR FONTANELLE. The soft spot on the skull of an infant that is located in the center of the head just behind the hairline.

ANTERIOR HORN CELLS. Subset of motor neurons within the spinal cord.

ANTI-ANDROGEN DRUGS. Drugs that block the activity of the male hormone.

ANTIBIOTICS. A group of medications that kill or slow the growth of bacteria.

ANTIBODY. A protein produced by the mature B cells of the immune system that attach to invading microorganisms and target them for destruction by other immune system cells.

ANTICIPATION. A genetic phenomenon in which the symptoms of a disease appear at an earlier age in each successive generation.

ANTICOAGULANT. Drugs used to prevent blood clots.

ANTIDIURETIC HORMONE (VASOPRESSIN). A hormone that acts on the kidneys to regulate water balance.

ANTIGEN. A substance or organism that is foreign to the body and stimulates a response from the immune system.

ANTIGEN PRESENTING CELL. Cells that are able to present foreign antigen in conjunction with MHC proteins to the immune system.

ANTINUCLEAR ANTIBODIES (ANAS). Abnormal antibodies against cell nuclei. They are found in the blood of people with autoimmune diseases such as lupus.

ANTIPSYCHOTICS. Medications for reducing symptoms of a severe mental disorder such as schizophrenia; sometimes used for behavioral ASD symptoms.

ANUS. The opening at the end of the intestine that carries waste out of the body.

AORTA. The main artery located above the heart that pumps oxygenated blood out into the body. Many congenital heart defects affect the aorta.

AORTIC DILATATION. Weakening and stretching of the aorta that can occur with TAAD-associated gene mutations and lead to an aneurysm or aortic dissection.

AORTIC DISSECTION. A splitting of the layers of the aorta wall that causes blood to leak between the layers.

AORTIC ROOT. The location where the aorta (main heart blood vessel) inserts in the heart. Enlargement of the aortic root can cause it to rupture.

AORTIC VALVE. Valve joining the left ventricle to the aorta in the heart.

APERT SYNDROME. A genetic syndrome characterized by syndactyly as well as malformations of the skull and face. It is named for Eugène Apert, the French physician who first described it in 1906.

APHASIA. Impairment of the ability to comprehend or communicate through speech, writing, or signs due to brain dysfunctions.

APLASIA. Defective development resulting in absence of all or part of an organ or tissue.

APLASIA CUTIS CONGENITA (ACC). A group of disorders with different causes and a common characteristic of absence of skin in a defined area.

APLASTIC ANEMIA. A disorder in which the bone marrow and its blood stem cells are damaged such that it cannot produce mature red blood cells, white blood cells, or platelets.

APNEA. An irregular breathing pattern characterized by abnormally long periods of the complete cessation of breathing.

APOENZYME. An enzyme that cannot function without assistance from other molecules called cofactors.

APOLIPOPROTEIN E (APOE). A protein that transports cholesterol and helps remove it from the bloodstream; the gene encoding one form of this protein, APOE-4, is associated with an increased risk of late-onset Alzheimer's disease.

APOPTOSIS. The normally programmed cell death process in which cells die in order to be replaced with new cells.

APPENDECTOMY. The procedure to surgically remove an appendix.

APPENDICITIS. Inflammation of the appendix.

APPENDIX. A portion of intestine attached to the cecum.

APRAXIA. Impairment of the ability to make purposeful movements without paralysis or loss of sensation.

AQUEOUS HUMOR. Fluid produced by the ciliary body and contained within the front chamber of the eye.

ARACHNODACTYLY. A condition characterized by abnormally long and slender fingers and toes.

ARNOLD-CHIARI MALFORMATION. A congenital anomaly in which parts of the brain protrude through the opening in the base of the skull into the spinal column.

ARRHYTHMIA. Abnormal heart rhythm, examples are a slow, fast, or irregular heart rate.

ARTERIAL. Term used to describe an artery or the entire system of arteries.

ARTERIOLE. The smallest type of artery.

ARTERIOPATHY. Damage to blood vessels.

ARTERIOSCLEROSIS. Hardening of the arteries that often results in decreased ability of blood to flow smoothly.

ARTERIOVENOUS MALFORMATION (AVM). Abnormal direct connection between the arteries and veins (blood vessels) that may range in size from very small to large. AVMs may lead to bleeding or aneurysm formation.

ARTERY. A blood vessel that carries blood away from the heart to peripheral tissues.

ARTHRITIS. An inflammation of one or more joints that causes pain, swelling, stiffness, and limited movement.

ARTHROCHALASIA. Excessive looseness of the joints.

ARTHROGRYPOSIS (PLURAL, ARTHROGRYPOSES). A congenital musculoskeletal condition in which the infant has contractures of the joints in two or more areas of the body.

ARTHROPATHY. Any disease or disorder that affects joints.

ARTIFICIAL INTELLIGENCE. Abbreviated as AI, artificial intelligence is the ability of computers or computer-driven devices to make decisions with real-time data based on machine learning.

ASCITES. An abnormal collection of fluid in the abdominal cavity. It is most often caused by cirrhosis, metastatic liver cancer, or other severe liver disease.

ASPERGER SYNDROME. A term previously used to describe mild autism in individuals with normal intelligence and language skills; now classified as an ASD.

ASPHYXIA. Lack of oxygen. In the case of cerebral palsy, lack of oxygen to the brain.

ASPIRATION PNEUMONIA. Lung infection due to food or liquids accidentally getting into lungs.

ASPLENIA. The absence of the spleen or of normal splenic function in the body. It may be either congenital or acquired.

ASSAY. A laboratory test designed to identify and measure the amount of a specific substance.

ASSISTED REPRODUCTIVE TECHNOLOGY (ART). A collective term for a group of procedures done to address problems with fertility. ART includes such techniques as in vitro fertilization, cryopreservation of donated gametes or embryos, and pre-implantation genetic diagnosis.

ASSOCIATION. A non-random occurrence in two or more individuals of the same group of anomalies that are not otherwise known to be a sequence or syndrome.

ASTIGMATISM. A cause of poor eyesight, usually due to a refractive error caused by an irregularly shaped cornea.

ASTROCYTES. Glial cells that occur in the brain and spinal cord.

ASTROCYTOMA. Tumor of the central nervous system derived from astrocytes.

ASYMMETRY. Lack of similar size, length, and shape on both sides of the body.

ASYMPTOMATIC. Without symptoms.

ATAXIA. A deficiency of muscular coordination, especially when voluntary movements are attempted, such as grasping or walking.

ATHEROSCLEROSIS. Thickening and hardening of the inner layer of the arteries due to the accumulation of plaque; a risk factor for Alzheimer's disease.

ATHETOSIS. A condition marked by slow, writhing, involuntary muscle movements.

ATLASTIN-1. A protein encoded by the *ATL1* gene that is important in building and maintaining the structure of the endoplasmic reticulum in the nerve cells of the brain and spinal cord.

ATP. Adenosine triphosphate. The molecule used by the cells of the body for energy.

ATRESIA. An abnormal condition in which a structure that should be hollow is fused shut.

ATRIA. The two chambers at the top of the heart, where blood from the lungs or body pools before entering one of the ventricles. (Singular: atrium.)

ATRIAL FIBRILLATION. An abnormal heart rhythm characterized by the rapid and irregular beating of the two upper chambers (atria) of the heart.

ATRIAL SEPTAL DEFECT (ASD). An abnormal opening between the two upper chambers of the heart (atria).

ATRIOVENTRICULAR COMMUNIS DEFECT. A birth defect of the heart in which the canal between the upper and lower chambers of the heart does not form correctly.

ATROPHIC DERMATOSIS. Wasting away of the skin.

ATROPHIC PHASE. The final phase of LHON where cells in the optic disc and optic nerve have atrophied, resulting in legal blindness. Peripheral vision remains.

ATROPHY. Wasting away of normal tissue or an organ due to degeneration of the cells.

ATTENTION DEFICIT DISORDER (ADD); ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD). Condition characterized by diverse symptoms including age-inappropriate attention span, hyperactivity, and impulsive behavior.

ATYPIA. Any abnormality in a cell.

ATYPICAL PERSONALITY DEVELOPMENT. Another term for pervasive development disorder (PDD-NOS). Other synonyms for this diagnostic category are atypical autism and atypical PDD.

AURA. A disturbance in one or more of the five senses before the beginning of an epileptic seizure.

AURAL ATRESIA. The absence of the external ear canal.

AURICULAR. Pertaining to the ear.

AUTISM SPECTRUM DISORDER (ASD). A general term for a group of neurodevelopmental disorders characterized by difficulties in social interactions, significant abnormalities in speech patterns, and limited but repetitive interests and activities. AUTS2 syndrome is classified as an autism spectrum disorder.

AUTISTIC PSYCHOPATHY. Hans Asperger's original name for Asperger syndrome. It is still used occasionally as a synonym for the disorder.

AUTOANTIBODY. An antibody against the body's own proteins that the immune system produces.

AUTOIMMUNE DISORDERS. Conditions caused by inappropriate immune system activity.

AUTOIMMUNE REACTION. When the body attacks itself, thinking it is being invaded by a foreign body like a bacteria.

AUTONOMIC NERVOUS SYSTEM. The part of the nervous system that regulates heart muscle, smooth muscle, and glands.

AUTOSOMAL. Describes a genetic trait found on a chromosome that is not involved in determining sex.

AUTOSOMAL CHROMOSOMES. Relating to any chromosome besides the X and Y sex chromosomes. Human cells contain 22 pairs of autosomal chromosomes and one pair of sex chromosomes.

AUTOSOMAL DOMINANT. A pattern of genetic inheritance in which only one abnormal gene is needed to display the trait or disorder.

AUTOSOMAL DOMINANT CONDITION. A disease or condition that results from a mutation in only one copy of a gene pair.

AUTOSOMAL DOMINANT MUTATION. An abnormal gene on one of the 22 pairs of non-sex chromosomes that will display the defect when only one copy is inherited.

AUTOSOMAL RECESSIVE. A pattern of genetic inheritance in which two abnormal genes are needed to display the trait or disease.

AUTOSOMAL RECESSIVE CONDITION. A disorder where two copies of a dysfunctional gene must be inherited for the trait to present. The gene is present on the non-sex chromosomes.

AUTOSOMAL RECESSIVE MUTATION. A pattern of genetic inheritance where two abnormal genes are needed to display the trait or disease.

AUTOSOME. Any chromosome that is not a sex chromosome. The human genome has 22 pairs of autosomes.

AXON. Very thin, wire-like extension of nerve cells.

AZOOSPERMIA. The absence of sperm in the seminal fluid.

AZOOSPERMIA FACTOR (AZF). A region of the Y chromosome containing genes that are important for male fertility.

B

B CELLS. Lymphocytes that originate in the bone marrow and make antibodies in response to antigens.

BACTERIOPHAGE. A virus that can destroy a bacterium.

BALANCED CHROMOSOME TRANSLOCATION. A rearrangement of the chromosomes in which two chromosomes have broken and exchanged pieces without the loss of genetic material.

BAND. A specific region of a chromosome that is identified by its characteristic staining pattern and location within a chromosome, as seen in a karyotype. A band is either part of the short arm (p arm) or the long arm (q arm) of a chromosome and is further defined by a numeric location, such as chromosome band 11q24.1.

BANDING. Striped patterns that are visible on stained chromosomes and that are distinctive for each chromosome.

BARDET-BIEDL SYNDROME. A human genetic disorder that affects many body systems. It is characterized principally by obesity, retinitis pigmentosa (a type of progressive retinal dystrophy), polydactyly (having additional fingers or toes), intellectual disability, hypogonadism (a defect of the gonads that results in underproduction of testosterone), and possibly kidney failure.

BIARIUM. A chemical put into a solution and swallowed to help with outlining the gastrointestinal system during an x-ray study.

BIARIUM ENEMA X RAY. A procedure that involves the administration of barium into the intestines by a tube inserted into the rectum. Barium is a chalky substance that enhances the visualization of the gastrointestinal tract on x-ray.

BASAL CELL CARCINOMA. A cancer originating from the skin.

BASAL GANGLIA. An area in the forebrain that contains seven nuclei (clusters of nerve cells) responsible for initiating and controlling voluntary movement along with procedural learning and some habitual actions.

BASE PAIR (BP). Any of the complementary nucleotide bases (adenine-thymine and cytosine-guanine in DNA; adenine-uracil and cytosine-guanine in RNA) held together by weak hydrogen bonds. Base pairs form links between the two strands of DNA.

BASEMENT MEMBRANE. A thin, fibrous, noncellular layer of tissue that anchors and separates the epithelium (the skin and the tissue that lines body cavities) from the underlying connective tissue.

BAYES' THEOREM. A theorem that estimates the probability of an event, based on knowledge of prior conditions that may be related to the event. It is named for Thomas Bayes (c. 1701–1761), an English Presbyterian minister and Fellow of the Royal Society. Bayes' theorem is used in genetic risk assessment for non-Mendelian disorders.

BECKWITH-WIEDEMANN SYNDROME. A collection of health problems present at birth including an omphalocele, large tongue, and large body size.

BENIGN. Referring to a noncancerous tumor that does not spread and is not life-threatening.

BENIGN PROSTATIC HYPERPLASIA (BPH). A noncancerous condition of the prostate that causes growth of the prostate tissue, thus enlarging the prostate and blocking urination.

BENIGN TUMOR. An abnormal proliferation of cells that does not spread to other sites.

BENZOQUINONE ACETIC ACID. Toxic compound that is formed when oxygen reacts with homogentisic acid.

BETA CELLS. The insulin-producing cells of the pancreas.

BETA-2 MICROGLOBULIN. A component protein of class I *MHC*.

BETA-ADRENERGIC BLOCKER. A drug that works by controlling the nerve impulses along specific nerve pathways.

BETA-AMYLOID PLAQUES. Dead or dying nerve cells and cell debris surrounding deposits of beta-amyloid protein in the brain; excess plaques are diagnostic of Alzheimer's disease.

BETA-GALACTOSIDASE. An enzyme that forms a complex with cathepsin A.

BETA-III SPECTRIN. A protein that forms the scaffolding (cytoskeleton) of cell membranes in combination with alpha spectrins.

BIALLELIC. Pertaining to both pair of genes or alleles in a set.

BIFID UVULA. The uvula is the small, teardrop-shaped piece of flesh hanging in the back of the throat; the uvula is bifid if the bottom area is split in two parts.

BILATERAL. Relating to or affecting both sides of the body or both of a pair of organs.

BILATERAL BREAST CANCER. Cancer of both breasts, caused by two separate cancer processes.

BILE. A substance produced by the liver and concentrated and stored in the gallbladder. Bile contains a number of different substances, including bile salts, cholesterol, and bilirubin.

BILE ACIDS. Steroid acids such as cholic acid that occur in bile, an alkaline fluid secreted by the liver and passed into a part of the small intestine where it aids in absorption of fats.

BILE ALCOHOL. A steroid acid with an alcohol group attached.

BILE DUCT. A passageway that carries bile (fluid secreted by the liver involved in fat absorption) from the liver to the gallbladder to the small intestine.

BILIRUBIN. A yellow pigment that is the end result of hemoglobin breakdown. This pigment is metabolized in the liver and excreted from the body through the bile. Bloodstream levels are normally low; however, extensive red blood cell destruction leads to excessive bilirubin formation and jaundice.

BIOBANK. A repository of biological samples (usually human samples) for use in research.

BIOCHEMICAL TESTING. Measuring the amount or activity of a particular enzyme or protein in a sample of blood, urine, or other tissue from the body.

BIOFEEDBACK. A technique in which patients are trained to gain some voluntary control over certain physiological conditions, such as blood pressure and muscle tension, and to promote relaxation.

BIOINFORMATICS. An interdisciplinary scientific field that combines statistics, engineering, mathematics, and computer science to capture and understand biological data.

BIOLOGICS. Substances, usually proteins, that occur naturally in the human body and that are used to treat disease.

BIOMARKER. A distinctive biological indicator of a process, event, disease, or other condition.

BIOPSY. The surgical removal and microscopic examination of living tissue for diagnostic purposes.

BIOPTICS. Glasses that have small telescopes fitted in the lens.

BIOSYNTHESIS. The manufacture of materials in a biological system.

BIOTIN. A growth vitamin of the vitamin B complex found naturally in liver, egg yolks, and yeast.

BIPOLAR DISORDER. Formerly called manic depression, this psychological disorder is characterized by periods of mania followed by periods of depression.

BITEMPORAL CONSTRICTION. Abnormal narrowing of both sides of the forehead.

BLADDER. The organ that stores urine after it flows out of the kidneys and through the ureters.

BLASTOCYST. The phase of human embryonic development that occurs about 5–9 days after fertilization. The blastocyst consists of an outer layer of cells; an inner mass of cells; and a fluid-filled cavity.

BLEPHAROPHIMOSIS. A small eye opening without fusion of the upper eyelid with the lower eyelid at the inner and outer corner of the eye.

BLEPHAROSPASM. An abnormal involuntary twitching or closing of the eyelid. It is the second most common type of focal dystonia.

BLM. The gene that makes a member of a protein family called RecQ helicases.

BLMASH. The mutation in the BLM gene, specifically a 6-bp deletion and 7-bp insertion at nucleotide position 2281 in the BLM cDNA, that causes Bloom syndrome in people of Ashkenazi Jewish ancestry.

BLOOD-BRAIN BARRIER. A mechanism that acts as a sentry for the brain and only allows certain substances in the circulating blood to pass into the brain.

BLOOD SERUM. The clear liquid portion of the blood.

BLOOD VESSELS. A general term for arteries, veins, and capillaries that transport blood throughout the body.

BMPR2. Bone morphogenetic protein receptor 2; it is the gene on which a mutation occurs that is most responsible for cases of familial pulmonary arterial hypertension.

BODY ASYMMETRY. Abnormal development of the body in which the trunk and/or the limbs are not of equal size from one side of the body to the other.

BODY MASS INDEX (BMI). A measure of body fat derived from a person's height and weight. It is calculated by taking the person's weight in kilograms and dividing by the square of the person's height in meters.

BOILS. Painful areas of inflammation.

BONE CYSTS. Fluid- or air-filled space within the bones.

BONE DYSPLASIA. Abnormal bone development.

BONE MARROW. The soft and spongy center of the bones where blood cells are made.

BONE MARROW TRANSPLANT (BMT). A medical procedure used to treat some diseases that arise from defective blood cell formation in the bone marrow. Healthy bone marrow is extracted from a donor to replace the marrow in an ailing individual. Proteins on the surface of bone marrow cells must be identical or very closely matched between a donor and the recipient.

BONE REMODELING. The process of breaking down old bone and building up new bone.

BONE SCLEROSIS. Increased bone density and hardness.

BOOMERANG DYSPLASIA. A lethal genetic syndrome in which fetal bones and cartilage fail to develop normally; the arm and leg bones are bent into the shape of a boomerang. Infants with this disorder die shortly after birth.

BOWMAN'S CAPSULE. A cup-shaped sac that surrounds the glomerulus in the kidney and receives the fluid (filtrate) from the blood filtered by the glomerulus.

BOWMAN'S LAYER. Transparent sheet of tissue directly below the basement membrane.

BRACHYCEPHALY. An abnormal thickening and widening of the skull.

BRACHYDACTYLY. Abnormal shortness of the fingers and toes.

BRACHYMELIA. A general medical term used to describe short limbs.

BRADYCARDIA. An irregularly slow heartbeat.

BRADYKINESIA. Extremely slow movement.

BRAILLE. An alphabet represented by patterns of raised dots that are felt with the fingertips. It is the main method of reading used by the blind.

BRAIN VENTRICLES. A set of four connected cavities that are located deep in the core of the brain. Cerebrospinal fluid (CSF) is made by cells lining the walls of the first two ventricles, then flows through the third, then through the fourth ventricle, before flowing out of the brain. The fluid-filled cavities provide mechanical cushion for the brain, and the CSF provides nutrients to, and carries metabolic wastes away from, the cells of the brain.

BRAINSTEM. The lower part of the brain that connects to the spinal cord.

BRANCHED-CHAIN. An open chain of atoms having one or more side chains.

BRANCHIAL ARCHES. Structures that form during the development of the human embryo as outpouchings of the developing pharynx. The first and second branchial arches in humans give rise to the bony and muscular structures of the face, jaw, and upper neck.

BRANCHING ENZYME. Enzyme responsible for building the branched structure of glycogen stores.

BRANCHIOOTORENAL (BOR) SYNDROME. The second most common autosomal dominant form of syndromic hereditary hearing loss.

BRCA1 AND BRCA2. Breast cancer susceptibility genes; specific inherited mutations in these genes greatly increase the risk of breast and ovarian cancers.

BREAST BIOPSY. A small sample of tissue taken from the breast and studied to diagnose and determine the exact type of breast cancer.

BREAST SELF-EXAM (BSE). Examination by an individual of their own breasts.

BREECH DELIVERY. Birth of an infant feet- or buttocks-first.

BRESLOW DEPTH. A measurement of the thickness of a cutaneous melanoma, used in staging the cancer. It is named for Alexander Breslow, an American pathologist who first identified it as a prognostic factor for melanoma in 1970.

BROAD LIGAMENT. The ligament connecting the ovaries to the uterus.

BRONCHI. Branching tube-like structures that carry air into and out of the lungs. The walls of the bronchi contain circular muscles that can constrict (tighten up to make airways narrower) or dilate (relax to make airways wider). The bronchi divide into smaller bronchioles within the lung tissue.

BRONCHIECTASIS. An abnormal condition of the bronchial tree, characterized by irreversible widening and destruction of the bronchial walls of the lungs.

BRONCHIECTASIS. Permanent enlargement of parts of the airways of the lung.

BRUCH'S MEMBRANE. A membrane in the eye between the choroid membrane and the retina.

BRUTON TYROSINE KINASE (BTK). An enzyme vital for the maturation of B cells.

BUCCAL. Related to the cheek.

BULBAR MUSCLES. Muscles that control chewing, swallowing, and speaking.

BUNDLES OF PROBST. Abnormally developed nerve fibers in the brain.

BUPHTHALMOS. A characteristic enlargement of one or both eyes associated with infantile glaucoma.

C

C1 INHIBITOR. Abbreviated C1-INH, this protein is responsible for preventing the action of the C1 complement molecules in the body. It is this protein that is either deficient or malformed in HANE.

CA-125 (CARBOHYDRATE ANTIGEN 125). A protein that is sometimes high when ovarian cancer is present. A blood sample can determine the level of CA-125 present.

CAESAREAN SECTION. Surgical method to deliver a baby that requires making an incision in the mother's abdomen to remove the infant.

CAFÉ-AU-LAIT SPOTS. Birthmarks that may appear anywhere on the skin; named after the French coffee drink because of the light-brown color of the marks.

CAHUB ACQUISITION OF NORMAL TISSUES. The Cancer Human Biobank, a section of which is dedicated to the storage of tissues for the GTEx project.

CALCIFICATION. The process by which tissue becomes hardened by the depositing of calcium.

CALORIE. A unit of energy that represents the amount of heat a specific amount of food will create in the human body.

CAMPTODACTYLY. A congenital disorder in which one or more fingers are permanently bent. It is a classic sign of FSS as well as of several other genetic syndromes.

CANCER. A disease caused by uncontrolled growth of the body's cells.

CANCER BIOMARKERS. A molecule found in the body like a protein or gene that can suggest prognosis and what type of therapies would be best. In some cases they can even predict the risk of cancer in people who do not have cancer.

CANCER CELLS. These cells have characteristics that distinguish them from normal cells and non-cancerous cells; they are threatening, harmful, and resistant to treatment.

CANCER GENOME ATLAS (CGA). A large multinational initiative for sequencing cancer genomes.

CAPILLARY. A very narrow tube that carries liquid like blood or lymphatic fluid.

CARBOHYDRATE. Any of various natural compounds of carbon, hydrogen, and oxygen (as in sugars and starches) that are burned by the body for energy.

CARCINOGEN. Any substance or radioactive material that is directly implicated in causing cancer.

CARCINOMA. Any cancer that arises in the epithelium, the tissue that lines the external and internal organs of the body.

CARDIAC ARREST. A sudden stop in the circulation of the blood due to the failure of the heart to contract effectively or at all. It is potentially reversible but if untreated can lead to sudden cardiac death.

CARDIAC CONDUCTION DEFECT. An abnormality of the electrical system of the heart that regulates the heartbeat.

CARDIAC MUSCLE. The muscle of the heart.

CARDIAC RHABDOMYOMA. Benign (noncancerous) tumor of the heart muscle.

CARDINAL SYMPTOMS. A group of symptoms that define a disorder or disease.

CARDIOLIPIN. A type of lipid (fatty substance) found almost exclusively in the inner mitochondrial membrane where it is essential for the optimal function of numerous enzymes involved in mitochondrial energy metabolism.

CARDIOMYOCYTES. The muscle cells that make up heart muscle tissue.

CARDIOMYOPATHY. Measurable deterioration of the heart muscle's ability to contract normally, eventually leading to heart failure.

CARNITINE. An amino acid necessary for metabolism of the long-chain fatty acid portion of lipids. Also called vitamin B7.

CARRIER. A person who possesses a gene for an abnormal trait without showing signs of the disorder. The person may pass the abnormal gene on to offspring.

CARRIER TESTING. Testing performed to determine whether someone possesses one changed copy and one unchanged copy of a particular gene.

CARTILAGE. Supportive connective tissue that cushions bone at joints or connects muscle to bone.

CARTILAGE OLIGOMERIC MATRIX PROTEIN GENE. A gene that codes for a specific protein involved in the formation of cartilage.

CASCADE TESTING. A term that refers to performing genetic counseling and testing in blood relatives of a person identified as having a specific genetic mutation. It is most commonly recommended for the relatives of patients carrying a genetic mutation linked to cancer.

CAT SCAN. Acronym for a computed axial tomography, a computerized x-ray examination of internal organs

CATABOLISM. The energy-releasing process of breaking down complex chemical compounds into simpler ones in the body.

CATAGEN. The breakdown phase of the hair growth cycle.

CATALYST. A substance that changes the rate of a chemical reaction but is not physically changed by the process.

CATALYZE. Facilitate. A catalyst lowers the amount of energy required for a specific chemical reaction to occur. Catalysts are not used up in the chemical reactions they facilitate.

CATAPLEXY. A symptom of narcolepsy in which there is a sudden episode of muscle weakness triggered by emotions. The muscle weakness may cause the person's knees to buckle, or the head to drop. In severe cases, the patient may become paralyzed for a few seconds to a few minutes.

CATARACT. A clouding of the eye lens or its surrounding membrane that obstructs the passage of light, resulting in blurry vision. Surgery may be performed to remove the cataract.

CATATONIA. Psychomotor disturbances that can include stupor, rigidity, muteness, purposeless, or bizarre movements; may occur with a severe ASD.

CATATONIC BEHAVIOR. Behavior characterized by muscular tightness or rigidity and lack of response to the environment.

CATECHOLAMINES. Biologically active compounds involved in the regulation of the nervous and cardiovascular systems, rate of metabolism, body temperature, and smooth muscle.

CATHETER. A narrow, flexible tube used to create a pathway for introducing drugs, nutrients, fluids, or blood products into the body and/or for removing fluid or other substances from the body.

CATHETERIZATION. The process of inserting a hollow tube into a body cavity or blood vessel.

CATIONIC TRYPSINOGEN GENE. A gene known to cause hereditary pancreatitis when significantly altered.

CAUDAL. Pertaining to the tail (bone).

CAUTERIZATION. Process of burning tissue either with a laser or electric needle to stop bleeding or destroy damaged tissue.

CAVEOLAE (SINGULAR, CAVEOLA). Tiny, flask-shaped pockets in the plasma membranes of human and animal cells.

CD4+ CELLS. A type of T cell that secretes small proteins (called cytokines) that regulate the body's active immune response to infections.

CD8+ CELLS. A type of T cell that kills cancer cells, cells infected with viruses, or cells that are damaged in other ways. CD81 cells are also known as cytotoxic T cells, killer T cells, and cytolytic T cells.

CDKN2A OR P16. Gene, when altered, known to cause Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome and possibly increased pancreatic cancer risk.

CECUM. The first part of the large bowel.

CELL. The smallest living units of the body that group together to form tissues and help the body perform specific functions.

CELL ADHESION MOLECULE. Any one of several thousand proteins that together control the cell-to-cell communication that must take place in order for cells to migrate to their proper places, develop into the proper types of cells, and make the appropriate connections with other cells.

CELL DANGER RESPONSE (CDR). A metabolic response of cells to various types of threats.

CELL DIFFERENTIATION. The act of a cell becoming a specific type of cell.

CELL LINE. A defined population of cells that can be maintained in culture for an extended period of time while retaining stable phenotypes and functions. Cell lines can be either finite (lasting for a limited period of time due to cellular senescence) or immortal (able to divide and reproduce indefinitely in a suitable culture medium as a result of mutations).

CELLULAR IMMUNITY. A type of acquired immunity mediated by killer T-cells; important in fighting "hidden" infections, such as those caused by cellular parasites and some viruses.

CELLULAR SENESCENCE. The point at which cell division stops in an average cell, usually around 50 successive divisions. This stopping point is called the Hayflick limit.

CEMENTOMA. A type of noncancerous tumor that contains a bony substance known as cementum.

CENTRAL NERVOUS SYSTEM (CNS). In humans, the central nervous system is composed of the brain, the cranial nerves and the spinal cord. It is responsible for the coordination and control of all body activities.

CENTRAL POLYDACTYLY. Occurring between the thumb and little finger or between the big toe and the little toe.

CENTRAL VISION. The ability to see objects located directly in front of the eye. Central vision is necessary for reading and other activities that require people to focus on objects directly in front of them.

CENTROMERE. A constricted region of a chromosome that is involved in cell division and is used to define the long arm (q) and short arm (p) of the chromosome.

CEREBELLAR ATAXIA. Unsteadiness and lack of coordination caused by a progressive degeneration of the part of the brain known as the cerebellum.

CEREBELLAR TONSILS. Lobes on the undersurface of each hemisphere of the cerebellum.

CEREBELLUM. The part of the brain between the brain stem and back of the cerebrum, consisting of two lateral lobes and a median lobe and involved especially in muscle coordination and maintenance of equilibrium.

CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY (CADASIL). An inherited type of vascular dementia.

CEREBRAL CORTEX. The outer surface of the cerebrum made up of gray matter and involved in higher thought processes.

CEREBRAL PALSY. Movement disability resulting from nonprogressive brain damage.

CEREBRAL VENTRICLES. Spaces in the brain that are located between portions of the brain and filled with cerebrospinal fluid.

CEREBRAL WHITE MATTER MIGRATION LINES. Pattern of defects found in the cerebral cortex of the brain probably caused by abnormal migration of neurons during brain formation.

CEREBRO-CEREBELLAR CIRCUITS. Neural pathways that originate in the cerebral cortex and travel through the deeper structures of the brain and back to the cerebral

cortex. They control verbal working memory and other higher-order brain functions.

CEREBROSIDES. Fatty carbohydrates that occur in the brain and nervous system.

CEREBROSPINAL FLUID (CSF). Clear fluid that circulates in the brain and spinal cord to nourish, cushion, and maintain uniform pressure.

CEREBRUM. The largest section of the brain, which is responsible for such higher functions as speech, thought, vision, and memory.

CEROID. The by-product of cell membrane breakdown.

CERULOPLASMIN. A protein circulating in the bloodstream that binds with copper and transports it.

CERVICITIS. Inflammation of the cervix.

CFTR. Cystic fibrosis transmembrane conductance regulator. The protein responsible for regulating chloride movement across cells in some tissues. When a person has two defective copies of the *CFTR* gene, cystic fibrosis is the result.

CHANNELOPATHY. A type of disease caused by disturbances in the function of ion channels or the proteins that regulate them. Channelopathies may be either genetic or acquired later in life.

CHAPERONIN. A molecule that captures and refolds misshapen proteins that might interfere with normal cellular functions; also called a protein cage.

CHELATION THERAPY. A form of therapy in which chelating agents are administered to remove heavy metals from the body. Chelating agents are chemicals that have a special affinity for metal ions. (Pronounced: key-LAY-shun.)

CHEMOTHERAPY. Treatment of cancer with synthetic drugs that destroy the tumor either by inhibiting the growth of the cancerous cells or by killing the cancer cells.

CHIARI II ANOMALY. A structural abnormality of the lower portion of the brain (cerebellum and brain stem) associated with spina bifida; the lower structures of the brain are crowded and may be forced into the foramen magnum, the opening through which the brain and spinal cord are connected.

CHILDHOOD DISINTEGRATIVE DISORDER. A type of ASD in which children develop normally until about age three or four and then, over a period of a few months, lose their previously learned motor, language, social, and other skills.

CHOANAL ATRESIA. A bony or membranous blockage of the passageway between the nose and pharynx at birth.

CHOLELITHIASIS. The formation of gallstones within the gallbladder.

CHOLESTEROL. A fatty-like substance that is obtained from the diet and produced by the liver. Cells require cholesterol for their normal daily functions.

CHOLINESTERASE INHIBITORS. Drugs that may slow the progression of Alzheimer's disease by inhibiting the enzymes that break down the neurotransmitter acetylcholine.

CHONDROCYTE. A specialized type of cell that secretes the material that surrounds the cells in cartilage.

CHONDRODYSTROPHY. A general term for any of several disorders of the skeleton caused by mutations that affect the normal development of cartilage.

CHONDROSARCOMA. A malignant tumor derived from cartilage cells.

CHOREA. An involuntary movement disorder characterized by short, jerky motions of the body.

CHOREOATHETOSIS. Involuntary rapid, irregular, jerky movements or slow, writhing movements that flow into one another.

CHORIOCAPILLARIS. Capillary layer of the choroid.

CHORION. The outer membrane of the amniotic sac. Chorionic villi develop from its outer surface early in pregnancy. The villi establish a physical connection with the wall of the uterus and eventually develop into the placenta.

CHORIONIC VILLUS. Cells that are present in the placenta that can be used for genetic analysis.

CHORIONIC VILLUS SAMPLING (CVS). A procedure used for prenatal diagnosis at 10–12 weeks gestation. Under ultrasound guidance a needle is inserted either through the mother's vagina or abdominal wall and a sample of cells is collected from around the early embryo. These cells are then tested for chromosome abnormalities or other genetic diseases.

CHOROID. A vascular membrane that covers the back of the eye between the retina and the sclera and serves to nourish the retina and absorb scattered light.

CHOROID PLEXUS. Specialized structures located in the ventricles of the brain that produce cerebrospinal fluid.

CHROMATID. Each of the two strands formed by replication (copying) of a chromosome; chromatids are held together by the centromere, which subsequently divides and

separates the two chromatids to form two new chromosomes.

CHROMATIN. A complex found in mammalian cells consisting of DNA, protein, and RNA. Chromatin serves to package DNA into a smaller volume that will fit within the cell to prevent damage to DNA and to control DNA replication and gene expression. It condenses to form chromosomes during the process of cell division.

CHROMOSOMAL ABERRATIONS. A general term for abnormalities in either the number or the structure of chromosomes.

CHROMOSOMAL ANEUPLOIDY. A condition in which the chromosomal number is either increased or decreased.

CHROMOSOMAL DELETION. Loss of a segment of DNA from a chromosome.

CHROMOSOMAL MICROARRAY (CMA) TESTING. A prenatal genetic test used to diagnose microdeletion syndromes and some aneuploidies. It consists of DNA samples from the patient and a reference source that have been labeled with fluorescent dyes and allowed to hybridize or bind to the synthetic DNA on the glass or plastic chip. The chip is then scanned by a computer to determine whether the patient's DNA binds to the normal DNA sequence or whether it binds to the sequence representing a DNA mutation.

CHROMOSOME. A microscopic threadlike structure found within each cell of the body that consists of a complex of proteins and DNA. Humans have 46 chromosomes arranged into 23 pairs. Changes in either the total number of chromosomes or their shape and size (structure) may lead to physical or mental abnormalities.

CHROMOSOME DELETION. A missing sequence of DNA or part of a chromosome.

CHROMOSOME INVERSION. Rearrangement of a chromosome in which a section of a chromosome breaks off and rejoins the chromosome upside down.

CHROMOSOME TRANSLOCATION. The exchange of genetic material between chromosomes, which can lead to extra or missing genetic material.

CHRONIC ATROPHIC GASTRITIS. Irritation and breakdown of the stomach wall over a period of time.

CHRONIC MYELOGENOUS LEUKEMIA (CML). A type of leukemia caused by the BCR-ABL oncogene created by a gene fusion formed by a chromosomal translocation.

CHYLOMICRON. A type of lipoprotein made in the small intestine and used for transporting fats to other tissues in the body. MTP is necessary for the production of chylomicrons.

CILIARY BODY. A structure within the eye that produces aqueous humor.

CILIOPATHY. A range of genetic disorders caused by mutations in cellular cilia, basal bodies, or by changes in ciliary function.

CILIUM. A slender protuberance from a larger cellular body. Required for sensing environmental and chemical stimuli, controlling signaling and developmental pathways. Plural: cilia.

CIRCUMCISION. The surgical removal of the foreskin of the penis.

CIRCUMFERENCE. The length around a circle.

CIRRHOISIS. A chronic degenerative disease of the liver in which normal cells are replaced by fibrous tissue. Cirrhosis is a major risk factor for the later development of liver cancer.

CLASS I MHC. Includes *HLA-A*, *HLA-B*, and *HLA-C*. Important in cellular immunity.

CLASS II MHC. *HLA-DP*, *HLA-DQ*, and *HLA-DR*. Important in humoral immunity.

CLASS III MHC. Includes the complement system.

CLAUDICATION. Pain in the lower legs after exercise caused by insufficient blood supply.

CLAVICLE. Also called the collarbone. Bone that connects the shoulder and the breast bone.

CLEFT. An elongated opening or slit in an organ.

CLEFT LIP. A separation of the upper lip that is present from birth but originates early in fetal development. A cleft lip may appear on one side (unilateral) or both sides (bilateral) and is occasionally accompanied by a cleft palate. Surgery is needed to completely repair cleft lip.

CLEFT PALATE. A congenital malformation in which there is an abnormal opening in the roof of the mouth that causes improper connection of the nasal passages and the mouth.

CLICKWRAP AGREEMENT. An online agreement between a user and a company in which users must click a box or button and read the agreement before they download content, make a purchase, or use a website.

CLINICAL BREAST EXAM (CBE). Examination of the breasts, performed by a physician or nurse.

CLINICAL LABORATORY IMPROVEMENT AMENDMENTS (CLIA). A set of regulations passed in 1988 that establish federal standards applicable to all laboratories or sites that test human specimens for health assessment or to diagnose, prevent, or treat disease.

CLINODACTYLY. A birth defect in which a finger (most often the little finger) is bent at an angle toward the neighboring finger (usually the fourth finger).

CLITORIS. A small mass of erectile tissue in the female genitalia.

CLONUS. Involuntary rhythmic muscular contractions and relaxations.

CLOVERLEAF SKULL. An abnormal, or cloverleaf, appearance to the skull caused by premature fusion of the bones in the skull of an infant.

CLUBFOOT. Abnormal permanent bending of the ankle and foot. Also called *talipes equinovarus*.

CLUTCH. The name for a group of eggs laid by zebrafish, other fish, amphibians, or birds.

COAGULATION. The process by which a liquid becomes a solid, as in blood clotting.

COAGULOPATHY. A disorder in which blood is either too slow or too quick to coagulate (clot).

COBB ANGLE. A measure of the curvature of scoliosis, determined by measurements made on x-rays.

COCHLEA. A bony structure shaped like a snail shell located in the inner ear. It is responsible for changing sound waves from the environment into electrical messages that the brain can understand, so people can hear.

COCHLEAR IMPLANTATION. A surgical procedure in which a small electronic device is placed under the skin behind the ear and is attached to a wire that stimulates the inner ear, allowing people who have hearing loss to hear useful sounds.

CO-DOMINANT. Describes the state when two alleles of the same gene are both expressed when inherited together.

CODON. A sequence of three nucleotides that code for specific amino acids.

CO-ENZYME. A small molecule such as a vitamin that works together with an enzyme to direct a biochemical reaction within the body.

COFACTOR. A substance that is required by an enzyme to perform its function.

COGNITIVE. Of, relating to, or involving conscious mental activities (such as thinking, understanding, learning, and remembering).

COGNITIVE-BEHAVIORAL THERAPY (CBT). A type of psychotherapy that teaches people to recognize and change negative patterns of thinking and behavior.

COHESINOPATHY. A condition, such as Cornelia de Lange syndrome, that affects the cohesion complex that separates chromosomes during cell division.

COLCHICINE. A compound that blocks the assembly of microtubules, which are protein fibers necessary for cell division and some kinds of cell movements, including neutrophil migration. Side effects may include diarrhea, abdominal bloating, and gas.

COLECTOMY. Surgical removal of the colon.

COLITIS. Inflammation of the colon.

COLLAGEN. The main structural protein found in the various types of connective tissue in humans and other animals. It is found in skin, ligaments, tendons, cartilage, and the intervertebral disks in the spine. Disorders of collagen are called collagenopathies.

COLOBOMA. A birth defect in which part of the eye does not form completely and appears to be cleft or notched.

COLON. The large intestine.

COLONOSCOPY. An examination of the rectum and colon with a long flexible instrument passed through the anus; also used to obtain biopsy samples.

COLORECTAL. Of the colon and/or rectum.

COLOSTOMY. The creation of an artificial opening into the colon through the skin for the purpose of removing bodily waste. Colostomies are usually required because key portions of the intestine have been removed.

COMBINED FIRST-TRIMESTER SCREENING. Blood tests for pregnancy-associated plasma protein A and human chorionic gonadotropin and an ultrasound exam for chromosomal abnormalities.

COMMON RULE. A federal policy for the protection of human research subjects in any study funded by the U.S. government; it was first defined in 1981 and amended in 2018. Formally stated in the Code of Federal Regulations, Title 45, Part 46, the Common Rule requires informed consent from all research subjects and the oversight of every study by an institutional review board (IRB).

COMPANION DIAGNOSTIC TEST. A test that provides information about the safety and efficacy of a corresponding medication. Some liquid biopsies are companion diagnostic tests.

COMPLEMENT SYSTEM. Part of the innate immune system that helps clear pathogens from an organism. It stimulates a cascade of enzyme activity that effectively lyses cells/pathogens open that are marked for destruction.

COMPLEMENTARY DNA (CDNA). DNA that is transcribed (copied) from messenger RNA using the enzyme reverse transcriptase.

COMPLETE BLOOD COUNT (CBC). A measurement of blood levels of red blood cells, white blood cells, and platelets.

COMPLETE PENETRANCE. Condition in which all who carry the gene display some symptoms.

COMPLETE SITUS INVERSUS. A laterality defect resulting in a mirror image of the normal organ formation with heart, spleen, and stomach on the right side, and the liver and gallbladder on the left.

COMPOUND HETEROZYGOTE. Having two different mutated versions of a gene.

COMPUTED TOMOGRAPHY (CT) SCAN. An imaging procedure that produces a three-dimensional picture of organs or structures inside the body, such as the brain.

COMPUTERIZED AXIAL TOMOGRAPHY (CAT) SCAN. An imaging technique that visualizes organs or tissues.

COMPUTERIZED TOMOGRAPHY (CT). A technique that uses a beam of radiation and a computerized analysis to produce an image of a body structure, often the brain.

COMT INHIBITORS. Drugs that block catechol-O-methyltransferase, an enzyme that breaks down dopamine. COMT inhibitors include entacapone and tolcapone.

CONCEPTUS. The products of conception, or the union of a sperm and egg cell at fertilization.

CONDUCTIVE HEARING LOSS. Hearing loss that is the result of a dysfunction of the parts of the ear responsible for collecting sound. In this type of hearing loss, the auditory nerve is generally not damaged.

CONES. Receptor cells that allow the perception of colors.

CONFETTI SKIN LESIONS. Numerous light or white spots seen on the skin that resemble confetti.

CONGENITAL. Occurring at or before birth.

CONGENITAL ANOMALY. An abnormality that is present at birth.

CONGENITAL BILATERAL ABSENCE OF VAS DEFERENS (CBAVD). The absence at birth of the vas deferens on each side of the male reproductive tract.

CONGENITAL CATARACT. Clouding of the lens in the eye that is present at birth.

CONGENITAL DISORDER OF DEGLYCOSYLATION (CDDG). NGLY1 deficiency or N-glycanase 1 deficiency,

in which sugar chains cannot be removed from misfolded proteins so that they can undergo degradation; caused by mutations in the NGLY1 gene.

CONGENITAL DISORDER OF GLYCOSYLATION (CDG). A family of genetic disorders that includes NGLY1 deficiency (congenital disorder of deglycosylation), as well as disorders in which sugars are not properly attached to proteins (glycosylation).

CONGENITAL HYPOPLASTIC ANEMIA (CHA). A significant reduction in the number of red blood cells present at birth, usually referring to deficient production of these cells in the bone marrow. Also sometimes called congenital aplastic anemia.

CONGENITAL MALFORMATION. A birth defect or physical abnormality present at birth.

CONNECTIVE TISSUE. A group of tissues responsible for support throughout the body; includes cartilage, bone, fat, tissue underlying skin, and tissues that support organs, blood vessels, and nerves throughout the body.

CONOTRUNCAL HEART ABNORMALITY. Congenital heart defects particularly involving the ventricular (lower chambers) outflow tracts of the heart includes subarterial ventricular septal defect, pulmonic valve atresia and stenosis, tetralogy of Fallot and truncus arteriosus.

CONSANGUINEOUS. Sharing a common bloodline or ancestor.

CONSANGUINITY. The property of belonging to the same blood kinship as another person. In genetics, marriages between two people who are second cousins or closer are regarded as consanguineous unions.

CONTIGUOUS GENE SYNDROME (CGS). An older term for microdeletion syndromes in which several genes lying closely together on the chromosome are lost as a group.

CONTINENCE. Normal function of the urinary bladder and urethra, allowing fluid flow during urination and completely stopping flow at other times.

CONTRACTURE. A tightening of muscles that prevents normal movement of the associated limb or other body part.

CONVULSION. Involuntary contractions of body muscles that accompany a seizure episode.

COPROLALIA. The involuntary expression of obscene words or phrases.

COPROPORPHYRIN. Excrement in the urine or feces indicative of unused porphyrin in the body due to overaccumulation of porphyrin.

COPROPAXIA. The involuntary display of unacceptable/obscene gestures.

COPY NUMBER VARIATION (CNV). A difference in the number of copies of a gene (normally two) or of a specific segment of DNA.

CORDOCENTESIS. A prenatal diagnostic test, usually done between 16 and 30 weeks of gestation. Using ultrasound guidance, a thin needle is introduced through the abdomen into the amniotic sac. A blood sample is taken directly from the umbilical cord. Tests can then be done on the blood sample.

CORNEA. The transparent structure of the eye over the lens that is continuous with the sclera in forming the outermost protective layer of the eye.

CORNEAL. Pertaining to the cornea of the eye, which is the clear covering that protects the front of the eyeball.

CORNEAL TRANSPLANT. Removal of impaired and diseased cornea and replacement with corneal tissue from a recently deceased person.

CORONAL SUTURE. The skull suture that lies behind the forehead area, across the head from the left side to the right side.

CORPUS CALLOSUM. A thick bundle of nerve fibers deep in the center of the forebrain that provides communication between the right and left cerebral hemispheres.

CORTICAL TUBER. Round (nodular) growth found in the cortex of the brain.

CORTICAL-THALAMIC CIRCUITS. A circular connection within the brain that travels between the cerebral cortex and the thalamus and back to the cerebral cortex. Scientists believe it helps the brain monitor its status.

CORTICOSPINAL TRACT. A bundle of long nerve fibers that runs from the motor control region of the cerebral cortex to the spinal cord, where it connects to nerves that control movement in the legs.

CORTICOSTEROIDS. Anti-inflammatory medications. They are related to cortisol, a naturally produced hormone that controls many bodily functions.

CORTISOL. Hydrocortisone; a glucocorticoid hormone produced by the adrenal glands that mediates various metabolic process and responds to stress; deficient in congenital adrenal hypoplasia.

COXA VARA. A deformed hip joint in which the neck of the femur is bent downward.

CRANIAL SUTURE. Any one of the seven fibrous joints between the bones of the skull.

CRANIOFACIAL. Relating to or involving both the head and the face.

CRANIOPAGUS. Conjoined twins with separate bodies and one shared head.

CRANIOSYNOSTOSIS. A condition in which one or more of the fibrous joints (sutures) in an infant's skull turns to bone prematurely. As a result, the shape of the head is affected as the infant continues to grow, and the facial features are often deformed.

CRANIUM. The skeleton of the head, which include all of the bones of the head except the mandible.

CREATINE KINASE (CK). An enzyme found in the brain, heart, and skeletal muscles; if elevated amounts are discovered, it can indicate the presence of one of several serious medical conditions.

CREATININE. A normal component of blood kept in low levels in urine by functioning kidneys.

CREUTZFELDT-JAKOB DISEASE (CJD). A degenerative disease of the central nervous system caused by an abnormal protein called a prion.

CRISPR (CLUSTERED REGULARLY INTERSPERSED SHORT PALINDROMIC REPEATS). A technique for genome editing that involves creating a short RNA sequence called guide RNA (gRNA) that matches a targeted sequence of DNA in the organism's genome. The gRNA guides an enzyme called Cas9 to the target DNA sequence. The enzyme cuts the genome at this location, and the researcher can either remove DNA, add new DNA, or modify the DNA.

CROHN'S DISEASE. A chronic inflammatory autoimmune disease similar to colitis.

CROUZON SYNDROME. A genetic disorder that is similar to Crouzonodermoskeletal syndrome but without acanthosis nigricans.

CRYPTOPHTHALMOS. A congenital malformation of the eye in which the eyelid fails to develop, the eye is either missing or rudimentary, and the orbit of the eye is covered by a fold of skin extending directly from the forehead to the cheek.

CRYPTORCHIDISM. A condition in which one or both testes fail to descend normally.

CURETTAGE. A surgical scraping or cleaning.

CUTANEOUS. Of, pertaining to, or affecting the skin.

CUTANEOUS SYNDACTYLY. Fusion of the soft tissue between fingers or toes resulting in a webbed appearance.

CYANOSIS. A bluish color of the skin that results from insufficient oxygen in the blood transported throughout the body.

CYANOTIC. Marked by bluish discoloration of the skin due to a lack of oxygen in the blood. It is one of the types of congenital heart disease.

CYCLOOXYGENASE-2 (COX-2) INHIBITORS. Anti-inflammatory drugs that work by blocking the COX-2 enzyme, which plays a role in the inflammatory process. COX-2 inhibitors do not block the COX-1 enzyme, which helps protect the digestive tract.

CYST. An abnormal sac or closed cavity filled with liquid or semi-solid matter.

CYSTIC FIBROSIS (CF). A respiratory disease characterized by chronic lung disease, pancreatic insufficiency, and an average age of survival of 20 years. Cystic fibrosis is caused by mutations in a gene on chromosome 7 that encode a transmembrane receptor.

CYSTIC HYGROMA. An accumulation of fluid behind the fetal neck, often caused by improper drainage of the lymphatic system in utero.

CYSTINE. A sulfur-containing amino acid, sometimes found as crystals in the kidneys or urine, that forms when proteins are broken down by digestion.

CYTOGENETICS. The branch of genetics that studies the components of a cell associated with heredity, particularly the chromosomes.

CYTOGENIC. Pertaining to the production of cells.

CYTOKINE. A protein associated with inflammation that, at high levels, may be toxic to nerve cells in the developing brain.

CYTOPLASM. The substance within a cell, including the organelles and the fluid surrounding the nucleus.

CYTOSKELETON. The network of proteins underlying and maintaining the integrity of the red blood cell membrane.

D

DANDY-WALKER MALFORMATION. A complex structural abnormality of the brain frequently associated with hydrocephalus, or accumulation of excess fluid in the brain. Abnormalities in other areas of the body may also be present. Individuals with Dandy-Walker malformation have varying degrees of mental handicap or none at all.

DEBRANCHING ENZYME. Enzyme responsible for breaking down the branched structure of glycogen stores to release glucose into the bloodstream.

DEBULKING. The removal of abnormal tissue.

DECIBEL (DB). A logarithmic unit for expressing loudness or intensity; normal speech is typically in the range of 20–50 dB.

DECIDUOUS TEETH. The first set of teeth or “baby teeth.”

DECREASED PENETRANCE. Individuals who inherit a changed disease gene, but do not develop symptoms.

DEEP VEIN THROMBOSIS. A blood clot in one of the systemic veins deep in the body.

DEFICIENCY OF ADENOSINE DEAMINASE 2 (DADA2). Syndromes caused by mutations in the *CECR1* gene.

DEFORMATION. An abnormal form or position of a part of the body caused by extrinsic pressure or mechanical forces.

DEGENERATIVE DISC DISEASE. Narrowing of the disc space between the spinal bones (vertebrae).

DEGRADATION. Lost or diminished function.

DE GROUCHY SYNDROME. Deletions in chromosome 18, originally identified in the 1960s by the French geneticist Jean de Grouchy.

DEHYDRATION. An extreme loss of water in the body, which, if untreated, can lead to brain damage and death.

DELAYED BONE AGE. An abnormal condition in which the apparent age of the bones, as seen in x-rays, is less than the chronological age of the patient.

DELETION. A mutation resulting in the loss of normal base pair sequence; a deletion may be of any size from one base pair to most of a chromosome.

DELTA-F508. The most common cystic fibrosis-causing mutation in Caucasians, resulting in a defective CFTR protein due to the deletion of the amino acid phenylalanine (F) at amino-acid position 508 of the protein.

DELUSION. A fixed, false belief that is resistant to reason or factual disproof.

DEMENTIA. A group of disorders and symptoms that impact memory, reasoning, social abilities, and intellectual functioning and that impair the ability to function normally in daily life.

DENDRITIC CELLS (DCS). Accessory cells in the mammalian immune system that acts as messengers between the adaptive and innate immune systems. Their name is derived from their tree-like shape.

DE NOVO MUTATION. A genetic mutation that is seen for the first time in the affected person, not inherited from the parents.

DENTAL AGENESIS. Failure of the teeth to form normally during embryonic development. The complete absence of all the teeth is called anodontia.

DENTAL PITS. Small, shallow holes or crevices in the tooth enamel.

DENTIN. A hard, calcareous material that covers the tooth root and, in turn, is covered by cementum and enamel.

DEOXYRIBONUCLEIC ACID (DNA). The genetic material in cells that carries the inherited instructions for growth, development, and cellular functioning.

DEPIGMENTATION. Loss of pigment or skin color.

DEPOLARIZATION. The dissipation of an electrical charge through a membrane. In the heart, depolarization causes the heart muscle to contract.

DEPOT DOSAGE. A form of medication that can be stored in the patient's body tissues for several days or weeks, thus minimizing the risk of the patient forgetting daily doses.

DERMABRASION. Scraping or sanding the epidermal layer of the skin to remove scars and other marks or wrinkles.

DERMATOLOGIC. Pertaining to the field of dermatology, the science of the skin and diseases that affect the skin.

DERMATOLOGIST. A physician who specializes in disorders of the skin.

DERMATOSPARAXIS. Skin fragility caused by abnormal collagen.

DERMIS. The layer of skin beneath the epidermis.

DESCMET'S MEMBRANE. Sheet of tissue that lies under the stroma and protects against infection and injuries.

DESFEROXAMINE. The oldest of three drugs used in iron chelation therapy. It aids in counteracting the life-threatening buildup of iron in the body associated with long-term blood transfusions.

DESMOID TUMOR. A benign, firm mass of scar-like connective tissue.

DESMOPRESSIN (DDAVP). A drug used in the treatment of von Willebrand's disease.

DEVELOPMENT. The process whereby undifferentiated embryonic cells replicate and differentiate into limbs, organ systems, and other body components of the fetus.

DEVELOPMENTAL DELAY. When children do not reach certain milestones at appropriate ages. For example, a

child should be able to speak by the time he or she is five years old.

DEVELOPMENTAL MILESTONES. Infants and toddlers develop skills at certain ages. For example, by nine months, a child should be able to grasp and toss a bottle.

DEXTROCARDIA. Right-sided positioning of the heart.

DFN2 OR DFNX1. A DeaFNess gene locus associated with nonsyndromic, progressive, X-linked hearing loss, now identified as the *PRPS1* gene locus.

DIABETES. An inability to control the levels of sugar in the blood due to an abnormality in the production of, or response to, the hormone insulin.

DIABETES INSIPIDUS. A disorder caused by insufficient secretion of vasopressin (antidiuretic hormone or ADH) or failure of the kidneys to respond to vasopressin, with symptoms similar to those of diabetes mellitus; it may be inherited, especially in children.

DIABETES MELLITUS. The clinical name for common diabetes. It is a chronic disease characterized by inadequate production or use of insulin.

DIABETIC KETOACIDOSIS (DKA). A life-threatening complication of diabetes mellitus.

DIAGNOSTIC TESTING. Testing performed to determine if someone is affected with a particular disease.

DIALYSIS. Filtering of blood to remove waste products that the kidneys would normally remove if they were present and functioning.

DIAPHRAGM. Dome-shaped muscle and fiber that separates the torso into two sections, thoracic and abdominal.

DIAPHRAGMATIC HERNIA. An abnormal opening in the diaphragm, the layer of muscle that separates the chest cavity from the abdominal cavity.

DIAPHYSIS. The middle portion, or shaft, of a long bone.

DIARRHEA. Loose, watery stool.

DIASTOLIC BLOOD PRESSURE. Blood pressure when the heart is resting between beats.

DICEPHALUS. Conjoined twins who share one body but have two separate heads and necks.

DIFFERENTIATE. Specialized development to perform a particular function.

DIGENIC INHERITANCE. A pattern of inheritance in which mutations in two (and only two) different genes are required for the manifestation of a genetic disorder.

FSHD type 2 is an example of a genetic disorder with digenic inheritance.

DIGESTIVE ENZYME. Proteins secreted by the pancreas that enter the small intestine and break down food so it can be absorbed by the body.

DIGIT. A finger or toe.

DIHYDROTESTOSTERONE (DHT). A male sex hormone formed from testosterone by the enzyme 5-alpha-reductase. DHT causes hair follicles to shut down, shortening the growth phase of the hair growth cycle and leading to miniaturization.

DILATED CARDIOMYOPATHY. A diseased and weakened heart muscle that is unable to pump blood efficiently.

DIOPTER (D). A unit of measure for describing refractive power.

DIPLEGIA. Paralysis affecting like parts on both sides of the body, such as both arms or both legs.

DIPLOID. Referring to a cell or nucleus that contains two copies of genetic material, or a complete set of chromosomes.

DISRUPTION. A type of anomaly formation in which a breakdown or inhibition of normal tissue development occurs.

DISTAL. Away from the point of origin.

DISTAL 18Q. A deletion of the end of the long arm of chromosome 18, including the tip.

DISTAL ARTHROGRYPOSIS. A disorder characterized by contractions of the muscles in the hands.

DISTAL MUSCLES. Muscles that are farthest away from the center of the body.

DIURETICS. Medications that increase the excretion of urine.

DIVERGENT STRABISMUS. Eyes that point in different directions due to imbalanced eye muscles.

DIVERTICULAE. Sacs or pouches in the walls of a canal or organ. They do not normally occur, but may be acquired or present from birth. Plural form of diverticula.

DIZYGOTIC. From two zygotes, as in nonidentical, or fraternal, twins. The zygote is the first cell formed by the union of sperm and egg.

DNA (DEOXYRIBONUCLEIC ACID). The genetic material that contains the instructions for creating proteins.

DNA BASE. One unit in a DNA sequence. The four DNA bases are adenine (A), guanine (G), thymine (T) and

cytosine (C). The sequence of these bases is the genetic code which contains the instructions for creating proteins.

DNA FINGERPRINTING. A laboratory technique used to identify individuals by extracting and identifying base-pair patterns in a person's DNA. Originally developed to solve crimes or identify human remains, DNA fingerprinting has been used to detect cross-contamination in cell lines since the early 1990s.

DNA METHYLATION. The addition of methyl groups (CH³) to nucleotide bases of DNA to regulate gene expression.

DNA MISMATCH REPAIR. A system for recognizing and replacing wrongly paired (mismatched) nucleotide bases during DNA replication. The system can also repair some forms of DNA damage.

DNA MUTATION ANALYSIS. A direct approach to the detection of a specific genetic mutation or mutations using one or more laboratory techniques.

DNA POLYMERASE. An enzyme that is required for DNA replication. It functions in the addition of new nucleotides in the production of new DNA strands.

DNA REPEATS. A three-letter section of DNA called a triplet, which is normally repeated several times in a row. Too many repeats often cause the gene to malfunction, resulting in disease.

DNA REPLICATION. The process in which a DNA molecule forms two identical copies of itself.

DNA SEQUENCE. The sequence of DNA bases that contains the instructions for creating proteins. A three-base sequence in the DNA contains the instructions for making a particular amino acid. For example, CGC codes for the amino acid alanine. Proteins are made up of one or more amino acids strung together. The instructions for a particular protein are made up of a number of three base sequences. Because DNA is double-stranded, it has two complementary sequences where the bases pair up together. C always pairs with G, and A always pairs with T. One example of double-stranded DNA sequence for alanine is GCG/CGC.

DNA TESTING. Analysis of DNA (the genetic component of cells) in order to determine changes in genes that may indicate a specific disorder.

DNA VIRUS. A virus whose genetic material is deoxyribonucleic acid (DNA). The instructions from DNA are transcribed into RNA. Some common DNA viruses are herpesvirus, papillomavirus, and parvovirus.

DOLICOCEPHALY. Elongated and narrow skull shape due to premature closure of the sagittal suture that runs from the forehead to the back of the skull.

DOMINANT. A genetic trait that is expressed when only one copy of it is present.

DOMINANT INHERITANCE. A type of genetic inheritance pattern that results in one form of a gene being dominant over other forms. Therefore, the dominant allele can express itself and cause disease, even if only one copy is present.

DOMINANT PROGRESSIVE HEARING LOSS (DPHL). The most common type of hereditary nonsyndromic progressive sensorineural hearing loss.

DOMINANT TRAIT. A genetic trait where one copy of the gene is sufficient to yield an outward display of the trait; dominant genes mask the presence of recessive genes; dominant traits can be inherited from a single parent.

DONOR RECRUITMENT AND TISSUE COLLECTION CENTERS (DRTCCS). Several locations designated for identifying and enrolling donors and acquiring multiple tissue samples from each, using best practices for sample collection, handling, fixation, and storage.

DOPAMINE. A neurochemical made in the brain that is involved in many brain activities, including movement and emotion.

DOPAMINE RECEPTOR ANTAGONISTS (DAS). The older class of antipsychotic medications, also called neuroleptics, which primarily block the site on nerve cells that normally receive the brain chemical dopamine.

DORSAL ANTERIOR CINGULATE CORTEX (DACC). An area of the cerebral cortex that is involved in fear, mood disorders, and PTSD.

DORSAL RHIZOTOMY. A surgical procedure that cuts nerve roots to reduce spasticity in affected muscles.

DORSAL ROOT GANGLIA. The subset of neuronal cells controlling impulses in and out of the brain.

DOWNSHOOT. Downward movement of the eye.

DOWN SYNDROME. Trisomy 21, a genetic disorder caused by all or part of an extra chromosome 21; characterized by intellectual disability, characteristic facial features, and various other developmental defects.

DRPLA. Dentatorubral-pallidoluysian atrophy; also called Haw River syndrome and Natito-Oyanagi disease. DRPLA is a disorder of ataxia, choreoathetosis, and dementia in adults, and ataxia, myoclonus, epilepsy, and intellectual disability in children.

DRUG METABOLISM. Chemical modification or breakdown of drugs. This usually occurs through the activity of specialized enzymatic pathways.

DRUSEN. Fatty deposits that can accumulate underneath the retina and macula and sometimes lead to AMD. Drusen formation can disrupt the photoreceptor cells, which causes central and color vision problems for people with dry AMD.

DUCT. A tube-like structure that carries secretions from glands.

DUCTUS. The blood vessel that joins the pulmonary artery and the aorta. When the ductus does not close at birth, it causes a type of congenital heart disease called patent ductus arteriosus.

DUCTUS ARTERIOSUS. The temporary channel or blood vessel between the aorta and pulmonary artery in the fetus.

DUODENUM. Portion of the small intestine nearest the stomach; the first of three parts of the small intestine.

DUPLICATION. A mutation in which part of the chromosome is repeated, adding extra genetic material.

DURA MATER. A thick membrane that is the outermost of the three layers of tissue (meninges) covering the brain and spinal cord. Tissue from this membrane has been used for transplantation in cases of head trauma but is now considered a risk factor for iatrogenic CJD.

DWARFISM. In general, a condition in which a person is considerably shorter than normal when fully grown (below an adult height of 4 feet 10 inches) as a result of an endocrine disorder, skeletal abnormality, or genetic disorder. There are about 200 different conditions that can cause dwarfism.

DYSARTHRIA. Refers to a group of speech disorders caused by disturbances in the strength or coordination of the muscles of the speech mechanism as a result of damage to the brain or nerves.

DYSKINESIA. Impairment or difficulty in performing voluntary movements, usually resulting in jerky or interrupted movements.

DYSMORPHIC. An abnormal body structure often associated with a genetic disorder.

DYSOSTOSIS. A general term for a disorder of bone development.

DYSOSTOSIS MULTIPLEX. A variety of bone and skeletal malformations.

DYSPHAGIA. Difficulty in swallowing.

DYSPHORIA. Feelings of anxiety, restlessness, and dissatisfaction.

DYSPLASIA. Abnormal development of tissues, organs, or cells.

DYSPLASTIC. Describing the abnormal growth or development of a tissue or organ.

DYSPNEA. Shortness of breath or difficulty in breathing.

DYSTHYMIA. A psychological condition of chronic depression that is not disabling but prevents the sufferer from functioning at his or her full capacity.

DYSTONIA. A movement disorder involving prolonged muscle contractions that cause twisting and repetitive movements or abnormal posture.

DYSTOPIA CANTHORUM. A wide spacing between the inner corners of the eyes, with the eyes themselves having normal spacing. Also called telecanthus.

DYSTROPHIN. A protein that supports muscle strength. Its absence or insufficiency is one of the basic causes of muscular dystrophy.

DYSTROPHY. Progressive abnormal changes in a tissue or organ.

E

EAR TAGS. Excess pieces of skin on the outside of the ear.

EARLY-ONSET AD. Alzheimer's disease that develops between the ages of 30 and 60.

E-CADHERIN/CDH1. A gene involved in cell-to-cell connection. Alterations in this gene have been found in several families with increased rates of gastric cancer.

ECCRINE. Pertaining to the sweat glands located over most of the human body. Their water-based sweat is the primary mechanism of cooling in humans.

ECHOCARDIOGRAM (ECHO). A diagnostic procedure that uses sound waves to produce images of the heart.

ECHOCARDIOGRAPH. A record of the internal structures of the heart obtained from beams of ultrasonic waves directed through the wall of the chest.

ECHOLALIA. Involuntary echoing of the last word, phrase, or sentence that is spoken by someone else or by sounds in the environment.

ECHOPRAXIA. The imitation of the movement of another individual.

ECLABIUM. Outward turning of the lip.

ECLAMPSIA. The onset of seizures in a pregnant woman with pre-eclampsia, a condition characterized by protein in the urine, high blood pressure, and sometimes other organ dysfunction.

ECTODERM. The outermost of the three embryonic germ layers, which later gives rise to the nervous system, skin, hair, teeth, and nails.

ECTODERMAL DYSPLASIA. A hereditary condition that results in the malformation of the skin, teeth, and hair. It is often associated with malfunctioning or absent sweat glands and/or tear ducts.

ECTOPIC. Tissue found in an abnormal location.

ECTRODACTYLY. A birth defect involving a split or cleft appearance of the hands and/or feet, also referred to as a "lobster-claw" malformation.

ECTROPION. An abnormal turning out, as of the eyelid.

ECZEMA. Inflammation of the skin with redness and other variable signs such as crusts, watery discharge, and itching.

EDEMA. An abnormal accumulation of fluid beneath the skin and in the cavities of the body.

EDWARDS SYNDROME. Trisomy 18; a genetic disorder caused by an extra chromosome 18 that can be screened for in the first trimester.

EFFLUVIUM. The medical term for massive hair loss or shedding.

ELASTIC FIBER. Fibrous, stretchable connective tissue made primarily from proteins, elastin, collagen, and fibrillin.

ELECTROCARDIOGRAM (ECG, EKG). A test that uses electrodes attached to the chest with an adhesive gel to transmit the electrical impulses of the heart muscle to a recording device.

ELECTROCONVULSIVE THERAPY. A treatment in which a series of controlled electrical impulses are delivered to the brain in order to induce a seizure.

ELECTRODESSICATION AND CURETTAGE. A procedure by which a papula is cut out of the skin (curettage) and bleeding controlled with an electric current (electrodesiccation).

ELECTRODESSICATION. A surgical technique for removing skin cancers by drying out tissue with an electric current and then removing the dead tissue with a curette.

ELECTROENCEPHALOGRAM (EEG). A test that measures the electronic waves of the brain.

ELECTROLYTE. A solution or a substance in a solution consisting of various chemicals that can carry electric charges. Electrolytes exist in the blood as acids, bases, and salts, such as sodium, calcium, potassium, chlorine, and magnesium.

ELECTROMYOGRAPHY (EMG). A test that uses electrodes to record the electrical activity of muscle. The information gathered is used to diagnose neuromuscular disorders.

ELECTRORETINOGRAM (ERG). A measurement of electrical activity of the retina.

ELECTRORETINOGRAPHY (ERG). A diagnostic test that records electrical impulses created by the retina when light strikes it.

EMBOLIZATION. A technique for treating some types of bleeding disorders or cancer by blocking blood vessels.

EMBOLIZATION THERAPY. Introduction of a coil or various substances into blood vessels in order to plug them and stop excessive bleeding.

EMBRYO. The earliest stage of development of a human infant, usually used to refer to the first eight weeks of pregnancy. The term “fetus” is used from roughly the third month of pregnancy until delivery.

EMBRYOGENESIS. The formation and growth of the embryo.

EMBRYOLOGY. The study of the growing embryo.

EMBRYONIC STEM CELLS (ESCS). Cells from early-stage embryos that have the capacity to differentiate into any cell type (pluripotency).

EMOLLIENT. Petroleum- or lanolin-based skin lubricants.

EMPHYSEMA. A chronic lung disease that begins with breathlessness during exertion and progresses to shortness of breath at all times, caused by destructive changes in the lungs.

EMPIRICAL. Relying on, or derived from, observations gained through the senses or by experimentation.

ENAMEL. The hard, white coating that covers teeth. Enamel is the hardest material in the body.

ENCAPSULATED. Referring to bacteria that have a thick capsule protecting their cell wall.

ENCEPHALITIS. Inflammation of the brain.

ENCEPHALOCELE. A congenital anomaly in which part of the brain is herniated through the skull.

ENCEPHALOPATHY. The medical term for any global dysfunction of the brain. It is not a single disease but rather a syndrome that has many different causes and prognoses.

ENCHONDROMAS. Benign cartilaginous tumors arising in the cavity of bone. They have the possibility of causing lytic destruction within the bone.

ENDOCARDIAL FIBROELASTOSIS (EFE). An abnormal thickening of the lining of the heart tissue due to a concentration of elastic collagen-like fibers.

ENDOCARDITIS. A dangerous infection of the heart valves caused by certain bacteria.

ENDOCRINE GLAND. Any gland that secretes its products directly into the bloodstream rather than through a duct. The hypothalamus, pituitary, and thyroid are all endocrine glands.

ENDOCRINE SYSTEM. A system of ductless glands that regulate and secrete hormones directly into the bloodstream.

ENDOLYMPH. The fluid in the inner ear.

ENDOMETRIUM. Lining of the uterus.

ENDONUCLEASE. Enzymes that recognize short pieces of DNA (often palindromic) and cleave either within or near the recognized sequence.

ENDOPLASMIC RETICULUM. A network of tubules and flattened sacs that serve a variety of functions within a cell, ranging from protein transport to the synthesis of carbohydrate and fat molecules.

ENDOPLASMIC RETICULUM-ASSOCIATED DEGRADATION (ERAD). An important cellular pathway that includes N-glycanase 1 and is responsible for breaking down (degrading) misfolded glycoproteins.

ENDOSCOPE. A slender, tubular optical instrument used as a viewing system for examining an inner part of the body. With an attached instrument, the endoscope can be used for biopsy or surgery.

ENDOSCOPIC MUCOSAL RESECTION. Removal of the mucosa during endoscopy.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP). A method of viewing the pancreas by inserting a thin tube down the throat into the pancreatic and bile ducts, injecting dye, and performing x rays.

ENDOSTEAL. Relating to the endosteum, which is the lining of the medullary cavity.

ENDOTHELIAL CELLS. The cells lining the inner walls of the blood vessels.

ENDOTHELIUM. Extremely thin innermost layer of the cornea.

END-STAGE RENAL DISEASE (ESRD). A potentially fatal condition that occurs when the kidneys can no longer effectively filter urine and excrete waste products from the body.

ENERGY HOMEOSTASIS. The ability of all living things to maintain energy balance.

ENHANCER. A DNA sequence that binds transcription factors to promote gene activity (transcription).

ENLARGED VESTIBULAR AQUEDUCT (EVA). An enlargement of a structure inside the inner ear called the vestibular aqueduct, which is a narrow canal that allows fluid to move within the inner ear. EVA is seen in approximately 10% of people who have sensorineural hearing loss.

ENTEROCOLITIS. Severe inflammation of the intestines that affects the intestinal lining, muscle, nerves, and blood vessels.

ENTEROSCOPY. A procedure used to examine the small intestine.

ENTHESITIS. Inflammation at the place where the ligaments insert into the bone.

ENTHESOPATHY. Disorder of the ligament attachment to the bone.

ENZYME. A protein that catalyzes a biochemical reaction or change without changing its own structure or function.

ENZYME EFFICIENCY. The rate at which an enzyme can perform the chemical transformation it is expected to accomplish. This is also called turnover rate.

ENZYME REPLACEMENT THERAPY (ERT). A treatment method used to replace missing enzymes. It is possible to synthesize enzymes and then inject them intravenously into patients.

EPENDYMOMA. A tumor of the central nervous system derived from cells that line the central canal of the spinal cord and the ventricles of the brain.

EPICANTHAL FOLD. A wrinkle in the skin extending from the nose up to the eyebrow; it is sometimes associated with genetic anomalies.

EPIDERMIS. The outermost layer of the skin.

EPIDERMOID CYST. A benign, cystic tumor derived from epithelial cells.

EPIDIDYMIS. A system of ducts emerging posteriorly from the testes that holds sperm during maturation and that forms a tangled mass before uniting into a single coiled duct that is continuous with the vas deferens.

EPIGENETIC. A modification to DNA, such as the addition of a methyl group, that does not change the DNA sequence.

EPIGENETICS. The study of how behaviors and environmental factors can lead to changes in how genes work. The changes are reversible and do not alter the DNA sequence.

EPIGENOME. All of the molecules that are added to DNA molecules to regulate the activity of genes without changing the DNA sequence.

EPI-LASIK. A surgical procedure that uses a blunt, plastic oscillating blade called an epithelial separator to cut a flap in the cornea.

EPILEPSY. Recurrent seizures that temporarily affect awareness, movements, sensations or consciousness; sometimes associated with ASD.

EPIPHYSEAL. The region of the bone responsible for growth of the bone.

EPIPHYSES. The growth areas at the end of bones. (Singular: epiphysis.)

EPISTAXIS. The medical term for nosebleed.

EPITHELIAL CELLS. The layer of cells that cover the open surfaces of the body such as the skin and mucous membranes.

EPITHELIUM. The layer of cells that cover the open surfaces of the body such as the skin and mucous membranes.

EPITOPE. The specific piece of an antigen that an antibody binds to.

EPSTEIN SYNDROME. A subgroup of the *MYH9*-related disorders characterized by the platelet disorder, kidney disease, and hearing loss.

EPSTEIN-BARR VIRUS (EBV). A human herpesvirus (HHV-4) that causes infectious mononucleosis and is associated with certain types of cancer and complications of HIV infection.

EQUAL EMPLOYMENT OPPORTUNITY COMMISSION (EEOC). The U.S. Government agency charged with enforcing Title II of GINA, which covers employment discrimination.

ERYTHEMA NODOSUM LEPROSUM. A complication of leprosy characterized by development of small, painful

swellings due to inflammation of a blood or lymph vessel. It is often accompanied by inflammation of a nerve or nerves, causing decreased function of the affected area.

ERYTHROBLAST. The immediate precursor of a normal red blood cell.

ERYTHROCYTE. The scientific name for a normal mature red blood cell. Erythrocytes do not contain cell nuclei.

ERYTHROPOIESIS. The process through which new red blood cells are created; it begins in the bone marrow.

ERYTHROPOIETIC. Referring to the creation of new red blood cells.

ESCHARS. Painful patches of dead, blackened tissue.

ESOPHAGUS. The part of the digestive tract that connects the mouth and stomach; the food pipe.

ESOTROPIA. A form of strabismus in which one or both eyes turns inward.

ESTROGEN. A female sex hormone.

ETHICS. The branch of philosophy dealing with questions of good and evil, and with moral duties and obligations in human society.

ETIOLOGY. The cause of a disease, syndrome, or anomaly.

EUGENICS. A set of beliefs and practices intended to improve the genetic quality of a country's human population, either by limiting the reproduction of people considered unfit or by encouraging the reproduction of healthier, more intelligent, and more attractive people.

EUSTACHIAN TUBE. Small tube that connects the middle ear to the throat.

EUTHYROID. Having normal thyroid gland function.

EVOKED RESPONSE TESTS. Tests that measure the speed of brain connections.

EXCISION. Surgical removal.

EXOCRINE PANCREAS. The secreting part of the pancreas.

EXOME. The protein-encoding DNA sequences (exons) of the genome.

EXOMPHALOS. An umbilical protrusion or hernia.

EXON. The expressed portion of a gene. The exons of genes are those portions that actually chemically code for the protein or polypeptide that the gene is responsible for producing.

EXOPHTHALMOS. The bulging of the eye forward from the orbit. It is a symptom of abnormally high levels of thyroid hormone.

EXOSOMES. Very small (between 30 and 150 nanometers in diameter) vesicles secreted by various types of cells that contain proteins, nucleic acids, or other biomolecules. Exosomes are of particular interest in liquid biopsy, because they can be found in blood, urine, and cerebrospinal fluid and thus may serve as biomarkers.

EXOSTOSIS. An abnormal growth (benign tumor) on a bone.

EXOTROPIA. A form of strabismus where the eyes are deviated outward.

EXPANSION. A genetic abnormality caused by a sequence of nucleotides that is repeated too many times in a section of a gene.

EXPRESSION QUANTITATIVE TRAIT LOCI (EQTL). Locations within the genomic loci that contribute to expression of mRNAs.

EXTERNAL MEATUS. The external opening through which urine and seminal fluid (in males only) leave the body.

EXTRA-INTESTINAL. Outside of the intestine.

EXTRAOCULAR MUSCLE FIBROSIS. Abnormalities in the muscles that control eye movement.

EXTRAPYRAMIDAL SYMPTOMS (EPS). A group of side effects associated with antipsychotic medications, including parkinsonism, akathisia, dystonia, and tardive dyskinesia.

EXTRAPYRAMIDAL. Refers to brain structures located outside the pyramidal tracts of the central nervous system.

EXUDATE. Fluid that accumulates and penetrates the walls of vessels, leaking into the surrounding tissue.

EX VIVO. The gene therapy is done on cells that are outside of the body.

F

FACIAL ANGIOFIBROMAS. Benign (noncancerous) tumors of the face.

FA CORE COMPLEX. A group of eight proteins encoded by FA genes that function as part of the FA pathway in DNA repair. The FA core complex has been described as a cellular "machine" for DNA repair.

FACTOR VIII. A protein involved in blood clotting that requires VWF for stability and long-term survival in the bloodstream.

FACTORS. Coagulation factors are substances in the blood, such as proteins and minerals, that are necessary for clotting. Each clotting substance is designated with roman numerals I through XIII.

FAILURE TO THRIVE. Significantly reduced or delayed physical growth.

FALLOPIAN TUBE. Either of a pair of tubes that conduct ova from the ovaries to the uterus.

FALSE NEGATIVE. A test result that indicates that a disease or condition is not present when it really is; sometimes called a type II error.

FALSE POSITIVE. A test result that indicates that a person has a disease or condition when they do not; it is sometimes called a type I error.

FAMILIAL. An inherited disease affecting multiple family members.

FAMILIAL ADENOMATOUS POLYPOSIS (FAP). An inherited syndrome causing large numbers of polyps and increased risk of colon cancer and other cancers.

FAMILIAL GASTRIC CANCER. Gastric cancer that occurs at a higher rate in some families.

FAMILIAL IDIOPATHIC BASAL GANGLIA CALCIFICATION (FIBGC). Fahr disease or primary familial brain calcification (PFBC).

FANCONI SYNDROME. A disorder of reabsorption in the kidney tubules.

FA PATHWAY. The biological process that is activated when DNA replication is shut down by interstrand cross-links and other types of DNA damage.

FASTING BLOOD GLUCOSE TEST (FGT). A diabetes test that measures blood glucose after an eight-hour fast.

FATTY ACIDS. The primary component of fats (lipids) in the body. Carnitine palmitoyl transferase (CPT) deficiency involves abnormal metabolism of the long-chain variety of fatty acids.

FBN2. The gene that encodes fibrillin-2; mutations in this gene can cause congenital contractural arachnodactyly.

FECAL OCCULT BLOOD TEST. Study of stool (feces) to identify loss of blood in the gastrointestinal system.

FECHTNER SYNDROME. A subgroup of the *MYH9*-related disorders characterized by the platelet disorder

and inclusion bodies in the white blood cells, kidney disease, hearing loss, and cloudiness of the eye.

FERRITIN. An intracellular protein that stores iron and releases it in a controlled manner. Ferritin in blood plasma is an indirect marker of the total amount of iron stored in the body.

FERTILE. Able to reproduce.

FERTILITY FRAUD. A recently coined term for physicians' use of their own sperm in assisted reproductive techniques.

FERTILITY TOURISM. The practice of traveling to another jurisdiction or country for fertility treatments unavailable or illegal in one's own country.

FETAL AKINESIA. A condition in which lack of fetal movement (akinesia) during pregnancy results in musculoskeletal abnormalities, underdevelopment of the lungs, and/or misshapen facial features. Fetal akinesia can result from a variety of conditions, ranging from abnormalities in the structure of the mother's uterus to infections or genetic disorders that affect fetal development.

FETAL ALCOHOL SYNDROME. Syndrome characterized by distinct facial features and varying mental retardation in an infant due to impaired brain development resulting from the mother's consumption of alcohol during pregnancy.

FETAL ECHOCARDIOGRAM. A detailed ultrasound of the fetal heart usually performed between 18 and 24 weeks of gestation.

FETAL FRACTION. The proportion of cell-free DNA in a pregnant woman's blood that comes from the placenta. The fetal fraction should be above 4% for the most accurate results.

FETAL HYDROPS. A condition in which there is too much fluid in the fetal tissues, fetal cavities, or both.

FETOSCOPE. A tubular instrument that can be inserted into the abdomen and uterus and used to visualize a fetus during pregnancy.

FETUS. The term used to describe a developing human from approximately the third month of pregnancy until delivery. The term "embryo" is used prior to the third month.

FETUS IN FETU. A fetus growing inside the body of the other twin.

FGFR2 AND FGFR3. The genes encoding fibroblast growth factor receptors 2 and 3; mutations in these genes can cause Crouzon syndrome.

FGFR-RELATED CRANIOSYNOSTOSIS. A group of eight disorders including Pfeiffer syndrome, Apert syndrome, Crouzon syndrome, Beare-Stevenson syndrome, *FGFR2*-related isolated coronal synostosis, Jackson-Weiss syndrome, Crouzon syndrome with acanthosis nigricans (AN), and Muenke syndrome (isolated coronal synostosis) all caused by a mutation of an *FGFR* gene.

FIBRILLATION. A rapid, irregular heartbeat.

FIBRILLIN. A glycoprotein secreted by fibroblasts into the extracellular matrix necessary for the deposition of elastin and the proper function of elastic fibers found in connective tissues.

FIBRILLIN-2. A protein that helps form microfibrils that provide strength and flexibility to connective tissue.

FIBRIN. The final substance created through the clotting cascade, which provides a strong, reliable plug to prevent further bleeding from the initial injury.

FIBRINOGEN. A fibrous protein that circulates in blood and participates in blood clotting by attaching to platelets.

FIBROBLAST. A cell that forms connective tissue fibers such as skin.

FIBROBLAST GROWTH FACTOR RECEPTOR GENE. A type of gene that codes for a cell membrane receptor involved in normal bone growth and development.

FIBROBLAST GROWTH FACTORS (FGFs). A family of proteins that signal through growth factor receptors to regulate cell division, cell proliferation, and wound healing in humans and many other species.

FIBROFOLLICULOMA. Small, white or yellow, dome-shaped benign growths on hair follicles.

FIBROID. A noncancerous tumor of connective tissue made of elongated, threadlike structures, or fibers, which usually grow slowly and are contained within an irregular shape. Fibroids are firm in consistency but may become painful if they start to break down or apply pressure to areas within the body. They frequently occur in the uterus and are generally left alone unless growing rapidly or causing other problems. Surgery is needed in order to remove fibroids.

FIBROMA. A nonmalignant tumor of connective tissue.

FIBROMATOSIS. The medical term for a group of conditions marked by benign soft-tissue tumors that are aggressive, infiltrate other tissues, and frequently recur even though they are not cancerous. HDD is sometimes categorized as a type of fibromatosis.

FIBROSIS. The abnormal development of fibrous tissue; scarring.

FINASTERIDE. An oral medication used to treat male pattern hair loss. Finasteride, sold under the trade names Proscar and Propecia, is an androgen inhibitor.

FINE NEEDLE ASPIRATION (FNA). Insertion of a thin needle through the skin to an area of sample tissue.

FIRST-DEGREE RELATIVE. A parent, child, or sibling is a first-degree relative. First-degree relatives have one half of their genes in common.

FIRST-RANK SYMPTOMS. A set of symptoms designated by Kurt Schneider in 1959 as the most important diagnostic indicators of schizophrenia: delusions, hallucinations, thought insertion or removal, and thought broadcasting.

FISTULA. An abnormal connection between two hollow body organs or spaces.

FITZPATRICK PHOTOTYPE SCALE. A set of six skin types based on the skin's response to the ultraviolet radiation in sunlight. The scale was devised in 1975 by Thomas Fitzpatrick, a dermatologist at Harvard University. Fitzpatrick types I and II are at the greatest risk of melanoma.

FLEXION CREASES. The lines on the palms of the hands and the soles of the feet from normal bending of these body parts. Some individuals affected with arthropoysis lack these characteristic lines.

FLOW CYTOMETRY. A method of analyzing cells in which cell properties are detected as they flow in a narrow stream through a measuring device.

FLUORESCEIN ANGIOGRAPHY. Procedure to look at the blood vessel system of the eye. Fluorescein, a dye, is injected and photographs are taken as the dye passes through the eye's blood vessels.

FLUORESCENCE IN SITU HYBRIDIZATION (FISH). A laboratory technique for detecting and identifying a specific sequence of DNA on a chromosome. The researcher designs a probe, which is a small DNA sequence that contains a fluorescent molecule. The probe then binds to its corresponding sequence on the chromosome.

FLUOROCHROME. A fluorescent compound used for visualization in FISH.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS). Formation of scar tissue in the filtering unit of the kidney. "Focal" means that only some of the glomeruli are affected; "segmental" means that only a segment or section of an affected glomerulus is damaged.

FOCAL SEIZURE. A seizure that causes a brief and temporary change in movement, sensation, or nerve function.

FOLATE-SENSITIVE FRAGILE SITE. A chromosome location that, under folate-deficient conditions, appears as a gap in a chromosome and is susceptible to breakage.

FOLLICLE. A pouch-like depression.

FOLLICLE-STIMULATING HORMONE (FSH). A hormone that stimulates estrogen production in females and sperm production in males.

FONTANELLE. One of several “soft spots” on the skull where the developing bones of the skull have yet to fuse.

FOOT DROP. A gait abnormality in which the affected person cannot raise the toes and front of the foot, or raise the foot at the ankle. Foot drop is an indication of a disease of the muscles or nerves; it is not a disease in itself.

FORAMEN. A small opening or hole in a body part or tissue.

FORAMEN MAGNUM. The round opening at the base of the skull through which the spinal cord passes to join the spine.

FOREBRAIN. The anterior of the front section of the brain.

FOREHEAD PLAQUE. Flat, fibrous skin growth on the forehead.

FORENSIC. Pertaining to the use of science or medicine in the investigation and establishment of evidence in a court of law.

FOUNDER EFFECT. Increased frequency of a gene mutation in a population that was founded by a small ancestral group of people, at least one of whom was a carrier of the gene mutation.

FRAGILE X SYNDROME. A genetic condition caused by a mutation in the *FMRI* gene on the X chromosome and characterized by intellectual disability.

FRAGILE X TREMOR/ATAXIA SYNDROME (FXTAS). A movement disorder caused by 55–200 CGG repeats in the *FMRI* gene.

FRONTAL BOSSING. The medical term for an unusually prominent forehead, typically accompanied by a heavy brow ridge.

FRONTAL LOBE. Region of the brain located in the frontal and upper cortex, it is responsible for higher mental functions like critical thinking and decision making.

FRONTAL PLAGIOCEPHALY. An abnormal condition of the skull in which the front is more developed on one side than it is on the other side.

FRONTONASAL DYSPLASIA (FND). A congenital malformation of the face characterized by wide, flat nose; abnormally widely spaced eyes; and a cleft that runs down the middle of the face across the nose.

FRONTOTEMPORAL DISORDERS (FTD). Various types of dementia that affect the frontal and temporal lobes of the brain; FTDP-17 is a rare inherited FTD.

FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI). A form of imaging of the brain that registers blood flow to functioning areas of the brain.

FUNDUS. The interior back wall of the eyeball.

G

G-6-P DEFICIENCY. An X-linked genetic disorder that predisposes patients to the spontaneous destruction of red blood cells in response to certain triggers that include certain foods, medications, and illnesses. It is caused by a mutation on the X chromosome at Xq28.

GABAERGIC SYSTEM. The system by which gamma-aminobutyric acid (GABA), the main neuro-inhibitory transmitter and its receptor, function within the brain during pre- and post-synaptic events to modulate ion channels.

GAIN-OF-FUNCTION MUTATION. A mutation that results in enhanced or new activity on a protein. Loss-of-function mutations are more common.

GAIT. A person’s habitual pattern of walking, or the pattern of movement of his or her lower limbs.

GAIT DISTURBANCES. Disturbances that affect the manner of walking.

GALACTOSE. One of the two simple sugars, together with glucose, that makes up the protein lactose, found in milk. Galactose can be toxic in high levels.

GALACTOSEMIA. A rare genetic disorder in which the person cannot metabolize galactose, a simple sugar found in dairy products.

GALLBLADDER. A small, pear-shaped organ in the upper right hand corner of the abdomen. It is connected by a series of ducts (tube-like channels) to the liver, pancreas, and duodenum (first part of the small intestine). The gallbladder receives bile from the liver and concentrates and stores it. After a meal, bile is squeezed

out of the gallbladder into the intestine, where it aids in digestion of food.

GAMETE. Reproductive cells of an organism that fuse together during fertilization.

GAMMA AMINO BUTYRIC ACID (GABA). An amino acid that functions as the major inhibitory neurotransmitter in the nervous system.

GAMMA KNIFE. Equipment that precisely delivers a concentrated dose of radiation to a predetermined target using gamma rays.

GANGLIOSIDE. A complex membrane lipid made up of a long-chain fatty acid, a long-chain amino alcohol, and an oligosaccharide containing sialic acid.

GANGRENE. Death of tissue due to deficient or absent blood supply.

GARDNER SYNDROME. A term that is sometimes used for patients with familial adenomatous polyposis (FAP) who have desmoid tumors in the tissues covering the colon in addition to polyps inside the colon.

GASTRIC. Associated with the stomach.

GASTRIC TUBE. A tube that is surgically placed through the skin of the abdomen to the stomach so that feeding with nutritional liquid mixtures can be accomplished.

GASTROENTEROLOGIST. A physician who specializes in disorders of the digestive system.

GASTROESOPHAGEAL REFLUX. The return of the contents of the stomach back up into the esophagus.

GASTROINTESTINAL. Concerning the stomach and intestine.

GASTROINTESTINAL (GI) SYSTEM. The body system involved in digestion, the breaking down and use of food.

GASTROINTESTINAL REFLUX DISEASE (GERD). A chronic condition, usually accompanied by heartburn, that can damage the esophagus.

GASTROINTESTINAL TRACT. The food intake and waste export system that runs from the mouth, through the esophagus, stomach, and intestines, to the rectum and anus.

GASTROSCHISIS. A small defect in the abdominal wall normally located to the right of the umbilicus, and not covered by a membrane, where intestines and other organs may protrude.

GASTROSTOMY. The construction of an artificial opening from the stomach through the abdominal wall to permit the intake of food.

GAUCHER DISEASE. A genetic disorder characterized by the accumulation of fatty substances in certain cells and organs. It is caused by a mutation in a gene on chromosome 1 and is inherited in an autosomal recessive pattern. It is named for the French physician Philippe Gaucher, who first described it in 1882.

GAVAGE. Feeding tube.

GENE. A building block of inheritance that contains the instructions for the production of a particular protein and is made up of a molecular sequence found on a section of DNA. Each gene is found at a precise location on a chromosome.

GENE AMPLIFICATION. The creation of multiple copies of a gene, which can result in the production of excessive amounts of a specific protein.

GENE EDITING. is a process that involves changing an organism's DNA by removing, adding, or changing it.

GENE EXPRESSION. The process in which a gene is transcribed into mRNA, and then translated into a protein. Multiple methods of regulation are used by cells to tightly control the levels of gene expression.

GENE EXPRESSION PANEL. A method for genetically characterizing specific types of cancer.

GENE MUTATION. A permanent change in genetic material that is transmittable.

GENE SEQUENCING. The process of mapping the order of DNA or genetic material in an organism.

GENE THERAPY. Replacing a defective gene with a normal copy.

GENEALOGY. The study or investigation of a person's lineage or family tree.

GENERATION TIME. The average length of time elapsed between two consecutive generations in an animal population. The generation time for zebrafish is about three months.

GENETIC ANTICIPATION. The tendency for an inherited disease to become more severe in successive generations.

GENETIC BIOMARKER. A variant in DNA, RNA, or protein that can be measured and is an indicator of disease. These biomarkers can be used to assess the expression, function, or regulation of a gene.

GENETIC CODE. A set of instructions for transferring genetic data stored in the form of DNA or RNA into proteins.

GENETIC COUNSELING. A short-term educational counseling process for individuals and families who have a genetic disease or who are at risk for such a disease. Genetic counseling provides patients with information about their condition and helps them make informed decisions.

GENETIC COUNSELOR. A health professional with advanced training in genetics and psychology who educates people about genetic conditions and testing.

GENETIC DISCRIMINATION. Discrimination against people in employment or health insurance on the basis of their genetic information, including genetic testing results or a family medical history that suggests genetic predisposition to a disease.

GENETIC DISEASE. A disease that is (partly or completely) the result of the abnormal function or expression of a gene; a disease caused by the inheritance and expression of a genetic mutation.

GENETIC DRIFT. Variations in gene frequency within a population due to chance rather than mutation or natural selection.

GENETIC HETEROGENEITY. The production of apparently identical genetic disorders by different genetic mechanisms or by different genes at different positions on the chromosomes.

GENETIC LOCUS. The specific location of a gene on a chromosome.

GENETIC MARKER. A DNA or RNA sequence variant. In plant breeding, markers can be linked to particular plant characteristic (traits).

GENETIC MOSAICISM. A mixture of cells of two or more genotypes.

GENETIC SEX. The gender determined by the sex chromosomes. XX is female; XY is male.

GENETIC TEST. Testing of chromosomes and genes from an individual or unborn baby for a genetic condition. Genetic testing can only be done if the gene is known.

GENETIC TESTING. Testing of chromosomes and genes from an individual or unborn baby for a genetic condition. Genetic testing can only be done if the gene is known.

GENETICIST. A specialist (MD or PhD) who has training and certification in diagnosing, managing, and counseling individuals/families with genetic disorders. Genetic counselors hold a master's degree in medical genetics and provide many of the same services as geneticists.

GENITAL HYPOPLASIA. Underdeveloped genitals.

GENITAL TRACT. The organs involved in reproduction. In a male, they include the penis, testicles, prostate, and various tubular structures to transport seminal fluid and sperm. In a female, they include the clitoris, vagina, cervix, uterus, fallopian tubes, and ovaries.

GENITALIA. The organs of reproduction.

GENITOURINARY. Related to the reproductive and urinary systems of the body.

GENOME. The total amount of genetic information within an organism's chromosomes, including its genes and DNA sequences.

GENOME EDITING. A technique used by researchers to change the sequence of genetic material, for example, the DNA, of an organism. It can be used to fix a pathogenic mutation that can cause disease.

GENOME-WIDE ASSOCIATION STUDY (GWAS). A method for identifying genes involved in human disease by searching a number of human genomes for small variations that occur more commonly in people with a given disease than in those who do not have the disease.

GENOMIC SELECTION. A method in plant breeding that predicts the value of breeding stock based on genetic information.

GENOMICS. The study of the structure, function, and evolution of genomes and how they interact with each other and the environment.

GENOTYPE. The complete set of an organism's genetic material. The term is sometimes used to refer to the genes or set of genes for a single trait, such as height or eye color.

GERM CELLS. The cells that create the egg and sperm cells (gametes).

GERM LINE. The population of a complex organism's cells that pass on genetic information to offspring. Germline cells include eggs, sperm, and fertilized eggs.

GERM-LINE MOSAICISM. A rare event that occurs when one parent carries an altered gene mutation that affects his or her germ-line cells (either the egg or sperm cells) but is not found in the somatic (body) cells.

GERM-LINE MUTATION. A heritable change in the DNA of a germ cell (a cell destined to become an egg or in the sperm). When passed from one generation to the next, a germ-line mutation is incorporated in every cell of the body.

GERM-LINE RETINOBLASTOMA. A type of retinoblastoma where all cells of the body have a variant in one

copy of the *RBI* gene. This can be inherited or result early in the development of the embryo.

GESTATIONAL AGE. An estimation of the age of a pregnancy. The beginning of gestation or pregnancy is counted from the first day of the woman's last menstrual period, although conception usually takes place about two weeks later.

GESTATIONAL DIABETES MELLITUS (GDM). Diabetes that develops during pregnancy and increases the risk of type 2 diabetes.

GIEMSA STAIN. A nucleic acid stain used to band chromosomes and to make a karyogram or map of chromosomes. The stain is named for Gustav Giemsa (1867–1948), the German pharmacist and bacteriologist who devised the stain in 1904.

GINGIVAL. Pertaining to the gums. Gingival fibromatosis refers to an overgrowth of the tissue of the gums.

GINGIVAL FIBROMAS. Fibrous growths found on the gums.

GINGIVITIS. Inflammation of the gums of the mouth, characterized by redness, swelling, and a tendency to bleed.

GLAUCOMA. A group of eye disorders resulting in damage to the optic nerve, in most cases as the result of increased intraocular pressure (fluid pressure within the eye). Untreated glaucoma can result in permanent loss of vision.

GLIAL CELLS. Supportive cells for nerve cells in the brain and spinal cord.

GLIOBLASTOMA MULTIFORME. A tumor of the central nervous system consisting of undifferentiated glial cells.

GLIOMA. A tumor of the brain's glial cells.

GLOBIN. One of the component protein molecules found in hemoglobin. Normal adult hemoglobin has a pair each of alpha-globin and beta-globin molecules.

GLOBOZOOSPERMIA. A genetic condition in which sperm have round heads and lack acrosomes, among other defects, resulting in male infertility.

GLOBUS PALLIDUS. A small paired structure present in the deep portion of the brain, in front of the brain stem, that is considered a part of the basal ganglia and helps in movement control.

GLOMERULI. The tiny networks of capillaries in the nephrons (filtering units) of the kidneys that serve to filter the blood during the first stage of urine formation.

GLOSSOPTOSIS. Downward displacement or retraction of the tongue.

GLUCOCEREBROSIDE. A cerebroside that contains glucose in the molecule.

GLUCOCORTICOIDS. Corticosteroids, such as cortisol and dexamethasone, that regulate metabolism, along with other functions; medications used to treat congenital adrenal hyperplasia.

GLUCOSE. One of the two simple sugars, together with galactose, that makes up the protein lactose, found in milk. Glucose is the form of sugar that is usable by the body to generate energy.

GLYCINE. An amino acid (a building block of proteins) that is important in the transmission of nerve impulses.

GLYCOGEN. The chemical substance used by muscles to store sugars and starches for later use. It is composed of repeating units of glucose.

GLYCOGENESIS. The metabolic process responsible for the formation of glycogen from many glucose molecules.

GLYCOGENOLYSIS. The metabolic process responsible for the breakdown of glycogen to mobilize glucose.

GLYCOLYSIS. The pathway in which a cell breaks down glucose into energy.

GLYCOPROTEIN. A protein with at least one carbohydrate group.

GLYCOPROTEIN IIB/IIIA (GP IIB/IIIA). Sugar-proteins on the surface of platelets that bind to the fibrous protein, fibrinogen. These sugar-proteins are defective in Glanzmann's thrombasthenia.

GLYCOSYLPHOSPHATIDYLINOSITOL (GPI). A molecule that attaches proteins to the membranes of cells.

GOITER. A swelling of the neck or larynx caused by enlargement of the thyroid gland.

GOLGI APPARATUS. An organelle within cells that packages proteins for secretion outside the cell. Also called the Golgi body, it is named for the Italian physician Camillo Golgi, who first identified it in 1897.

GOLTZ SYNDROME. Focal dermal hypoplasia (FDH).

GONAD. The sex gland in males (testes) and females (ovaries).

GONADOTROPHIN. Hormones that stimulate the ovary and testicles.

GONADOTROPHIN-RELEASING HORMONE (GNRH).

The hormone produced by the hypothalamus that stimulates the release of gonadotropins such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

GONIOSCOPE.

An instrument used to examine the trabecular meshwork; it consists of a magnifier and a lens equipped with mirrors.

GOWERS' SIGN.

An indication of weakness in the proximal muscles of the legs. The child has to use his hands and arms to rise from a squatting or kneeling position.

GRADE.

As a noun: a classification of the cancerous qualities of an individual tumor. A higher grade indicates a more serious disease than does a lower grade. As a verb: to classify the cancerous qualities of an individual tumor.

GRAFT-VERSUS-HOST DISEASE.

In bone marrow transplantation, the complication that occurs when the donor's cells attack the recipient's tissues, in part due to non-identical donor-recipient HLA types.

GRAND MAL SEIZURE.

A seizure that causes a loss of consciousness, a loss of bladder control, generalized muscle contractions, and tongue biting.

GRANULOCYTOPENIA.

A reduced number of white blood cells in the circulation.

GRANULOMA.

A group of noncancerous, nodular cells that form as a result of inflammation in the tissue.

GRANULOMATOSIS WITH POLYANGITIS.

Permanent enlargement of parts of the airways of the lung.

GRAY MATTER.

Areas of the brain and spinal cord that are made up mostly of unmyelinated nerves.

GREAT TOE.

The first and largest toe on the foot.

GRIEF REACTION.

The normal sadness felt after a traumatic major life occurrence, such as the loss of a loved one.

GROWTH FACTORS.

Cellular-signaling components that stimulate cell division or other cell processes.

GROWTH HORMONE (GH).

A hormone that stimulates growth. Also called somatotropin.

G-TUBE.

A gastrostomy tube, which is inserted surgically into the stomach and used for feeding and for administering medications.

GUIDE RNA (GRNA).

A combined tracer RNA and spacer RNA (pre-crRNA) that, when used in conjunction

with a Cas9 nuclease (crRNA), can target and cut specific DNA sequences.

GUSTATORY LACRIMATION.

Abnormal development of the tear ducts causing tears when chewing.

H**HALF-LIFE.**

The amount of time that it takes for a drug, cell, or other component of blood to drop to half of its initial value.

HALLUCINATION.

A sensory experience of something that does not exist outside the mind.

HALLUX.

The great toe.

HAMARTOMA.

An overgrowth of normal tissue.

HAMARTOMATOUS RECTAL POLYPS.

Benign (non-cancerous) growths found in the rectum.

HAPLOID.

Referring to cells that have only one chromosome of each type, and therefore have only one complete set of genes. Gametes (sperm and eggs) normally have a haploid number of chromosomes.

HAPLOINSUFFICIENCY.

The lack of one of the two normal copies of a gene. Haploinsufficiency can result in a genetic disorder if normal function requires both copies of the gene. Haploinsufficiency is one explanation for a dominant pattern of inheritance.

HAPLOTYPE.

A set of alleles that are inherited together as a unit on a single chromosome because of their close proximity.

HAYFLICK LIMIT.

The number of times (usually around 50) that a normal differentiated human cell will divide before its telomeres shorten to a critical length and cell division stops. The limit is named for Leonard Hayflick, an American professor of anatomy who first described it in 1961.

HB BART'S SYNDROME.

The form of alpha thalassemia most likely to cause hydrops fetalis in the fetus. The name of the syndrome refers to a defective type of hemoglobin (Hb) that has almost no ability to carry oxygen to the fetus's tissues and to the hospital in London (St. Bartholomew's, or Bart's) where the syndrome was first identified.

HEAD TURN.

Habitual head position that has been adopted to compensate for abnormal eye movements.

HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA). A 1996 federal statute that includes a privacy rule regulating the use and disclosure of

protected health information (PHI). DTC genetic testing is not subject to HIPAA privacy regulations.

HEARING LEVEL (HL). Hearing threshold; the sound level that can just barely be heard.

HEART ARRHYTHMIA. An abnormal heart rhythm, in which the heartbeats may be too slow, too rapid, too irregular, or too early.

HELICASE. An enzyme, such as BLM, that unwinds and separates DNA during replication (chromosome copying prior to cell division).

HELICOBACTER PYLORI (H. PYLORI). A bacterium that infects humans and may be associated with an increased risk of gastric cancer.

HELLER'S SYNDROME. Another name for Childhood Disintegrative Disorder (CDD). It is also sometimes called dementia infantilis.

HELPER T-CELL. Specialized white blood cell that assists in humoral and cellular immunity.

HEMANGIOBLASTOMA. A tumor of the brain or spinal cord arising in the blood vessels of the meninges or brain.

HEMANGIOMA. Benign tumor made up of clusters of newly formed blood vessels.

HEMATIN. A drug administered intravenously to halt an acute porphyria attack. It causes heme biosynthesis to decrease, preventing the further accumulation of heme precursors.

HEMATOLOGY. The branch of medicine that deals with the diagnosis and treatment of diseases of the blood and bone marrow.

HEMATOMA. An accumulation of blood, often clotted, in a body tissue or organ, usually caused by a break or tear in a blood vessel.

HEMATOPOIESIS. The process of blood cell formation from stem cells in the medulla of the bone (bone marrow).

HEMATURIA. The presence of blood in the urine.

HEME. The iron-containing molecule in hemoglobin that serves as the site for oxygen binding. Each of the four hemoglobin chains has one heme molecule.

HEMI. One-sided.

HEMIHYPERPLASIA. A condition in which overdevelopment or excessive growth of one-half of a specific organ or body part on only one side of the body occurs.

HEMIPLEGIA. Paralysis of one side of the body.

HEMIVERTEBRA. A defect in which one side or half of a vertebra fails to form.

HEMIZYGOUS. Having only one copy of a gene or chromosome.

HEMOCHROMATOSIS. A condition in which iron accumulates in the body, as a result of either a genetic mutation or frequent blood transfusions. It is also known as iron storage disease.

HEMOCHROMATOSIS. Accumulation of large amounts of iron in the tissues of the body.

HEMOGLOBIN. A protein-iron compound in the blood that carries oxygen to the cells and carries carbon dioxide away from the cells.

HEMOGLOBIN A (HBA). Normal adult hemoglobin; it consists of two alpha globins and two beta globins.

HEMOGLOBIN A1C (HBA1C). A blood test that indicates average blood glucose levels over the previous two or three months.

HEMOGLOBIN E. An abnormal hemoglobin with a single-point mutation in the beta chain. People who inherit the hemoglobin E gene from one parent and the beta thalassemia gene from the other develop hemoglobin E beta thalassemia, which is a severe disease.

HEMOGLOBIN ELECTROPHORESIS. A laboratory test that separates molecules based on their size, shape, or electrical charge.

HEMOGLOBIN F (HbF). Fetal hemoglobin; it consists of two alpha and two gamma globins. HbF is produced by the fetus in utero and until about 48 weeks after birth. At this stage, the production of HbA rapidly increases while that of HbF drops off.

HEMOGLOBIN S. The most common type of abnormal hemoglobin; it is the basis of sickle cell trait and sickle cell anemia.

HEMOLYTIC. Refers to the type of anemia caused by the breakdown of red blood cells, as compared to anemia due to decreased production, for example.

HEMOLYTIC ANEMIA. Anemia that results from premature destruction and decreased numbers of red blood cells.

HEMORRHAGE. Very severe, massive bleeding that is difficult to control. Hemorrhage can occur in people with hemophilia after what would be relatively minor injuries for persons with normal clotting factors.

HEMOSIDERIN. An iron storage complex found only within cells (not in blood plasma) and consisting of ferritin, denatured ferritin, and other materials.

HEMOSTASIS. The arrest of bleeding by blood coagulation.

HEPATECTOMY. The medical term for surgical removal of the liver. A hepatectomy may be either partial or total.

HEPATIC. Pertaining to the liver.

HEPATITIS. A viral disease characterized by inflammation of the liver cells (hepatocytes). People who are infected with hepatitis B or hepatitis C virus are at an increased risk for developing liver cancer.

HEPATOMEGALY. Abnormal enlargement of the liver.

HEPATOSPLENOMEGALY. Abnormal enlargement of the liver and spleen.

HER2. Human epidermal growth factor receptor 2 (EGFR2); also called HER2/neu or erbB-2; a protein overproduced in HER2-positive cancers.

HEREDITARY. The passing of traits from parents to their offspring.

HEREDITARY ANGIONEUROTIC EDEMA. Abbreviated HANE, or HAE, this is an inherited kind of angioneurotic edema. Type I HANE is caused by a deficiency of C1-INH. Type II HANE is caused by a malformation of the C1-INH protein.

HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC). Lynch syndrome; the most common familial cancer syndrome that increases the risk of colorectal cancer; caused by inherited mutations in any of several genes, most of which are involved in DNA repair.

HERMANSKY-PUDLAK SYNDROME (HPS). A rare form of albinism that can include other problems, such as blood clotting, and lung and bowel disorders; there are four types of HPS caused by defects in four different genes.

HERNIA. A rupture in the wall of a body cavity, through which an organ may protrude.

HERNIATION. The abnormal protrusion of an organ or other structure through a defect or natural opening in a membrane, muscle, bone, or other tissue.

HERTZ (HZ). A measurement of sound frequency; 1 Hz equals one cycle per second.

HETEROCHROMIA IRIDES. A medical term for individuals with different-colored eyes.

HETEROGENEOUS. A set of symptoms or a disorder caused by several different gene mutations.

HETEROGENEOUS TRAIT. A trait that is caused by both genetic and nongenetic factors.

HETEROPLASMY. The presence of two or more sources of mitochondrial DNA within a cell, person, or mitochondrion. It is an important factor in determining the likelihood or severity of a mitochondrial disease.

HETEROTAXY. A condition in which the thoracic and abdominal viscera are arranged abnormally across the left-right axis of the body. It is also referred to as heterotaxy syndrome or visceral heterotaxy.

HETEROTOPIA. Small nodules of gray matter that are present outside the cortex.

HETEROZYGOTE. Having two different versions of the same gene.

HETEROZYGOUS. Referring to the genetic condition of having inherited two different forms (alleles) of a particular gene from each of a person's two parents.

HETEROZYGOUS MUTATION. A mutation in which both copies of a gene are mutated.

HIATAL HERNIA. A structural defect in the digestive tract in which the upper part of the stomach protrudes (herniates) through an opening or weak area in the diaphragm into the chest.

HIGH-DENSITY LIPOPROTEIN (HDL). A cholesterol carrying substance that helps remove cholesterol from the cells of the body and deliver it to the liver where it is digested and removed from the body.

HIGHLY AEROBIC TISSUES. Tissue that requires the greatest amount of oxygen to thrive.

HIPPOCAMPUS. A part of the brain that is involved in learning and memory formation.

HIRSCHSPRUNG DISEASE. A deformation in which the colon becomes enlarged (megacolon) due to abnormal nerve control of that portion of the large intestine.

HIRSUTISM. The presence of coarse hair on the face, chest, upper back, or abdomen in a female as a result of excessive androgen production.

HISTAMINE. A substance released by immune system cells in response to the presence of an allergen. Histamine stimulates widening of blood vessels and increased porousness of blood vessel walls so that fluid and protein leak out from the blood to surrounding tissue, causing inflammation.

HISTOCOMPATIBILITY. The degree to which two people's genetically determined human leucocyte antigen (HLA) alleles (tissue types) match. The higher the level of histocompatibility, the greater the likelihood of successful organ transplantation.

HISTOLOGIC. Pertaining to histology, the study of cells and tissues at the microscopic level.

HISTOLOGICAL STUDIES. Laboratory tests performed on tissue samples and cells.

HISTONE ACETYLATION. The addition of an acetyl group, a three-carbon molecule, at one end of a histone molecule. This DNA acetylation alters gene function without changing any DNA base pairings.

HISTONES. Alkaline proteins found in cell nuclei that act as spools for winding strands of DNA, allowing the DNA to be stored compactly within the cell nucleus.

HITCHHIKER THUMBS. A congenital anomaly of the thumb in which it is abnormally positioned at a right angle to the first joint.

HLA TYPE. The unique set of proteins called human leukocyte antigens. These proteins are present on each individual's cells. They allow the immune system to recognize 'self' from 'non-self'. HLA type is particularly important in organ and tissue transplantation.

HLA-B27. Stands for a specific form of human leukocyte antigen, the proteins involved in immune system function. Strongly associated with ankylosing spondylitis.

HOLOPROSENCEPHALY. A malformation of the brain in which the two hemispheres or lobes of the brain do not separate properly.

HOLT-ORAM SYNDROME. An inherited disorder characterized by congenital heart defects and abnormalities of the arms and hands; may be associated with Duane retraction syndrome.

HOMEOSTASIS. A state of physiological balance.

HOMEOTIC GENES. Developmental control genes active in the embryo.

HOMOCYSTEINE. An amino acid that is not used to produce proteins in the human body.

HOMOGENTISATE 1,2-DIOXYGENASE (HGD). Homogentisic acid oxidase, the fourth enzyme in the metabolic pathway for the breakdown of phenylalanine.

HOMOGENTISIC ACID (HGA). 2,5-Dihydroxyphenylacetic acid, the third intermediate in the metabolic pathway for the breakdown of phenylalanine.

HOMOLOGOUS. Similar in relation, position, value, or structure.

HOMOLOGOUS CHROMOSOMES. The two members of a chromosome pair, one inherited from each parent.

HOMOPLASMY. When all copies of mitochondrial DNA are the same, or have the same mutation.

HOMOZYGOUS. Having two identical copies of a gene or chromosome.

HORMONE. A chemical messenger produced by the body that regulates specific bodily functions such as growth, development, and reproduction.

HORMONE THERAPY. Treatment of cancer by changing the hormonal environment, such as testosterone and estrogen.

HOST. The body that a virus has infected.

HRAS. The gene encoding the H-Ras protein that helps regulate cell growth and division; mutations in *HRAS* can cause Costello syndrome.

HUMAN CHORIONIC GONADOTROPIN (HCG). A protein produced in early pregnancy; fetal chromosomal abnormalities can significantly increase hCG levels in maternal blood.

HUMAN GENOME PROJECT (HGP). An international collaboration begun in 1990 and completed in 2003 that sequenced the entire DNA sequence of the human genome.

HUMAN LEUKOCYTE ANTIGENS (HLAS). Proteins that form the major histocompatibility complex (MHC); some common HLA alleles are associated with the development of type 1 diabetes.

HUMORAL IMMUNITY. A type of acquired immunity mediated by B-cells and their secreted antibodies; important in fighting bacterial and some viral infections.

HUNTINGTON'S DISEASE. A hereditary disease that typically appears in midlife, marked by gradual loss of brain function and voluntary movement; some symptoms resemble those of schizophrenia. Also called Huntington's chorea.

HYALINE. A clear substance that occurs in cell deterioration.

HYDRANENCEPHALY. Congenital enlargement of the head and brain.

HYDROCEPHALUS. The excess accumulation of cerebrospinal fluid around the brain that often causes enlargement of the head.

HYDROLASE. An enzyme that uses water to break down substances.

HYDROLYSIS. The breakdown of chemical bonds by the addition of water.

HYDROMETROCOLPOS. An abnormal accumulation of fluids in the uterus and vagina.

HYDRONEPHROSIS. Obstruction of the tube that carries urine from the kidney into the bladder causing the pelvis and kidney duct to become swollen with excess urine.

HYDROPS FETALIS. A condition in which excess fluid builds up in a fetus's body prior to birth.

HYDROXYAPATITE. A complex phosphate of calcium $\text{Ca}_5(\text{PO}_4)_3\text{OH}$ that occurs as a mineral and is the chief structural element of vertebrate bone.

HYDROXYUREA. A drug that has been shown to induce production of fetal hemoglobin. Fetal hemoglobin has a pair of gamma-globin molecules in place of the typical beta-globins of adult hemoglobin. Higher-than-normal levels of fetal hemoglobin can prevent sickling from occurring.

HYGROMA. A condition in which fluid builds up in a sac or cyst.

HYPERAMMONEMIA. An excess of ammonia in the blood.

HYPERAROUSAL. Symptoms of traumatic stress characterized by abnormally intense reactions, such as a heightened startle response.

HYPERCALCEMIA. High levels of calcium in the blood.

HYPERCALCIURIA. Abnormally high levels of calcium in the urine.

HYPEREXCITABILITY. The abnormally intense response of muscle fiber membranes to stimulation.

HYPEREXTENSIBILITY. The ability to extend a joint beyond the normal range.

HYPEREXTENSION. The movement or extension of joints, bones, or muscles beyond the normal range of motion.

HYPERGLYCEMIA. High blood sugar.

HYPERHIDROSIS. Excessive perspiration that may be either general or localized to a specific area.

HYPERHOMOCYSTEINEMIA. Increased levels of homocysteine in the blood.

HYPERKERATOSIS. Abnormal thickening of the outermost layer of the skin, the stratum corneum.

HYPERLIPOPROTEINEMIA. An increase in the amount of lipoproteins in the body.

HYPERLORDOSIS. An exaggerated curve in the lower (lumbar) portion of the back.

HYPERMOBILITY. Unusual flexibility of the joints, allowing them to be bent or moved beyond their normal range of motion.

HYPEROSTOSIS. Overgrowth of the bone.

HYPERPHAGIA. Overeating.

HYPERPIGMENTATION. An abnormal condition characterized by an excess of melanin in localized areas of the skin, which produces areas that are much darker than the surrounding unaffected skin.

HYPERPLASIA. An overgrowth of normal cells within an organ or tissue.

HYPERREFLEXIA. Having overactive or overresponsive reflexes.

HYPERSENSITIVE. Referring to a process or reaction that occurs at above-normal levels; over-reacting to a stimulus.

HYPERSENSITIVITY. A process or reaction that occurs at above normal levels; overreaction to a stimulus.

HYPERTELORISM. A birth defect in which the child's eyes are spaced abnormally far apart.

HYPERTENSION. High blood pressure.

HYPERTHERMIA. Body temperature that is much higher than normal (above 98.6°F, 37°C).

HYPERTONIA. Excessive muscle tone or tension, causing resistance of muscle to being stretched.

HYPERTRICHOSIS. Excessive hair growth; also called hirsutism.

HYPERTROPHY. Increase in the size of a tissue or organ brought on by the enlargement of its cells rather than cell multiplication.

HYPNAGOGIC HALLUCINATIONS. Dream-like auditory or visual hallucinations that occur while falling asleep.

HYPOALBUMINEMIA. An abnormally low level of albumin in the blood.

HYPOCHONDROGENESIS. A condition similar to Langer-Saldino achondrogenesis caused by different mutations in the *COL2A1* gene.

HYPOCHONDROPLASIA. An autosomal dominant form of dwarfism where physical features are similar but milder than those of achondroplasia. Affected individuals have mild short stature and a normal facial appearance.

HYPOCRETIN. A neuro-hormone involved in the regulation of sleep, wakefulness, and eating behaviors, also known as orexin.

HYPOGENITALISM. Incomplete or hindered development of the external reproductive organs.

HYPOGLYCEMIA. An abnormally low glucose (blood sugar) concentration in the blood.

HYPOGONADISM. Small testes in men and scarce or irregular menstruation for females.

HYPOGONADOTROPIC HYPOGONADISM (HH). Underdevelopment of the gonads due to a deficiency of gonadotropin-releasing hormone.

HYPOHIDROSIS. Insufficient perspiration or absent perspiration that may be either general or localized to a specific area.

HYPOKETOSIS. Decreased levels of ketone bodies.

HYPOMELANOTIC MACULES. Patches of skin lighter than the surrounding skin.

HYPOMYELINATION. The death of myelin on a nerve or nerves.

HYPOPHOSPHATEMIA. A decrease in the blood circulation of phosphate.

HYPOPIGMENTATION. Decreased or absent color (pigment) in a tissue.

HYPOPLASIA. Incomplete or underdeveloped tissue or organ.

HYPOPLASTIC RADIUS. Underdevelopment of the radius, the outer, shorter bone of the forearm.

HYOSPADIAS. A birth defect in which the opening to the urinary tract, called the urethra, is located away from the tip of the penis.

HYPOTHALAMUS. A part of the forebrain that controls heartbeat, body temperature, thirst, hunger, body temperature and pressure, blood sugar levels, and other functions.

HYPOTHYROID. Deficiency in thyroid gland activity or thyroid hormone levels.

HYPOTHYROIDISM. A condition in which the patient's thyroid gland does not produce enough thyroid hormone.

HYPOTONIA. A state of low muscle tone that often involves loss of muscle strength as well. Infants with hypotonia are often described as having "floppy baby syndrome"; they may have difficulty lifting their heads and usually have problems with feeding.

IATROGENIC. Referring to a symptom or disorder caused inadvertently by a medical intervention or diagnostic procedure.

ICHTHYOSIS. A skin condition characterized by a fish-scale appearance.

IDIOPATHIC. Referring to a disease of unknown origin or arising spontaneously.

IGE. An antibody composed of protein; specific forms of IgE produced by cells of the immune system in response to different antigens that contact the body; a major factor that stimulates the allergic response.

ILIAC ARTERIES. Arteries that supply blood to the lower body including the pelvis and legs.

IMMUNE RESPONSE. Defense mechanism of the body provided by its immune system in response to the presence of an antigen, such as the production of antibodies.

IMMUNE SYSTEM. The complex group of organs and cells that defends the body against infection and disease.

IMMUNODEFICIENCY. A defect in the immune system, leaving an individual vulnerable to infection.

IMMUNOGLOBULIN. A protein molecule formed by mature B cells in response to foreign proteins in the body; the building blocks for antibodies.

IMMUNOLOGIC. Related to immunology, the study of how the body's immune system fights disease. Many immunologic disorders are characterized by the body's use of antibodies.

IMMUNOTHERAPY. A form of treatment that uses biologic agents to enhance or stimulate normal immune function.

IMPERFORATE ANUS. Also known as anal atresia. A birth defect in which the opening of the anus is absent or obstructed.

IMPOTENCE. The inability to have a penile erection, which can be due to tissue damage resulting from sickling within the penis (priapism).

IMPRINTING. A process that silences a gene or group of genes. The genes are silenced depending on whether they are inherited through the egg or the sperm.

INBORN ERROR OF METABOLISM. Any of a number of rare genetic disorders that inhibit the body's ability to turn food into energy.

INCLUSION BODY. An abnormal storage compartment inside a cell.

INCOMPLETE PENETRANCE. Absence of disease in an individual known to carry the gene for that disease.

INDIRECT COOMBS TEST. A test given to pregnant women to detect the presence of circulating antibodies against red blood cells.

INDUCED PLURIPOTENT STEM CELLS. Adult stem cells whose genes have been changed so that they act like embryonic stem cells. They can make copies of themselves indefinitely and can develop into many types of cell.

INDUCTION. Process where one tissue (the prechordal plate, for example) changes another tissue (for example, changes tissue into neural tissue).

INFANTILE SPASMS. The form of grand mal or focal seizures experienced by infants prior to the development of many voluntary muscular controls.

INFECTIVE ENDOCARDITIS. An infection of the tissue lining the walls of the heart.

INFERIOR OLIVARY NUCLEUS. A small collection of cells seen in the lower part of the brain stem, which has connections to the cerebellum and is involved in control of movements.

INFERTILE. Incapable of reproduction.

INFLAMMATION. An immune-system response, usually resulting from irritation, infection, or injury and causing redness, swelling, and pain.

INFORMED CONSENT. The process in which health-care professionals explain the purpose, risks, benefits, and alternatives of a proposed test or treatment to a patient, and make sure that the patient understands the explanation.

INGUINAL HERNIA. A condition in which part of the intestines protrudes through a tear in the muscles of the abdomen.

INHERITED GIANT PLATELET DISORDER (IGPD). A group of hereditary conditions that cause abnormal blood clotting and other conditions.

INNATE IMMUNE SYSTEM. A population of cells and mechanisms that defends the body against invasive

organisms. This protection is generic and not long lasting. The innate immune system is sometimes considered to be the first responder against infection.

INSEMINATION. The process by which sperm is placed into the female reproductive tract for the purpose of impregnation.

INSERTION. A mutation in which part of a chromosome is deleted from its normal location and implanted into another chromosome.

INSOMNIA. An inability to either fall or stay asleep, particularly at a time of day when sleep is expected. A number of medications are available, and may be used, for treatment.

INSULIN. A hormone encoded by the *INS* gene that is required for the metabolism of carbohydrates, fats, and proteins and that regulates blood sugar levels; lack of insulin or insulin insensitivity results in high blood sugar levels and diabetes.

INSULIN-LIKE GROWTH FACTOR I. A hormone released by the liver in response to high levels of growth hormone in the blood. This growth factor is very similar to insulin in chemical composition, and like insulin, it is able to bring about cell growth by causing cells to undergo mitosis (cell division).

INSULIN RECEPTOR GENE. The gene responsible for the production of insulin receptor sites on cell surfaces. Without properly functioning insulin receptor sites, cells cannot attach insulin from the blood for cellular use.

INSULIN RESISTANCE. An inability to respond normally to insulin in the bloodstream.

INTEGRATED SCREENING. Blood tests and ultrasound in the first trimester, followed by blood tests for three or four proteins in the second trimester, to screen for chromosomal abnormalities and neural tube defects.

INTELLECTUAL DISABILITY. Significant impairment in intellectual function and adaptation in society. Usually associated with an intelligence quotient (IQ) below 70.

INTERFERON. Any of a group of cells signaling proteins that are made and released by cells in response to the presence of viruses, bacteria, and other disease organisms. The name is derived from the way in which these proteins interfere with the replication of viruses by protecting cells from virus infections.

INTERPERSONAL THERAPIES. This type of psychological counseling focuses on determining how dysfunctional interpersonal relationships of the affected individual may be causing or influencing symptoms of depression.

INTERSTITIAL DELETION. The deletion of a piece of one chromosome.

INTRACRANIAL HEMORRHAGE. Abnormal bleeding within the space of the skull and brain.

INTRACRANIAL PRESSURE. The pressure of the fluid between the brain and skull.

INTRACYTOPLASMIC SPERM INJECTION (ICSI). In vitro fertilization in which sperm is injected directly into the cytoplasm of the egg.

INTRAGENIC. Occurring within a single gene.

INTRAGENOMIC. Pertaining to components of one genome.

INTRAUTERINE. Of, situated in, used in, or occurring within the uterus.

INTRAUTERINE GROWTH RETARDATION (IUGR). The slow or poor growth of a fetus during the mother's pregnancy. It can be caused by malnutrition or lack of an adequate oxygen supply to the fetus, as well as by genetic disorders.

INTRAVENOUS. A route for administration of fluids, nutrients, blood products, or medications. A small flexible plastic tube is inserted into a vein by way of a needle to establish this route.

INTRAVENOUS PYELOGRAM. An x-ray assessment of kidney function.

INTRON. A portion of the DNA sequence of a gene that is not directly involved in the formation of the chemical that the gene codes for.

INTUSSUSCEPTION. One piece of bowel inside another, causing obstruction.

IN UTERO. While in the uterus; before birth.

INVERSION. A rearrangement of genetic material within a chromosome that occurs when a portion of the chromosome breaks off, is reversed end to end, and is reattached.

IN VITRO FERTILIZATION (IVF). A form of assisted reproduction technology in which a human ovum (egg) is combined with sperm outside the body in a laboratory container ("in vitro" means "in a glass").

IN VIVO. The gene therapy is done directly on cells that are inside of the body.

ION CHANNEL. A transmembrane protein that transports ions across a plasma membrane in the direction of their concentration (electrochemical) gradient; also called ion pump. Also called an ion transporter.

IONIZING RADIATION. High-energy radiation such as that produced by x-rays.

IPSILATERAL. Situated or appearing on or affecting the same side of the body.

IRIS. The colored ring between the cornea and lens of the eye that controls the amount of light entering through the pupil.

IRON DEFICIENCY ANEMIA. A decrease in the number of red cells in the blood caused by too little iron in the diet, poor absorption of iron by the body, or loss of blood.

IRON OVERLOAD. A side effect of frequent blood transfusions in which the body accumulates abnormally high levels of iron. Iron deposits can form in organs, particularly the heart, and cause life-threatening damage.

ISCHEMIC ATTACK. A period of decreased or no blood flow.

ISCHIOPAGUS. Conjoined twins who are attached at the lower half of the body.

ISOCHROMOSOME. A chromosome is normally composed of two sections referred to as p and q; instead, an isochromosome is an abnormal chromosome made up of two p sections or two q sections.

ISOMERISM. In human anatomy, a condition in which organs normally found on only one side of the body are found on both sides. In reference to the heart, isomerism refers to a condition in which the heart has either two right sides with two right atria or two left sides with two left atria.

ISOTOPE. Any of two or more species of atoms of a chemical element with the same atomic number and nearly identical chemical behavior but with differing atomic mass and physical properties.

ISOZYME/ISOENZYME. A group of enzymes that perform the same function, but are different from one another in their structure or how they move.

IVEMARK SYNDROME. A rare disorder characterized by cardiovascular anomalies as well as asplenia or hypoplasia of the spleen. It is named for Biörn Ivemark (1925–2005), the Swedish pediatrician who first identified the syndrome in 1955.

J

JAUNDICE. Yellowing of the skin or eyes due to excess of bilirubin in the blood.

JOINT CONTRACTURE. Inability of the limbs to fully extend.

JOINT DISLOCATION. The displacement of a bone from its socket or normal position.

K

KABUKI. Traditional Japanese popular drama performed with highly stylized singing and dancing using special makeup and cultural clothing.

KALLIKREIN. A protein necessary for the activation of chemicals that cause dilation of blood vessels to allow increased blood flow to an area that requires more blood than normal. It is also capable of cleaving the complement, C5, into C5a, a much more robust and active form of this complement molecule.

KANNER'S SYNDROME. Another name for autism.

KARYOTYPE. A standard arrangement of photographic or computer-generated images of chromosome pairs from a cell in ascending numerical order, from largest to smallest.

KARYOTYPING. A laboratory procedure in which chromosomes are separated from cells, stained, and arranged so that their structure can be studied under a microscope.

KERATIN. A tough, non-water-soluble protein found in the nails, hair, and outermost layer of skin. Human hair is made up largely of keratin.

KERATINIZATION. The conversion of the epidermis into the stratum corneum.

KERATINOCYTES. Skin cells.

KERATOACANTHOMA. A firm nodule on the skin typically found in areas of sun exposure.

KERATOLYTIC. An agent that dissolves or breaks down the outer layer of skin (keratins).

KERATOSIS. A raised thickening of the outer horny layer of the skin.

KETOACIDOSIS. A condition that results when organic compounds (such as propionic acid, ketones, and fatty acids) build up in the blood and urine.

KETOGENIC DIET. A high-fat, low-carbohydrate diet used to treat epilepsy in children who do not respond to anticonvulsant medications.

KETOLACTIC ACIDOSIS. The overproduction of ketones and lactic acid.

KETONE BODIES. Products of fatty acid metabolism in the liver that can be used by the brain and muscles as an energy source.

KETONURIA. The presence of excess ketone bodies (organic carbohydrate-related compounds) in the urine.

KETOSIS. An abnormal build-up of compounds called ketones in the blood. This condition usually indicates a problem with blood sugar regulation.

KIDNEY STONES. Mineral deposits that form inside the kidney.

KIDNEY TUBULES. A portion of the kidneys that causes water to be excreted as urine or reabsorbed into the body.

KIDNEYS. The two organs in the lumbar region that filter the blood, excreting the end products of the body's metabolism in the form of urine, and regulating the concentrations of hydrogen, sodium, potassium, phosphate, and other ions in the body.

KLINEFELTER SYNDROME. A genetic disorder characterized by one or more extra X chromosomes in a male, with a 47,XXY, 48,XXXY, or 49,XXXXY karyotype. Most men with this syndrome are infertile or have reduced fertility. The syndrome is named for Harry Klinefelter (1912–1990), an American endocrinologist who first described it in 1942.

KNOBLOCH SYNDROME. A rare genetic disorder characterized by cataracts in the eye, degeneration and detachment of the retina, and occipital encephalocele.

KNOCK-IN. Referring to an organism that has been genetically engineered to alter a specific genetic locus by a one-for-one substitution of DNA sequence information or by the addition of DNA sequence information that is not found on the genetic locus in question.

KNOCKOUT. Referring to an organism that has been genetically engineered to lack one or more specific genes.

KURU. An incurable neurodegenerative disease that is classified as a transmissible spongiform encephalopathy. It is transmitted among humans by cannibalism.

KYPHOSCOLIOSIS. Abnormal front-to-back and side-to-side curvature of the spine.

KYPHOSIS. Abnormal outward curvature of the spine resulting in a hunchback.

L

L1 SYNDROME. Inherited disorder that primarily affects the nervous system caused by mutations in the *LICAM* gene. L1 syndrome involves a variety of features including muscle stiffness (spasticity) of the lower limbs,

intellectual disability, hydrocephalus, and thumbs bent toward the palm (adducted thumbs).

LABIA. The two parts of the vulva (the external female genitalia).

LABORATORY, DATA ANALYSIS, AND COORDINATING CENTER (LDACC). The center designated for the coordination for the GTEx project, including sample processing and de-identification, database management, and eQTL analysis.

LACRIMAL DUCTS. Tear ducts.

LACTIC ACID. The major by-product of anaerobic (without oxygen) metabolism.

LACTIC ACIDOSIS. A condition characterized by the accumulation of lactic acid in bodily tissues. The cells of the body make lactic acid when they use sugar as energy. If too much of this acid is produced, the person starts feeling ill with symptoms such as stomach pain, vomiting, and rapid breathing.

LACTOSE. A sugar made up of glucose and galactose. It is the primary sugar in milk.

LAMININ. A protein in connective tissue that is important for cell adhesion.

LAMININ, BETA-2. A protein involved in various biological processes that include cell migration, adhesion, and the formation of basement membranes in the kidneys and the smooth muscle lining of arteries and veins. Mutations in the gene that encode this protein are responsible for Pierson syndrome.

LAPAROSCOPIC. Visual examination of the abdomen by means of a laparoscope.

LAPAROSCOPY. A diagnostic procedure in which a small incision is made in the abdomen and a slender, hollow, lighted instrument is passed through it. The doctor can view the ovaries more closely through the laparoscope and, if necessary, obtain tissue samples for biopsy.

LAPAROTOMY. An operation in which the abdominal cavity is opened up.

LARYNX. The voice box, or the organ that contains the vocal cords.

LASER ABLATION. Removal of a skin papula with a laser beam.

LASER-ASSISTED IN-SITU KERATOMILEUSIS (LASIK). A surgical procedure that uses a cutting tool and a laser to modify the cornea and correct moderate to high levels of myopia.

LASER-ASSISTED SUB-EPITHELIAL KERATOMILEUSIS (LASEK). A surgical procedure in which the epithelium is loosened on the corneal surface. The loosened epithelium is then reflected away from the cornea, and laser ablation performed.

LATE-ONSET AD. Alzheimer's disease that develops after age 65.

LATENCY. The ability of some viruses to remain dormant in the body after the acute infection has subsided.

LATERAL RECTUS MUSCLE. The muscle that turns the eye outward toward the ear (abduction).

LATERALITY. The right-left distribution of the internal organs.

L-CARNITINE. A substance made in the body that carries wastes from the body's cells into the urine.

LEADER SEQUENCE/LEADER RNA. Also known as the 5' untranslated region (5' UTR or five prime UTR), the section of mRNA found immediately before the initiation codon for translation of a transcript.

LEARNING DISABILITY. Refers generally to a group of disorders manifested by significant difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning, or math abilities.

LEBER HEREDITARY OPTIC ATROPHY OR LEBER HEREDITARY OPTIC NEUROPATHY (LHON). Discovered in 1871 by Theodore Leber, the painless loss of central vision in both eyes, usually occurring in the second or third decade of life, caused by a mutation in mitochondrial DNA. Other neurological problems, such as tremors or loss of ankle reflexes, may also be present.

LEFT VENTRICLE. Portion of the heart from which blood is pumped into the system.

LEFT VENTRICULAR ENLARGEMENT. Abnormal enlargement of the left lower chamber of the heart.

LEFT-RIGHT AXIS. The developmental feature in a fetus that determines which side of the body is left and which side is right; it conducts the location and positioning of the fetus's internal organs.

LEIGH SYNDROME. A rare genetic disease associated with mutations in either mitochondrial DNA or nuclear DNA, and characterized by degeneration of the central nervous system. It is named for Archibald Denis Leigh, a British psychiatrist who first described the syndrome in 1951.

LEIOMYOMAS. Benign tumors in the smooth muscle tissue of the uterus. They are also known as fibroids.

LENS. The transparent, elastic, curved structure behind the iris (colored part of the eye) that helps to focus light on the retina.

LENTIGO (PLURAL, LENTIGINES). A dark colored spot on the skin.

LEPROSY. A chronic, contagious skin and nervous system disease that leads, in the more serious form, to numbness, muscle weakness, and paralysis. Leprosy is sometimes referred to as Hansen's disease.

LEPTOMENINGEAL ANGIOMA. A swelling of the tissue or membrane surrounding the brain and spinal cord, which can enlarge with time.

LESION. A defective or injured section or region of the brain (or other body organ).

LETHARGY. Fatigue.

LEUCOPENIA. A decrease in white blood cells.

LEUKEMIA. Cancer of the blood-forming organs, which results in an overproduction of white blood cells.

LEUKOCEPHALOPATHIES. Defects in the white matter of the brain.

LEUKOCORIA. An abnormal white reflection from the retina.

LEUKOCYTE. A white blood cell. The neutrophils are a type of leukocyte.

LEUKOCYTOSIS. An increase in the number of leukocytes in the blood.

LEUKODYSTROPHY. A disease that affects the white matter, called myelin, in the CNS.

LEUKOENCEPHALOPATHY. Any of various diseases, including leukodystrophies, affecting the brain's white matter.

LEVODOPA. A chemical produced naturally in the body that is a precursor to such neurotransmitters as serotonin and epinephrine. It is also manufactured as a drug and used to treat Parkinson's disease and the dopa-responsive dystonias.

LEVOTHYROXINE. A form of thyroxine (T4) for replacement of thyroid hormones in hypothyroidism.

LEWY BODY DEMENTIA (LBD). A common progressive form of dementia in which protein aggregates called Lewy bodies form in neurons.

LHERMITTE-DUCLOS DISEASE. A rare form of benign brain tumor.

LIFETIME RISK. A risk that exists over a person's lifetime; a lifetime risk to develop disease means that the chance is present until the time of death.

LI-FRAUMENI SYNDROME. A rare familial cancer syndrome characterized by high risk for early-onset breast cancer and soft-tissue sarcomas.

LIGAMENT. A type of connective tissue that connects bones or cartilage and provides support and strength to joints.

LIGHT CHAINS. The two small polypeptide chains found in an immunoglobulin (antibody) molecule. The other two components of the antibody are so-called heavy chains.

LIMB GIRDLES. The areas of the body around the shoulders and hips.

LIMITED SCLERODERMA. A subtype of systemic scleroderma with limited skin involvement. It is sometimes called the CREST form of scleroderma, after the initials of its five major symptoms.

LINCOLN ATAXIA (SCA5). Spinocerebellar ataxia type 5; an adult-onset cerebellar ataxia caused by autosomal dominant mutations in the SPTBN2 gene.

LINKAGE. The association between separate DNA sequences (genes) located on the same chromosome.

LINKAGE ANALYSIS. A method of finding mutations based on their proximity to previously identified genetic landmarks.

LIPASE. A digestive enzyme found in pancreatic fluid that breaks down fats.

LIPIDS. A class of organic compounds defined by their tendency to dissolve in organic liquids, such as alcohol and ether, but not in water.

LIPODYSTROPHY. A medical condition characterized by abnormal or degenerative conditions of the body's adipose tissue.

LIPOFUSCIN. Pigment granules that are produced from lysosomal degradation. Lipofuscin normally accumulates over time and with age.

LIPOMA. A benign tumor composed of well-differentiated fat cells.

LIPOPIGMENTS. Substances made up of fats and proteins that can accumulate in different tissues of the body. They have a yellowish color to them under UV light. Lipopigments can result from oxidation of fatty acids and may be symptomatic of damage or aging.

LIPOPROTEIN. A complex molecule consisting of a lipid molecule joined with one or more protein molecules.

LIQUID BIOPSY. An informal term used to describe the use of cell-free tumor DNA in identifying the presence of cancer, staging it, evaluating its risk of metastasis, and monitoring the effects of treatment on the cancer's progression.

LISSENCEPHALY. A condition in which the brain has a smooth appearance because the normal convolutions (gyri) failed to develop.

LITHOTRIPSY. A procedure for treating kidney stones that involves the use of external shockwaves to break down the stones into small pieces that can be passed in the patient's urine.

LIVEDO RETICULARIS. Bluish net-like patterns of skin discoloration caused by blood-vessel abnormalities; usually present in children with recurrent fevers and strokes caused by *CECR1* gene mutations.

LOCALIZED SCLERODERMA. Thickening of the skin from overproduction of collagen.

LOCUS. Position occupied by a gene on a chromosome.

LONG BONES. The femur in the leg and the humerus in the arm.

LORDOSIS. An abnormal curvature of the spine in which the lumbar, or lower section, is excessively curved (also known as pigeon chest).

LOSS-OF-FUNCTION MUTATION. Any mutation that causes a gene to lose its ability to encode a protein, either partially or completely.

LOW-DENSITY LIPOPROTEINS (LDL). A cholesterol-carrying substance that can remain in the bloodstream for a long period of time.

LOWE SYNDROME. A rare X-linked recessive disorder characterized by congenital eye disorders as well as renal tubular dysfunction, and caused by mutations in the same gene as Dent disease 2.

LUMBAR LORDOSIS. Abnormal inward curvature of the spine.

LUPUS ERYTHEMATOSUS. A chronic inflammatory disease that affects many tissues and parts of the body including the skin.

LUTEINIZING HORMONE (LH). A hormone secreted by the pituitary gland that regulates the menstrual cycle and triggers ovulation in females. In males it stimulates the testes to produce testosterone.

LYMPH NODE. A bean-sized mass of tissue that is part of the immune system and is found in different areas of the body.

LYMPHANGIOMYOMATOSIS. Serious lung disease characterized by the overgrowth of an unusual type of muscle cell resulting in the blockage of air, blood, and lymph vessels to and from the lungs.

LYMPHATIC SYSTEM. Lymph nodes and lymphatic vessels that transport infection-fighting cells around the body.

LYMPHEDEMA DISTICHIASIS. A genetic syndrome caused by a mutation in the *FOXC2* gene on chromosome 16 and characterized by localized fluid retention and swelling of the limbs (lymphedema) and a double row of eyelashes (distichiasis).

LYMPHOCYTE. Any of three types of white blood cells that play an important role in the immune system. They include T cells, B cells, and natural killer (NK) cells.

LYMPHOMA. A general term for a group of cancers that affect the immune system; they develop from lymphocytes, cells in the lymphatic system.

LYMPHOPENIA. A condition marked by an abnormally low level of lymphocytes in the blood.

LYMPHOSCINTIGRAPHY. Procedure that helps to look at the lymph nodes in the body. Requires an injection of radioactive material to help see the lymph nodes and lymphatic system.

LYNCH SYNDROME. A genetic syndrome causing increased cancer risks, most notably colon cancer. Also called hereditary non-polyposis colon cancer (HNPCC).

LYSINE. A crystalline basic amino acid essential to nutrition.

LYSIS. Area of destruction.

LYSOSOMAL. Pertaining to the lysosomes, special parts (organelles) of cells that contain a number of enzymes important in the breakdown of large molecules such as proteins and fats.

LYSOSOMAL ACID LIPASE. An enzyme that catalyzes the hydrolytic breakdown of lipids in the lysosome. This enzyme is coded by the *LIPA* gene.

LYSOSOMAL STORAGE DISEASES. A group of more than 40 human genetic disorders that result from defects in lysosomal function.

LYSOSOME. A membrane-enclosed compartment in cells that contains many hydrolytic enzymes where large molecules and cellular components are broken down.

LYST. The gene that encodes the lysosomal trafficking regulator protein that is required for normal functioning of lysosomes and similar subcellular compartments.

M

MACHINE LEARNING. A subtype of artificial intelligence (AI) based on the concept that a computer can learn and adapt to new data inputs without human intervention. Applied to polygenic risk scoring, machine learning is said to improve the accuracy of PRS scores as the computer is given new population data without the need for a human operator to adjust the computer's algorithm.

MACROCEPHALY. Having an abnormally large head.

MACROGLOSSIA. Abnormal enlargement or thickening of the tongue.

MACROPHAGE. Specialized white blood cells that play a role in breaking down old or abnormal red blood cells.

MACROSOMIA. Overall large size due to overgrowth.

MACROTIA. Abnormally large ears.

MACROZOOSPERMIA. Macrocephalic sperm head syndrome; male infertility due to sperm with abnormally large heads and multiple (usually four) flagella; caused by mutations in the *AURKC* gene.

MACULA. A small spot located in the back of the eye that provides central vision and allows people to see colors and fine visual details.

MACULAR DEGENERATION. Progressive condition that affects the macula, a small portion of the retina at the back of the eye.

MACULE. A flat, discolored spot or patch on the skin.

MADAROSIS. The medical term for loss of hair from the eyebrows or eyelashes. Madarosis may be associated with a form of alopecia areata called alopecia totalis. It may also result from such diseases as leprosy and syphilis, or from trauma.

MADLUNG DEFORMITY. A forearm bone malformation characterized by a short forearm, an arced or bow-shaped radius, and dislocation of the ulna, resulting in wrist abnormalities.

MAFFUCCI DISEASE. A manifestation of Ollier disease (multiple enchondromatosis) with hemangiomas, which present as soft tissue masses.

MAGNETIC RESONANCE IMAGING (MRI). A diagnostic procedure that uses a combination of high powered

magnets, radio frequencies, and computers to generate detailed images of structures within the body.

MAJOR DEPRESSION. A psychological condition in which the patient experiences one or more disabling bouts of depression lasting two or more weeks.

MAJOR HISTOCOMPATIBILITY COMPLEX (MHC). Includes HLA, as well as other components of the immune system. Helps the immune system function, in part by helping it to distinguish "self" from "non-self."

MALAR HYPOPLASIA. Small or underdeveloped cheekbones.

MALFORMATION. An abnormality in an organ or body structure caused by a dysfunctional developmental process.

MALIGNANT. Referring to a tumor growth that spreads to another part of the body, usually cancerous.

MALIGNANT HYPERTHERMIA. A rare, potentially fatal condition triggered by exposure to certain inhalational anesthetics, in which the body's metabolism speeds up and overwhelms its ability to regulate body temperature.

MALINGERING. Exaggerating or faking the symptoms of a physical or psychiatric illness in order to avoid work, school, or military service; obtain fraudulent financial compensation; or attract sympathy or attention.

MALOCCLUSION. Misalignment or incorrect relation between the teeth in the upper and lower jaws as the jaws close.

MALROTATION. An abnormality that occurs during the normal rotation of an organ or organ system.

MAMMOGRAPHY. A procedure in which both breasts are compressed (or flattened) and exposed to low doses of x rays in order to visualize the inner breast tissue.

MANDIBLE. The lower jaw bone.

MANNOSE. A type of sugar that forms long chains in the body and is important in metabolism and the glycosylation of proteins.

MANOMETRY. A balloon study of internal anal sphincter pressure and relaxation.

MAO-B INHIBITORS. Inhibitors of the enzyme monoamine oxidase B. MAO-B helps break down dopamine; inhibiting it prolongs the action of dopamine in the brain. Selegiline is an MAO-B inhibitor.

MARFAN SYNDROME. A syndrome characterized by skeletal changes (arachnodactyly, long limbs, lax joints), ectopia lentis, and vascular defects.

MARFANOID. Term for a body type that is similar to that of people with Marfan syndrome. Characterized by tall, lean body with long arms and long fingers.

MASCULINIZATION. Development of excess body and facial hair, deepening of the voice, and increase in muscle bulk in a female due to a hormone disorder.

MASSETER SPASM. Stiffening of the jaw muscles. Often one of the first symptoms of malignant hyperthermia susceptibility that occurs after exposure to a trigger drug.

MATERNAL SERUM SCREENING. A blood test offered to pregnant women usually under the age of 35, which measures analytes in the mother's blood that are present only during pregnancy, to screen for Down syndrome, trisomy 18, and neural tube defects.

MATERNAL UNIPARENTAL DISOMY. A chromosome abnormality in which both chromosomes in a pair are inherited from one's mother.

MATERNALLY INHERITED DIABETES AND DEAFNESS (MIDD). A rare type of diabetes caused by a mitochondrial gene inherited from the mother.

MATURITY-ONSET DIABETES OF THE YOUNG (MODY). A rare form of diabetes inherited in an autosomal dominant fashion. It is similar to type 2 diabetes but develops before the age of 25.

MAXILLAE. The two facial bones that fuse to form the upper jaw and the roof of the mouth in humans.

MAY-HEGGLIN ANOMALY. A subgroup of the *MYH9*-related disorders characterized by the platelet disorder and inclusion bodies in the white blood cells.

MECKEL SYNDROME. A fatal genetic disorder characterized by occipital encephalocele as well as other central nervous system defects, large polycystic kidneys, and incompletely developed lungs.

MECONIUM. The first waste products to be discharged from the body in a newborn infant, usually greenish in color and consisting of mucus, bile, and so forth.

MEDIAL RECTUS MUSCLE. The muscle that turns the eye inward toward the nose (adduction).

MEDIATOR COACTIVATOR COMPLEX. A large protein complex that binds to super enhancers to activate genes.

MEDIUM-CHAIN ACYL-COA DEHYDROGENASE. Abbreviated MCAD, this is the enzyme responsible for the breakdown of medium chain fatty acids in humans. People affected with MCAD deficiency produce a form of MCAD that is not as efficient as the normal form of MCAD.

MEDIUM-CHAIN FATTY ACIDS. Fatty acids containing between 4 and 14 carbon atoms.

MEDULLA. In general, the central portion of a body organ; with regard to bone, the marrow that lies at the center of the long bones. The English word is derived from the Latin word for marrow.

MEDULLARY CAVITY. The marrow-filled cavity inside of a long bone (such as the femur).

MEDULLARY THYROID CANCER (MTC). A slowly growing tumor associated with MEN.

MEDULLOBLASTOMA. Tumor of the central nervous system derived from undifferentiated cells of the primitive medullary tube.

MEGA BASE PAIRS (MBP). A million base pairs.

MEGACOLON. Extreme swelling of the colon that is a rare but life-threatening complication of colitis.

MEGALENCEPHALY. Enlarged brain.

MEIOSIS. The process of cell division during the production of ova and sperm, in which the material in the chromosomes undergoes recombination (first-stage meiosis), and the chromosomes are reduced to a single set of 23 instead of the normal number of 23 pairs (second-stage meiosis).

MEIOTIC DRIVER. A gene that affects or modifies the processes that control meiosis.

MELANIN. A pigment produced by the body that gives color to the skin, hair, and eyes.

MELANOCYTE. A cell that can produce melanin.

MELANOCYTIC NEVUS. A nevus that contains pigmented skin cells called melanocytes. Melanocytic nevi are skin lesions that are also commonly described as moles.

MELANOMA. Cancer that develops in melanocytes, the pigmented skin cells.

MELANOSOMES. Granules of pigment within melanocytes that synthesize melanin.

MELATONIN. A sleep-inducing hormone secreted by the pineal gland.

MEMORY CELLS. B-cells whose antibodies recognized antigens from a previous infection; able to mount a quick, efficient response upon a second infection by the same organism.

MENARCHE. The medical term for the first menstrual period in girls, typically between the ages of 10 and 16. Pronounced MEH-nar-key.

MENDEL, GREGOR. Austrian monk who discovered the basic principles of heredity.

MENDELIAN DISEASE. A disease caused by a single mutated gene; also called a single-gene disease. These diseases are named for Gregor Mendel (1822–1884), an Austrian monk who discovered the basic principles of inheritance of single-gene traits through experimentation with plants in his garden.

MENDELIAN GENETICS. A set of parameters describing the traditional method of the transmission of genes from one generation to the next.

MENINGES. The two-layered membrane that covers the brain and spinal cord.

MENINGITIS. An infection of the covering of the brain and spinal cord.

MENOPAUSE. The transition in a woman's life whereby menstrual periods stop.

MENSTRUATION. Discharge of blood and fragments of the uterine wall from the vagina in a monthly cycle in the absence of pregnancy.

MENTAL STATUS EXAMINATION (MSE). An evaluation of the ability to communicate, follow instructions, recall information, and complete movement and coordination tasks, as well as emotional state and general sense of space and time.

MERMAID SYNDROME. Alternate name for sirenomelia, often used in older references. An extremely rare birth defect in which affected infants are born with a single lower extremity or with two legs that are fused together.

MESENTERY. Tissue that attaches the intestines to the abdominal wall.

MESODERM. The middle germ layer in the developing embryo, lying between the ectoderm and the endoderm. It gives rise to muscle, cartilage, bone, and the subcutaneous layer of the skin.

MESOMELIA. Shortness of the portion of arm connecting the elbow to the wrist or forearm.

MESOMELIC. The anatomical term used to describe the middle of a limb. The bones that constitute the middle of the arm are the radius and ulna, and mesomelic bones of the leg are the tibia and fibula.

MESONEPHRIC DUCT. Embryonic structure that in the male becomes the vas deferens, and in both sexes gives rise to the ureters leading to the kidney.

MESSENGER RNA (MRNA). The single-stranded RNA molecule that delivers genetic instructions from the nucleus of a cell to the ribosomes, where proteins are made.

METABOLIC ACIDOSIS. High acidity (low pH) in the body due to abnormal metabolism, excessive acid intake, or retention in the kidneys.

METABOLIC DISORDER. A disorder that affects the metabolism of the body.

METABOLIC MYOPATHIES. A broad group of muscle diseases whose cause is a metabolic disturbance of some type.

METABOLIC PATHWAY. A sequence of chemical reactions that lead from some precursor to a product, where the product of each step in the series is the starting material for the next step.

METABOLISM. The total combination of all of the chemical processes that occur within the cells and tissues of a living body.

METABOLIZED. When a drug is converted into one or more compounds.

METACARPAL. A hand bone extending from the wrist to a finger or thumb.

METACENTRIC. A centromere in the middle of the chromosome.

METACHRONOUS. Occurring at separate time intervals.

METAGENOME. Genetic material taken directly from an environment.

METANEPHRIC BUD. An embryological precursor to renal organs.

METAPHASE. A stage in the cycle of cell division in which the cell's genetic material condenses into chromosomes, which become visible and line up in the center of the dividing cell.

METAPHYSEAL FLARING. A characteristic found only by x-rays. If present, it means that the ends of the bone are wider than normal.

METAPHYSIS. The growth zone of the long bones located between the ends (epiphyses) and the shaft (diaphysis) of the bone.

METASTASIS. The spreading of cancer from the original site to other locations in the body.

METASTASIZE. To spread to another part of the body.

METASTATIC CANCER. A cancer that has spread to an organ or tissue from a primary cancer located elsewhere in the body.

METATARSAL. A foot bone extending from the ankle to a toe.

METHEMOGLOBINEMIA. A medical condition of the blood characterized by the presence of an altered form of hemoglobin, known as methemoglobin.

METHYL GROUPS. Groups of one carbon and three hydrogen atoms attached to DNA. The number of methyl groups attached to a section of a chromosome influences the level of gene activity (repression or activation).

METHYLATION. The process in which methyl groups are added to DNA. Methylation typically acts to suppress a gene's ability to code for proteins.

METHYLATION TESTING. DNA testing that detects whether a gene is active, or whether it is imprinted.

METHYLMALONIC ACID. An intermediate product formed when certain substances are metabolized.

MICROARRAY. A supporting material (usually glass or plastic) to which DNA fragments of known sequence are attached for the identification and sequencing of DNA samples.

MICROBE. A microorganism.

MICROBIOME. All of the microorganisms normally present in a given environment, such as the human body.

MICROBIOTA. Microscopic living organisms.

MICROCEPHALIC. Having an abnormally small head.

MICROCEPHALIC PRIMORDIAL DWARFISM SYNDROMES. A group of disorders characterized by profound growth delay and small head size.

MICROCEPHALY. A birth defect in which the brain and head are too small.

MICROCORNEA. Abnormal smallness of the cornea.

MICROCYTE. An abnormally small red blood cell.

MICROCYTIC, HYPOCHROMIC ANEMIA. An anemia marked by too little hemoglobin and small red blood cells.

MICRODELETION. A chromosome deletion that is too small to be detected by standard karyotyping methods. Microdeletions are typically 1 to 3 mega bases in length (1 to 3 million base pairs), whereas standard deletions are 5 mega bases or longer.

MICRODELETION SYNDROME. A group of signs and symptoms caused by the deletion of a very small amount of chromosomal material.

MICRODONTIA. Abnormally small teeth.

MICRODUPLICATION. The abnormal doubling of a small segment of a chromosome that is too small to be detected by standard karyotyping.

MICROGNATHIA. A term used to describe a small, underdeveloped lower jaw and chin.

MICROMELIA. The state of having extremely short limbs.

MICROPTHALMIA. Small or underdeveloped eyes.

MICROSATELLITE INSTABILITY (MSI). An abnormally high rate of change in repeated short sequences of DNA (microsatellites) that indicates impairment of DNA mismatch repair.

MICROSCOPIC COLITIS. A form of colitis that can only be diagnosed by examining tissue under a microscope.

MICROSOMIA. A general term for an abnormally small body or body part.

MICROSTOMIA. The medical term for an abnormally small mouth.

MICROSURGICAL EPIDIDYMAL SPERM ASPIRATION (MESA). A surgical sperm retrieval method where a small needle is inserted into the epididymis and a syringe attached by tubing to the needle is used to withdraw the sperm under the observation of a microscope.

MICROTIA. A birth defect in which the external ear is underdeveloped. The condition is called anotia if the outer ear is completely missing.

MIDFACIAL HYPOPLASIA. Subnormal growth of the central face.

MIDLINE. An imaginary line that divides the body into right and left parts.

MIDLINE DEFECTS. Defects involving organs along the center of the body such as the lips, penis, and corpus callosum.

MIDLINE ORGANS. Organs found along the center of the body such as the lips, penis, and corpus callosum.

MIGRAINE. A condition marked by severe headaches, often on one side of the head and accompanied by nausea, light and sound sensitivity, and other symptoms. Migraines are believed to involve the nerves and blood vessels of parts of the brain and head.

MINIATURIZATION. The process of shortening and thinning of the hair shafts that is found in androgenetic alopecia. It is caused by the effects of DHT on the hair follicle.

MINOXIDIL. A topical medication sold under the trade name Rogaine for the treatment of male pattern hair loss. It is applied to the scalp as a 2% or 5% solution.

MIOSIS. The medical term for constriction of the pupil of the eye.

MISCARRIAGE. Spontaneous pregnancy loss.

MISMATCH REPAIR. Repair of gene alterations due to mismatching.

MISSEGREGATION OF CHROMOSOMES. The faulty segregation of chromosomes into the appropriate daughter cells, in either mitosis (cell division) or meiosis (reproductive cell [sperm or egg] production).

MISSENSE. A portion of mRNA in which the coding is changed because of an abnormal change in the protein base sequence.

MITOCHONDRIA. Structures found in the cell (organelles) surrounded by two layers of membrane. Mitochondria turn energy from food into energy that powers the cell. They also help the cell produce heat and store calcium, and they help choose which damaged cells need to be destroyed.

MITOCHONDRIAL DISEASE. Any of several hundred inherited conditions caused by functional failure of the mitochondria within cells.

MITOCHONDRIAL DNA (MTDNA). The DNA (genetic material) found in the mitochondria. MtDNA contains the instructions for about 37 genes. These genes produce proteins that help the mitochondria function. MtDNA is only passed from the mother to her offspring.

MITOCHONDRIAL GENES. A group of 37 genes contained in the DNA of mitochondria (mDNA), the energy-producing organelles in cells. In humans, mDNA is inherited solely from the mother.

MITOCHONDRIAL GENOME. The DNA (genetic material) found in the mitochondria. The mitochondrial genome contains the instructions for about 37 genes. These genes produce proteins that help the mitochondria function. Mitochondrial DNA is only passed from the mother to her offspring.

MITOCHONDRIAL INHERITANCE. Inheritance associated with the mitochondrial genome, which is inherited almost exclusively from the mother.

MITOCHONDRIAL MUTATION. Variation in the mitochondrial DNA that can affect how well the mitochondria function.

MITOCHONDRIAL REPLACEMENT THERAPY (MRT). A technique to prevent or treat certain genetic diseases by

replacing the mitochondria in one or more cells. It is also called mitochondrial donation.

MITOSIS. A process that takes place in the nucleus of a dividing cell, involves typically a series of steps consisting of prophase, metaphase, anaphase, and telophase, and results in the formation of two new nuclei each having the same number of chromosomes as the parent nucleus.

MITRAL VALVE. The heart valve that lies between the left ventricle of the heart and the left atrium. It is also called the bicuspid valve because it has two leaves or flaps.

MITRAL VALVE PROLAPSE. A heart defect in which one of the valves of the heart (which normally controls blood flow) becomes floppy. Mitral valve prolapse may be detected as a heart murmur, but there are usually no symptoms.

MODEL ORGANISM. A nonhuman species (which may be a plant, animal, or bacterium) that is studied to yield understanding of particular biological events or processes in the expectation that discoveries made in the model organism can be applied to other species.

MOHS SURGERY. A form of microscopically controlled surgery that allows for the precise removal of cancerous tissue. It is commonly used to treat various types of skin cancer, particularly in areas of the body where preserving as much tissue as possible is essential. Mohs surgery is also known as micrographic surgery.

MOLECULAR ANALYSIS. Evaluation of molecules, tests that may identify single gene mutations.

MOLECULAR GENETIC TESTING (GENE TESTS). Medical test that examines single genes or short lengths of DNA to identify changes or mutations that cause genetic disorders.

MONOCLONAL ANTIBODY (MAB). A protein, produced in large quantities in a laboratory, designed to attack a specific target in the body.

MONOGENETIC DISORDER. A disorder or disease that is caused by a mutation or defect in one gene.

MONOGENIC DISEASE. Another term for a single-gene disorder.

MONOSOMY. Missing an entire copy of a chromosome or a piece of one copy of a chromosome.

MONOZYGOTIC. From one zygote, as in identical twins. The zygote is the first cell formed by the union of sperm and egg.

MORPHEA. The most common form of localized scleroderma.

MORPHOGENESIS. The normal developmental process of the body's structure and form.

MOSAIC. A term referring to a genetic situation in which an individual's cells do not have the exact same composition of chromosomes. In Down syndrome, this may mean that some of the individual's cells have a normal 46 chromosomes, while other cells have an abnormal 47 chromosomes.

MOSAIC RETINOBLASTOMA. A type of retinoblastoma where a variant in one copy of the *RBI* gene is found in only some cells of the body.

MOSAICISM. A genetic condition resulting from a mutation, crossing over, or nondisjunction of chromosomes during cell division, causing a variation in the number of chromosomes in the cells.

MOTOR NEURONS. Class of neurons that specifically control and stimulate voluntary muscles.

MOTOR SKILLS DISORDER. A disorder that affects motor coordination or its development and the control of particular groups of muscles that perform activities.

MOTOR UNITS. Functional connection with a single motor neuron and muscle.

MOTTLED RETINA. Changes in the retina of the eye causing a loss of visual acuity.

MRNA (MESSENGER RNA). The single-stranded RNA molecule that delivers genetic instructions from the nucleus of a cell to the ribosomes, where proteins are made.

MUCOCILIARY ESCALATOR. The coordinated action of tiny projections on the surfaces of cells lining the respiratory tract, which moves mucus up and out of the lungs.

MUCOLIPID. A lipid that accumulates in cells in mucopolipidosis disorders.

MUCOLIPIN-1. A protein in the cell membrane, probably a calcium ion channel, involved in recycling membrane lipids and deficient in mucopolipidosis IV.

MUCOLYTIC. An agent that dissolves or destroys mucin, the chief component of mucus.

MUCOPOLYSACCHARIDE. A complex molecule made of smaller sugar molecules strung together to form a chain. Found in mucous secretions and intercellular spaces.

MUCOSA. Mucus-secreting membrane lining all body cavities or passages that communicate with the exterior.

MUCUS MEMBRANE. Thin, mucus-covered layer of tissue that lines organs such as the intestinal tract.

MÜLLERIAN DUCTS. Two embryo structures that in the female develop into vagina, uterus, and oviducts, and in the male disappear except for the vestigial vagina masculina and the appendix testis.

MULTIFACTORIAL. Describes a disease that is the product of the interaction of multiple genetic and environmental factors.

MULTIFACTORIAL DISORDERS. A general term for polygenic disorders complicated by the effects of environmental factors. Multifactorial disorders do not have clear patterns of inheritance. They are sometimes called complex diseases or disorders. PCOS in women is a multifactorial disorder.

MULTIFACTORIAL INHERITANCE. A type of inheritance pattern in which many factors, both genetic and environmental, contribute to the cause.

MULTIFOCAL. A pathological term meaning that instead of finding one tumor in the tissue, multiple tumors are found.

MULTIFOCAL BREAST CANCER. Multiple primary cancers in the same breast.

MULTIPLE CARBOXYLASE DEFICIENCY. A type of propionic acidemia characterized by an inability to metabolize biotin.

MULTIPLE SCLEROSIS (MS). A progressive degeneration of nerve cells that causes episodes of muscle weakness, dizziness, and visual disturbances, followed by periods of remission.

MULTIPLEX ASSAY. A procedure that allows the testing of several gene samples simultaneously.

MUSCULAR DYSTROPHY. A group of inherited diseases characterized by progressive wasting of the muscles.

MUTAGEN. An environmental influence that causes changes in DNA.

MUTANT. A change in the genetic material that may alter a trait or characteristic of an individual or manifest as disease.

MUTATED GENE. A change of DNA sequence that causes a change of the function of the gene and a subsequent disease.

MUTATION. A change in the DNA sequence of a gene that may alter a trait or characteristic of an individual and can be transmitted to offspring. The change may manifest itself as a disease.

MUTATION RATE. How often a virus makes errors when copying itself.

MYDRIATICS. Medications given to induce dilation of the pupil, usually as part of an eye examination.

MYELIN. A fatty sheath surrounding nerves in the peripheral nervous system that helps them conduct impulses more quickly.

MYELINATION. Production and maintenance of the myelin sheath.

MYELODYSPLASTIC SYNDROME (MDS). A bone marrow disorder that can develop into aplastic anemia, requiring bone marrow or stem cell transplantation.

MYELOMENINGOCELE. A sac protruding through an abnormal opening in the spinal column.

MYOCARDIAL DISARRAY. A condition in which the cells in the heart muscle are aligned in a disorderly fashion rather than in parallel lines.

MYOCARDIUM. The medical term for the muscle of the heart.

MYOCLONIC EPILEPSY. Epilepsy characterized by sudden jerking or twitching in the arms, legs, or upper body.

MYOCLONUS. Twitching or spasms of a muscle or an interrelated group of muscles.

MYOFIBROBLAST. A fibroblast (cell that forms connective tissue) that has some of the characteristics of a smooth muscle cell.

MYOGLOBINURIA. The abnormal presence of myoglobin, a product of muscle disintegration, in the urine. Results in dark-colored urine.

MYOPATHY. Any abnormal condition or disease of the muscle.

MYOPIA. Nearsightedness. Difficulty seeing objects that are far away.

MYOSIN. The most common protein in muscle cells, which interacts with actin during muscle contraction to form actomyosin.

MYOSIN HEAVY CHAIN 9 (MYH9)-RELATED DISORDERS (MYH9-RD). A group of inherited macrothrombocytopenias caused by mutations in the *MYH9* gene that cause abnormal blood clotting and other symptoms.

MYOTONIA. Sustained contraction or delayed relaxation of a muscle following voluntary contraction of that muscle.

MYOTONIC DYSTROPHY. A form of muscular dystrophy, also known as Steinert's condition, characterized by delay in the ability to relax muscles after forceful

contraction and wasting of muscles, as well as other abnormalities.

MYOTUBULE. An intermediate stage in muscle fiber development, where the fiber is tubular with a centrally placed nucleus, instead of a peripheral eccentric nucleus.

MYXEDEMA. Swelling of the face, hands, feet, and genitals due to hypothyroidism.

MYXOID. Resembling mucus.

N

N-ACETYLGLUCOSAMINE-1-PHOSPHOTRANSFERASE (GNPTA). Enzyme that attaches a signal to other enzymes and directs those enzymes to the lysosome; deficient in mucopolidoses II and III.

NANISM. Short stature.

NARCOTICS. Strong prescription medication that can be effective in treating pain, but have the potential to be habit-forming if their use is not supervised correctly.

NASOGASTRIC TUBE. A long flexible tube inserted through the nasal passageways, down the throat, and into the stomach. Used to drain the contents of the stomach.

NATURAL IMMUNITY. First line immune response that is non-specific. Includes action of phagocytes, natural killer cells, and complement cells.

NATURAL KILLER CELLS (NK CELLS). White blood cells that fight virally infected cells and tumor cells within the body.

NATURAL SELECTION. The evolutionary pressure that affects the survival and reproduction of individuals based on their differing phenotypes within a population.

NECROSIS. Death of a portion of tissue differentially affected by disease or injury.

NECROTIZING ENCEPHALOMYELOPATHY. A progressive degeneration of the brain and central nervous system. This condition is fatal in nearly all individuals affected with type A pyruvate carboxylase deficiency.

NECROTIZING PANNICULITIS. Raised bumps under the skin that develop into ulcers.

NEGATIVE SYMPTOMS. Symptoms of schizophrenia characterized by the absence or elimination of certain behaviors: affective flattening, poverty of speech, and loss of will or initiative.

NEONATAL. Neonatal refers to the first 28 days after birth.

NEONATE. A newborn infant up to six weeks of age.

NEONATOLOGIST. A physician (pediatrician) who has special training in the care of newborns (neonates).

NEOPLASIA. An abnormal proliferation of cells, which results in an abnormal mass of tissue known as a neoplasm.

NEOPLASM. An abnormal growth of tissue; for example, a tumor.

NEPHRECTOMY. Surgical removal of a kidney.

NEPHROCALCINOSIS. An abnormal increase in calcium levels in kidney tissue.

NEPHROLITHIASIS. The medical term for the process of kidney stone formation.

NEPHRON. Basic functional filtration unit of the kidney.

NEPHRONOPHTHISIS. An autosomal recessive genetic disorder of the kidneys that usually affects children.

NEPHROPATHY. Kidney disease.

NEPHROTIC SYNDROME. A kidney disorder characterized by high levels of protein in the urine, low levels of albumin in the blood, and edema (abnormal accumulation of fluid in the body). It may be caused by genetic mutations, infections, certain medications, or such other disorders as diabetes and cancer.

NERVE CONDUCTION TESTING. Procedure that measures the speed at which impulses move through the nerves.

NERVOUS SYSTEM. The complete network of nerves, sense organs, and brain in the body.

NEURAL. Pertaining to a nerve or the nervous system.

NEURAL CREST CELLS. A group of cells in the early embryo, located on either side of the area that will eventually develop into the spinal cord. The cells migrate (move) away from the area and give rise to various body structures, including melanocytes (pigment producing cells), certain structures of the face and head, and parts of the nervous system.

NEURAL FOLDS AND TUBE. Portions of the developing embryo from which the brain and spinal cord arise.

NEURAL TUBE DEFECTS (NTDS). A group of disorders in which an opening in the brain or spinal cord persists after the fourth week of fetal development.

NEUROCRISTOPATHY. A disorder that results from abnormal development and/or migration of the neural crest cells in the embryo.

NEUROFIBRILLARY TANGLES. Accumulations of twisted tau protein fragments inside nerve cells in the brain that are diagnostic of Alzheimer's disease.

NEUROFIBROMA. A soft tumor usually located on a nerve.

NEUROFIBROMATOSIS. A progressive genetic condition often including multiple café-au-lait spots, multiple raised nodules on the skin known as neurofibromas, developmental delays, slightly larger head sizes, and freckling of the armpits, groin area, and iris.

NEUROIMAGING. Imaging studies of the brain, such as x-ray, computed tomography (CT) scans, or magnetic resonance imaging (MRI) scans.

NEUROLEPTIC. Another name for the older type of antipsychotic medications given to schizophrenic patients.

NEUROLOGICAL. Relating to the brain and central nervous system.

NEUROLOGIST. A physician who specializes in disorders of the nervous system, including the brain, spine, and nerves.

NEUROMETABOLIC DISORDER. Any disorder or condition that affects both the CNS and the metabolism of the body.

NEUROMUSCULAR. Involving both the muscles and the nerves that control them.

NEUROMUSCULAR JUNCTION. The site at which nerve impulses are transmitted to muscles.

NEURON. The fundamental nerve cell that conducts impulses in the brain and nervous system.

NEURONAL CEROID LIPOFUSCINOSES. A family of eight genetically distinct progressive neurological disorders that are all a result of overaccumulation of lipopigments.

NEURONAL SPECTRINOPATHIES. Neurological disorders such as SPARCA1 and SCA5 that are caused by mutations in genes encoding brain spectrins.

NEUROPATHY. A general term for disorders of the nerves of the peripheral nervous system.

NEUROPROTECTIVE. Conveying some form of protection from injury to the nervous system.

NEUROTRANSMITTERS. Chemicals that carry nerve impulses from one nerve cell to another; Alzheimer's disease causes a drop in the production of several important neurotransmitters.

NEUTROPENIA. A condition in which the number of leukocytes (a type of white or colorless blood cell) is

abnormally low, mainly in neutrophils (a type of blood cell).

NEUTROPHIL. The primary type of white blood cell involved in inflammation. Neutrophils are a type of granulocyte, also known as a polymorphonuclear leukocyte.

NEVUS. The medical term for mole; it is derived from the Latin word for birthmark. (Plural: nevi.)

NEVUS FLAMMEUS. A flat blood vessel tumor present at birth, also known as a “port wine stain.”

NEWBORN SCREENING. The act of testing all infants for a specific disease shortly after birth for the purpose of preventing disease progression through prompt medical treatment.

NEXT-GENERATION SEQUENCING (NGS). A platform that allows for the simultaneous sequencing of a number of regions of interest in a patient’s DNA.

N-GLYCANASE 1. An enzyme encoded by the NGLY1 gene that removes (cleaves) sugars called glycans from misfolded proteins.

NITRATES/NITRITES. Chemical compounds found in certain foods and water that, when consumed, may increase the risk of gastric cancer.

NONDISJUNCTION. An error in chromosome separation that occurs during cell division resulting in a woman receiving an extra X chromosome, leading to triple X syndrome.

NONHOMOLOGOUS. Referring to chromosomes that are not members of the same pair.

NONINVASIVE PRENATAL TESTING (NIPT). A blood test administered to a pregnant woman to screen for an abnormal number of chromosomes (aneuploidy) in the developing fetus. It is also known as noninvasive prenatal screening or NIPS.

NONKETOTIC HYPERGLYCEINEMIA (NKH). Glycine encephalopathy.

NONRENAL HAMARTOMA. Benign (noncancerous) tumor-like growths not found in the kidneys that often disrupt the normal function of a particular organ system.

NONSPHEROCYTIC. Literally means not sphere-shaped. Refers to the shape of red blood cells in nonspherocytic hemolytic anemia.

NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID). A pain reliever, such as ibuprofen or naproxen.

NONSYNDROMIC HEARING LOSS (NSHL). Hereditary hearing loss that is not part of another underlying genetic disorder.

NONTRAUMATIC UNGUAL OR PERIUNGUAL FIBROMA. Fibrous growth that appears around the fingernails and/or toenails.

NOONAN SYNDROME. A genetic syndrome that possesses some characteristics similar to cardiofaciocutaneous syndromes. It is unclear whether the two syndromes are different or two manifestations of the same disorder.

NOSOLOGY. A branch of medicine that aims to classify diseases by means of disease etiology (cause), pathogenesis (mechanism), and/or symptoms.

NUCHAL. Referring to the nape of the neck.

NUCHAL TRANSLUCENCY. A pocket of fluid at the back of an embryo’s neck visible via ultrasound. When thickened, it may indicate that the infant will be born with a congenital heart defect.

NUCHAL TRANSLUCENCY ULTRASOUND. Specialized ultrasound imaging that looks for a larger-than-normal space and fluid at the back of the first-trimester fetal neck to screen for chromosomal abnormalities.

NUCLEAR DNA (DEOXYRIBONUCLEIC ACID). The genetic material that contains the instructions for creating proteins. The nuclear DNA is packaged into chromosomes and is found in the control center (nucleus) of the cell.

NUCLEAR GENOME. The complete set of nuclear DNA found in the nucleus of the cell.

NUCLEAR ISOLATE. An isolated preparation of the contents of the nucleus of a cell, which contains the DNA.

NUCLEASE. A type of enzyme responsible for breaking the chemical bonds between the subunits (nucleotides) that make up DNA and RNA. A specific nuclease called Cas9 is used in CRISPR genome editing technology.

NUCLEI. Plural for nucleus, a special part of the cell that is essential for cell function.

NUCLEIC ACIDS. Any of various acids (such as DNA or RNA) that are found in living cells.

NUCLEOSOME. A basic unit of DNA packaging consisting of a segment of DNA wrapped around eight histone proteins.

NUCLEOTIDE. A building block of a nucleic acid (DNA or RNA), consisting of a sugar molecule, a phosphate group, and one of the nitrogen-containing bases (adenine, cytosine, guanine, and thymine in DNA; adenine, cytosine, guanine, and uracil in RNA).

NUCLEUS. The central part of a cell that contains most of its genetic material, including chromosomes and DNA.

NYSTAGMUS. Involuntary rapid eye movements.

O

OBLIGATE CARRIER. An individual who, based on pedigree analysis, must carry a genetic mutation for a particular genetic disease. Parents of a child with an autosomal recessive disorder are obligate carriers.

OBSESSIVE-COMPULSIVE DISORDER (OCD). Disorder characterized by persistent, intrusive, and senseless thoughts (obsessions) or compulsions to perform repetitive behaviors that interfere with normal functioning.

OCCIPITAL LOBE. An anatomical subdivision, located at the back of the brain, that contains the visual cortex.

OCHRONOSIS. A condition marked by pigment deposits in cartilage, ligaments, and tendons.

OCULAR. A broad term that refers to structure and function of the eye.

OCULAR ALBINISM (OA). Forms of albinism that primarily affect the eyes.

OCULO. Related to the eye.

OCULO-DIGITAL REFLEX. A reflex causing an individual to press on his or her eyes with fingers or fists.

OCULOCUTANEOUS ALBINISM (OCA). Forms of albinism that can affect the hair, skin, and eyes; there are several inherited forms of OCA that are caused by defects in different genes.

OCULOMOTOR NERVE. Cranial nerve III; the nerve that extends from the midbrain to several of the muscles that control eye movement.

OFF-LABEL. The decision to prescribe a drug for purposes other than those specifically approved by the U.S. Food and Drug Administration.

OKIHIRO SYNDROME. An inherited disorder characterized by abnormalities of the hands and arms and hearing loss; may be associated with Duane retraction syndrome.

OLIGODACTYLY. The absence of one or more fingers on a hand or toes on a foot.

OLIGODENDROCYTE. A cell in the central nervous system that insulates the parts of nerve cells called axons.

OLIGODONTIA. The absence of one or more teeth.

OLIGOHYDRAMNIOS. A reduced amount of amniotic fluid. Causes include nonfunctioning kidneys and premature rupture of membranes. Without amniotic fluid to

breathe, a baby will have underdeveloped and immature lungs.

OLIGOSACCHARIDE. Several monosaccharide (sugar) groups joined by glycosidic bonds.

OLIGOSPERMIA. A low concentration of sperm in a semen sample, usually defined as fewer than 15 million sperm per milliliter.

OLLIER DISEASE. Also termed multiple enchondromatosis. Excessive cartilage growth within the bone extremities that results in benign cartilaginous tumors arising in the bone cavity.

OMPHALOCELE. A birth defect where the bowel and sometimes the liver protrudes through an opening in the baby's abdomen near the umbilical cord.

OMPHALOPAGUS. Conjoined twins who are attached at the abdomen.

ONCOGENE. A gene that allows the uncontrolled division and proliferation of cells that lead to tumor formation and often to cancer.

ONCOLOGY. The branch of medicine concerned with the study, diagnosis, treatment, and prevention of cancer.

ON-TARGET POINT MUTATION. The substitution of one DNA base for another or insertion or deletion of one base.

ONYCHOGRYPHOSIS. Overgrowth of the fingernails and toenails.

OOCYTE (PRONOUNCED OH-EH-SITE). A diploid cell in females from which an egg or ovum develops by meiosis.

OOGONIAL STEM CELLS. Cells that develop into mature eggs.

OPEN-ANGLE JUVENILE GLAUCOMA. Hereditary glaucoma that develops in childhood or early adulthood and can be caused by mutations in the *MYOC* or *CYP11* genes.

OPERON. A functional unit of genomic DNA containing several genes under the control of one promoter.

OPHTHALMOLOGIST. A physician specializing in the medical and surgical treatment of eye disorders.

OPHTHALMOLOGY. The medical specialty of vision and the eye.

OPHTHALMOSCOPE. An instrument with special lighting, designed to view structures in the back of the eye.

OPISTHOTONOS. An arched position of the body in which only the head and feet touch the floor or bed when the patient is lying on their back.

OPPORTUNISTIC INFECTIONS. Infections that would not usually cause illness in people with a healthy immune system.

OPTIC DISC. The circular area at the back of the eyeball where the optic nerve connects to the retina.

OPTIC NERVE. A bundle of nerve fibers that carries visual messages from the retina in the form of electrical signals to the brain.

OPTOMETRIST. A medical professional who examines and tests the eyes for disease and treats visual disorders by prescribing corrective lenses and/or vision therapy. In many states, optometrists are licensed to use diagnostic and therapeutic drugs to treat certain ocular diseases.

ORAL GLUCOSE TOLERANCE TEST (OGTT). A diabetes test that measures blood sugar at intervals after drinking a sugary solution.

ORAL LOADING TEST. A procedure in which cystine is administered orally to a patient and plasma levels of cystine are measured. Under normal circumstances, amino acids are absorbed by the intestine and result in an increase in plasma amino acid levels. However, in cystinuria, there is a problem in the absorption process and blood levels of amino acids do not rise or rise slowly after eating.

ORBITAL CYSTS. Small fluid-filled sacs that abnormally develop inside the bony cavity of the skull that holds the eyeball.

ORGAN. An organ is a group of cells that form a structure that has a specific function. For example, the heart, stomach, or brain.

ORGANELLE. A specialized structure found within a cell that performs a specific function or carries out a specific life process. Mitochondria are organelles.

ORGANIC ACIDURIA. The condition of having organic acid in the urine.

ORTHODONTIST. Dentist who specializes in the correction of misaligned teeth.

ORTHOKERATOLOGY. A method of reshaping the cornea using a contact lens. It is not considered a permanent method to reduce myopia.

ORTHOPEDIC. Pertaining to the field of orthopedics, the science of the bones and diseases of the bones.

ORTHOSTATIC. Posture that is maintained while standing.

ORTHOSTATIC HYPOTENSION. A sudden decrease in blood pressure upon sitting up or standing. It may be a side effect of several types of drugs.

ORTHOTICS. A field of science that deals with the use of external mechanical devices to support or assist weak or abnormal joints, limbs, or muscles.

OSMOLARITY. The concentration of an osmotic solution, especially when measured in osmoles or milliosmoles per liter of solution.

OSMOTICALLY. Referring to the movement of a solvent through a semipermeable membrane (as of a living cell) into a solution of higher solute concentration that tends to equalize the concentrations of solute on the two sides of the membrane.

OSSICLES. The three bones of the middle ear, including the malleus, incus, and stapes.

OSSIFICATION. The process of bone formation.

OSTEOARTHRITIS. A group of diseases and mechanical abnormalities involving degradation of joints.

OSTEOBLASTS. A bone cell that makes bone.

OSTEOCHONDROMATOSIS. Another name for hereditary multiple exostoses, meaning a growth of bone and cartilage.

OSTEOCLASTS. A bone cell that breaks down and reabsorbs bone.

OSTEODYSPLASIA. A general term for a disorder of bone development.

OSTEOGENIC SARCOMA. A form of cancer that originates in the bone.

OSTEOGENIC. Derived from or containing bone cells.

OSTEOMA. A bony tissue tumor, either benign or malignant.

OSTEOMALACIA. The medical term for bone softening in adults due to inadequate levels of dietary calcium or phosphate, or the resorption of calcium from the bones by excessive secretion of parathyroid hormone.

OSTEOPOROSIS. Loss of bone density that can increase the risk of fractures.

OTITIS MEDIA. Inflammation of the middle ear, often due to fluid accumulation secondary to an infection.

OTOLARYNGOLOGIST. A physician who specializes in the care of the ear, nose, and throat and their associated structures.

OTOSCLEROSIS. Growth of spongy bone in the inner ear that causes progressive hearing loss and deafness.

OVA. Another name for the egg cells that are located in the ovaries.

OVARIES. The female reproductive organs that produce the reproductive cells (ova) and female hormones.

OVULATION. The monthly process by which an ovarian follicle or cyst ruptures, releasing a mature egg cell.

OXALATE. A naturally occurring molecule in the human body and in nature, too much of which can cause kidney stones.

OXALOSIS. A metabolic process in the body that happens in patients with primary hyperoxaluria whose kidneys fail. When the body stops removing extra oxalate, it accumulates in the blood and organs and leads to serious complications.

OXYGENATED BLOOD. Blood carrying oxygen through the body.

OXYTOCIN. A hormone that stimulates uterine contractions during childbirth and the secretion of breast milk.

OZENA. Also called atrophic rhinitis, it is a condition in which the bony ridges and mucous membranes of the nose waste away (atrophy), resulting in a foul-smelling bacteria-infected discharge.

P

PACEMAKER. A medical device placed in the chest that helps regulate heart rate.

PACHYDERMA. An abnormal skin condition in which excess skin is produced that appears similar to that of an elephant (pachyderm).

PACHYGYRIA. The presence of a few broad gyri (folds) and shallow sulci (grooves) in the cerebral cortex.

PAGET'S DISEASE. A non-cancerous disease marked by excessive growth of abnormal bone material.

PALATE. The roof of the mouth.

PALLIATIVE. Treatment given for relief of symptoms rather than a cure.

PALMAR. Referring to the palms of the hand.

PALMOPLANTAR KERATODERMA. Group of mostly hereditary disorders characterized by thickening of the corneous layer of skin (hyperkeratosis) on the palms and

soles as a result of excessive keratin formation (protein in the skin, hair, and nails).

PALMOPLANTAR KERATOSIS. A raised thickening of the outer horny layer of the skin on the palms of the hands and the soles of the feet.

PALPEBRAL FISSURES. The opening between the upper and lower eyelids.

PALPITATIONS. Perceived rapid or abnormal heartbeats associated with awareness of the heart's contractions in the chest. Palpitations may be caused by anxiety, caffeine, some drugs of abuse, or certain prescription medications, as well as by structural abnormalities of the heart.

PALSY. Uncontrollable tremors.

PANCREAS. An organ located in the abdomen that secretes pancreatic juices for digestion and hormones for maintaining blood sugar levels.

PANCREATIC INSUFFICIENCY. Reduction or absence of pancreatic secretions into the digestive system due to scarring and blockage of the pancreatic duct.

PANCREATIC ISLET CELL. Cells located in the pancreas that serve to make certain types of hormones.

PANCREATITIS. Inflammation of the pancreas.

PANCYTOPENIA. An abnormal reduction in the number of erythrocytes (red blood cells), leukocytes (a type of white or colorless blood cell), and blood platelets (a type of cell that aids in blood clotting) in the blood.

PANHYPOPITUITARISM. Generalized deficiency of all of the anterior pituitary hormones.

PAPILLOMA. Any benign localized growth of the skin or the linings of the respiratory and digestive tracts. The most common papillomas are warts.

PAPILLOMATOUS PAPULES. Skin-colored, raised bumps (not warts) found on the skin; most of these growths are benign (noncancerous) and rarely become malignant (cancerous).

PAPULA. A small raised area of the skin that lacks visible fluid.

PARALYSIS. Complete loss of muscle function for one or more muscle groups, often with loss of feeling and mobility in the affected area.

PARAMUTATION. a heritable change in the expression of one allele that results from an interaction of this allele with another allele for the same trait. The paramutation affected allele can be passed to subsequent generations.

PARAPAGUS. Conjoined twins who are joined at the side of their lower bodies.

PARAPLEGIA. Impairment in the sensory or motor functions of the lower limbs.

PARASITIC TWINS. Twins who include a smaller, malformed twin who is dependent on the larger, stronger twin for survival.

PARASYMPATHETIC GANGLION CELL. Type of nerve cell normally found in the wall of the colon.

PARATHYROID GLANDS. A pair of glands adjacent to the thyroid gland that primarily regulate blood calcium levels.

PARENCHYMA. Functional (rather than structural) tissues of an organ.

PARESTHESIA. The sensation of prickling, burning, or “pins-and-needles” in the limbs.

PARKINSON'S DISEASE. A progressive disease occurring most often after the age of 50, associated with the destruction of brain cells that produce dopamine and characterized by tremor, slowing of movement, and gait difficulty.

PARKINSONISM. A set of symptoms originally associated with Parkinson disease that can occur as side effects of neuroleptic medications: trembling of the fingers or hands, a shuffling gait, and tight or rigid muscles.

PATAU SYNDROME. Trisomy 13; an extra chromosome 13.

PATELLA. The kneecap.

PATENT DUCTUS ARTERIOSUS (PDA). A congenital anomaly of the heart occurring when the ductus arteriosus (the temporary fetal blood vessel that connects the aorta and the pulmonary artery) does not close at birth.

PATERNAL. Relating to one's father.

PATHOGENESIS. The biological mechanism that leads to a disease or disorder, or the origin and development of the disease.

PATHOGENIC VARIANT. A mutation or variation in a gene that causes a genetic disorder.

PECTORALIS MUSCLES. Major muscles of the chest wall.

PECTUS CARINATUM. An abnormality of the chest in which the sternum (breastbone) is pushed outward. It is sometimes called “pigeon breast.”

PECTUS EXCAVATUM. An abnormality of the chest in which the sternum (breastbone) sinks inward; sometimes called “funnel chest.”

PEDIGREE. A genetic diagram of a family tree that shows the appearance of a trait or disorder across several generations.

PELVIC EXAMINATION. A physical examination performed by a physician, often associated with a Pap smear. The physician inserts his or her finger into a woman's vagina, attempting to feel the ovaries directly.

PENDRIN. A protein encoded by the *SLC26A4* gene located on chromosome 7q31. Pendrin protein is believed to transport iodide and chloride within the thyroid and the inner ear.

PENETRANCE. The proportion of individuals who actually exhibit a trait for which they have gene or gene variant.

PEPTIC ULCER. A wound in the bowel that can be caused by stomach acid or a bacterium called *Helicobacter pylori*.

PEPTIDASE. Any enzyme that breaks down proteins. The gene whose mutations cause CODAS syndrome codes for a peptidase enzyme. Peptidases are also called proteases.

PERCHLORATE DISCHARGE TEST. A test used to check for Pendred syndrome by measuring the amount of iodine stored inside the thyroid gland. Individuals with Pendred syndrome usually have more iodine stored than normal, and thus their thyroid will release a large amount of iodine into the bloodstream when they are exposed to a chemical called perchlorate.

PERCUSSION. A technique used in physical diagnosis in which the examiner taps on the surface of the body to determine the condition of the structure beneath the skin. Percussion is used when examining a patient for myotonia congenita to see whether the tapping will cause the muscle beneath the skin to contract.

PERICARDITIS. Inflammation of the pericardium, the membrane surrounding the heart.

PERINATOLOGIST. A physician (obstetrician) who has special training in managing difficult pregnancies. Some prenatal tests, such as chorionic villus sampling and level II ultrasound, are performed primarily by perinatologists.

PERIOD OF SUSCEPTIBILITY. The time when teratogens can cause harm to the developing fetus.

PERIODONTITIS. Inflammatory reaction of the tissues surrounding and supporting the teeth that can progress to bone destruction, abscess formation, and eventual tooth loss.

PERIORBITAL PURPURA. A purplish or brownish discoloration caused by bleeding from the fragile capillaries in the skin around the eyes.

PERIOSTEAL. Relating to the periosteum, which is the connective tissue that covers all human bones.

PERIPHERAL NERVES. Nerves throughout the body that communicate motor and sensory information to and from the spinal cord.

PERIPHERAL NEUROPATHY. Any disease of the nerves outside of the spinal cord, usually resulting in weakness and/or numbness.

PERIPHERAL VISION. The ability to see objects that are not located directly in front of the eye. Peripheral vision allows people to see objects located on the side or edge of their field of vision.

PERITONEAL DIALYSIS. A form of therapy for kidney disorders that involves using the patient's abdomen (peritoneal cavity) as the site of treatment. Fluid is infused into the abdomen through a catheter and remains in the abdomen for several hours while waste products diffuse into the fluid from the abdominal blood vessels. The fluid is then removed and replaced with fresh fluid four to six times per day.

PERITONITIS. Inflammation of the peritoneum, the membrane surrounding the abdominal contents.

PERNICIOUS ANEMIA. A blood condition with decreased numbers of red blood cells related to poor vitamin B12 absorption.

PERONEAL. The outer part of the leg.

PEROXISOME. A cellular organelle containing different enzymes responsible for the breakdown of waste or other products.

PERSONALIZED MEDICINE. The tailoring of medical treatment to the individual patient based on his or her genetic profile. It is also called precision medicine.

PERVASIVE DEVELOPMENTAL DISORDER NOT OTHERWISE SPECIFIED (PDD-NOS). A term previously used to describe individuals who met some but not all of the criteria for classic autism or Asperger syndrome; now classified as an ASD.

PES PLANUS. Flat feet.

PEUTZ-JEGHERS SYNDROME (PJS). An inherited syndrome causing polyps in the digestive tract and spots on the mouth as well as increased risk of cancer.

PHAGOCYTE. White blood cells capable of engulfing and destroying foreign antigen or organisms in the fluids of the body.

PHALANGES. Long bones of the fingers and toes, divided by cartilage around the knuckles.

PHALILALIA. Involuntary echoing of the last word, phrase, sentence, or sound vocalized by oneself.

PHARMACODYNAMICS. Study of how a drug affects the body.

PHARMACOGENETICS. The study of how medication metabolism is affected by genetic inheritance.

PHARMACOGENOMICS. The branch of medicine that studies the role of the human genome in response to medications.

PHARMACOKINETICS. Study of how the body breaks down and uses a drug.

PHENOTYPE. The physical expression of an individual's genes.

PHENYLALANINE (PHE). An essential amino acid that must be obtained from food since the human body cannot manufacture it.

PHENYLALANINE HYDROXYLASE. The enzyme responsible for converting dietary phenylalanine to tyrosine. If phenylalanine hydroxylase is not working efficiently, phenylalanine levels in the blood increase.

PHENYLKETONURIA (PKU). An inherited inability to metabolize dietary phenylalanine, resulting in blood phenylalanine levels above 20 mg/dL. If left untreated, elevated blood phenylalanine levels can result in damage to the nervous system, including severe cognitive impairment, often referred to as intellectual disability.

PHEOCHROMOCYTOMA. A small vascular tumor of the inner region of the adrenal gland. The tumor causes uncontrolled and irregular secretion of certain hormones.

PHILTRUM. The grooved space between the nose and the upper lip.

PHLEBOTOMIST. A nurse or other health-care worker with special training in drawing venous blood for testing or analysis.

PHLEBOTOMY. The taking of blood from the body through an incision in the vein, usually in the treatment of disease.

PHOBIA. An exaggerated fear.

PHOSPHORIBOSYLPYROPHOSPHATE (PRPP). A molecule that is required for making new purine and pyrimidine nucleotides and for salvaging and recycling purines; PRPP synthesis requires phosphoribosylpyrophosphate synthetase 1 (PRPP synthetase 1), which is encoded by the *PRPS1* gene.

PHOSPHORYLATION. The addition of a phosphate group to a protein molecule. Protein phosphorylation plays an important role in many biological processes, including the activation of growth factor receptors.

PHOTOPHOBIA. Extreme sensitivity to light.

PHOTOPIGMENT. Pigment that is most sensitive to a particular wavelength of light.

PHOTORECEPTOR. Cells at the back of the eye that process the light that hits them; examples are cone and rod cells.

PHOTORECEPTOR CELLS. Specialized cells that convert light into nerve signals that ultimately get transmitted to the brain through the optic nerve.

PHOTOREFRACTIVE KERATECTOMY (PRK). A procedure that uses an excimer laser to make modifications to the cornea and permanently correct myopia.

PHOTOSENSITIVITY. Sensitivity to light.

PHYTANIC ACID. A substance found in various foods that, if allowed to accumulate, is toxic to various tissues. It is metabolized in the peroxisome by phytanic acid hydroxylase.

PHYTANIC ACID HYDROXYLASE. A peroxisomal enzyme responsible for processing phytanic acid. It is defective in Refsum disease.

PIERRE ROBIN SEQUENCE. A malformation of the jaw, mouth, and tongue that includes a cleft palate, a small lower jaw (micrognathia), and a tongue set too far back in the mouth. It is named for Pierre Robin, the French physician who first described the sequence in 1923.

PIERSON SYNDROME. A rare genetic disorder characterized by congenital nephrotic syndrome as well as congenital microcoria. It is named for Michel Pierson, the French physician who first described it in 1963.

PITUITARY GLAND. A small gland at the base of the brain that is responsible for releasing many hormones, including luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

PLACENTA. The organ responsible for oxygen and nutrition exchange between a pregnant mother and her developing baby.

PLANTAR. Referring to the sole of the foot.

PLASMA. The liquid part of the blood and lymphatic fluid that contains antibodies and other proteins.

PLASMA CELLS. White blood cells that originate in the bone marrow and secrete large quantities of antibodies.

PLASMALOGENS. The fat molecules that are important components of cells and of the myelin sheath that protects nerve cells.

PLASMAPHERESIS. A procedure in which the fluid component of blood is removed from the bloodstream and sometimes replaced with other fluids or plasma.

PLASMIN. The blood protein that is responsible for dissolving blood clots.

PLATELETS. Small disc-shaped structures that circulate in the blood stream and participate in blood clotting.

PLEURITIS. Inflammation of the pleura, the membrane surrounding the lungs.

PLOIDY. The number of sets of chromosomes in the nucleus of a cell.

PLURIPOTENT STEM CELLS. Can develop into any type of cell in the body and have the ability to replicate themselves.

PNEUMONIA. An infection of the lungs.

PNEUMOTHORAX. Abnormal accumulation of air in the chest cavity, outside the lung, often responsible for a collapsed lung.

PODOCYTES. Specialized cells in the Bowman's capsule of the kidney that wrap around the capillaries in the glomerulus and serve to prevent large protein molecules from passing into the urine while allowing water and small molecules like salt to pass through.

POIKILODERMA. A condition characterized by skin atrophy, widening of the small blood vessels (telangiectasia), and pigment changes giving a mottled appearance.

POIKILOTHERM. A term applied to any animal that cannot regulate its core body temperature and has a body temperature that varies with its surroundings. The opposite is a homeotherm, which refers to an organism (including humans) that can maintain a warm and fairly constant body temperature independent of the surrounding temperature.

POINT MUTATION (DNA). An error in the DNA sequence where one DNA base is substituted for another or inserted or deleted. This can sometimes cause the production of an abnormal protein or absence of a protein.

POLAR BODY. Either of two small cells produced during the two meiotic divisions in the production of an oocyte. Polar bodies contain only small amounts of cytoplasm and eventually disintegrate.

POLYARTERITIS NODOSA (PAN). An inflammatory disease that affects all layers of blood vessel walls and may be caused by *CECR1* gene mutations.

POLYCYSTIC OVARY SYNDROME (PCOS). A multifactorial disorder in women characterized by absent or infrequent ovulation, hirsutism (excessive body hair), infertility, acne, and increased susceptibility to obesity and type 2 diabetes.

POLYDACTYLY. The presence of extra fingers or toes.

POLYGENIC. Referring to an inherited disorder or trait whose phenotype is influenced by more than one gene.

POLYHYDRAMNIOS. A condition in which there is too much fluid around the fetus in the amniotic sac, seen in about 1% of pregnancies.

POLYMER. A very large molecule, formed from many smaller, identical molecules.

POLYMERASE CHAIN REACTION (PCR). A laboratory process used to make a large number of copies of specific genetic information from small amounts of DNA.

POLYMORPHIC. Describes a gene for which there exist multiple forms, or alleles.

POLYMORPHISM. A variation in a gene or chromosome that occurs with fairly high frequency in the general population.

POLYMYOSITIS. An inflammation of many muscles.

POLYNEUROPATHY. A disorder in which a number of nerves in the peripheral nervous system malfunction simultaneously.

POLYP. An abnormal tissue growth arising from a mucous membrane. The formation of an unusually large number of polyps is called polyposis.

POLYPECTOMY. Surgical removal of polyps.

POLYPLOIDY. A condition in which the nucleus of a cell contains more than two paired sets of chromosomes.

POLYPOSIS. The formation of numerous polyps in a body structure, most often the digestive tract or the nasal passages.

POLYSACCHARIDE. A linear or branched macromolecule composed of numerous monosaccharide (sugar) units linked by glycosidic bonds.

POLYSYNAPTIC CORTICAL PATHWAYS. The pathway by which stimuli enter the brain.

POLYSYNDACTYLY. Having both extra digits (toes, fingers) as well as webbing (syndactyly) between the digits.

PONS. A mass of nerve fibers in the brain stem that relay nerve impulses between the cerebellum and the rest of the brain.

PONTOCEREBELLAR HYPOPLASIA (PCH). Underdevelopment of the pons and cerebellum of the brain; PCH10 is caused by a mutation in the *CLP1* gene.

POOR MUSCLE TONE. The condition of muscles that are weak and floppy.

PORENCEPHALY. A congenital anomaly of the brain in which there are abnormal holes or cavities in the brain.

PORPHYRIA. Any one of a number of diseases, usually genetic in character, in which the conversion of porphyrins to heme is disrupted; usually associated with neurological problems.

PORPHYRIN. A large cyclic molecule shaped like a four-leaf clover. Combined with an iron atom, it forms a heme molecule.

PORT-WINE STAIN. Dark-red birthmarks seen on the skin, named after the color of the dessert wine.

POSER CRITERIA. Criteria proposed in 1983 as an update to the Schumacher criteria for diagnosing MS; developed to aid neurologists in determining the existence of lesions and other para-clinical evidence of MS.

POSITIONAL CLONING. Cloning a gene simply on the basis of its position in the genome, without having any idea of the function of the gene.

POSITIVE SYMPTOMS. Symptoms of schizophrenia that are characterized by the production or presence of behaviors that are grossly abnormal or excessive, including hallucinations and thought-process disorder.

POSITRON EMISSION TOMOGRAPHY (PET). A form of nuclear medicine scanning that measures brain activity using low doses of a radioactive substance.

POST-AXIAL POLYDACTYLY. An extra finger or toe on the outside of the hand or foot.

POSTERIOR FOSSA. The area at the base of the skull attached to the spinal cord.

POST-ICTAL STATE. A period of lethargy, confusion, and deep breathing following a grand mal seizure that may last from a few minutes to several hours.

POVERTY OF SPEECH. A negative symptom of schizophrenia, characterized by brief and empty replies to questions.

PRADER-WILLI SYNDROME (PWS). A disorder caused by the deletion or absence of active imprinted genes.

PREAURICULAR PITS. Small pits in the skin on the outside of the ear.

PRE-AXIAL POLYDACTYLY. An extra finger or toe on the inside of the hand or foot.

PREBIOTIC. Chemicals or compounds that induce growth in micro-organisms.

PRECISION MEDICINE. An approach to health care that bases the prevention and treatment of disease on each individual's unique genetic makeup and lifestyle habits. It is sometimes called personalized medicine.

PRECOCIOUS PUBERTY. An abnormal condition in which a person undergoes puberty at a very young age. This condition causes the growth spurt associated with puberty to occur before the systems of the body are ready, which causes these individuals to not attain normal adult heights.

PRECURSOR COMPONENTS. Components in an enzymatic pathway that are formed by previous cellular events.

PREFRONTAL CORTEX (PFC). The anterior gray matter of the frontal lobe of the brain that regulates complex cognition, emotions, and behaviors.

PREGNANCY-ASSOCIATED PLASMA PROTEIN A (PAPP-A). An early pregnancy protein in maternal blood and urine; fetal chromosomal abnormalities can cause decreased PAPP-A levels.

PREIMPLANTATION GENETIC TESTING (PGT). A screening test performed on embryos created by IVF to analyze the genetics of each embryo prior to transfer into the intended mother's uterus. Also called preimplantation genetic diagnosis (PGD).

PREMATURE OVARIAN INSUFFICIENCY (POI). Premature ovarian failure; the cessation of ovarian function before age 40.

PREMUTATION. A change in a gene that precedes a mutation; this change does not alter the function of the gene.

PRENATAL DIAGNOSIS. The determination of whether a fetus possesses a disease or disorder while it is still in the womb.

PRENATAL TESTING. Testing for a disease such as a genetic condition in an unborn baby.

PRENATAL ULTRASOUND. An imaging test using high-frequency sound waves to create images of internal organs. "Prenatal" indicates the test is performed on a fetus while still in the womb.

PRESENILIN (PS-1 OR PS-2). Proteins involved in processing amyloid precursor protein; mutations in the genes encoding these proteins can cause early-onset familial Alzheimer's disease.

PREVALENCE. The number of individuals living with a particular illness within a particular population at any

given time. Prevalence is often expressed in terms of number of individuals per 100 or per 1,000 members of the population.

PRIMARY ATRIAL SEPTATION. An improper division of the atria of the heart, or a "hole in the heart," which results in the formation of a common atrium rather than the normal two-chambered atrium.

PRIMARY CANCER. The first or original cancer site before any metastasis.

PRIMARY CONGENITAL GLAUCOMA (PCG). Glaucoma that is present at birth or develops during the first year of life and can be caused by mutations in the *CYPB1* or *LTBP2* genes.

PRIMARY CRANIOSYNOSTOSIS. Abnormal closure of the cranial sutures caused by an abnormality in the sutures themselves.

PRIMARY IMMUNE DEFICIENCY DISEASES (PIDDs). A group of rare genetic disorders caused by inherited defects in specific cells of the immune system. XMEN is one of about 200 known PIDDs. Also referred to as primary immunodeficiency diseases (PIDs).

PRIMARY POSITION, PRIMARY GAZE. When both eyes are looking straight ahead.

PRIMARY TUMOR. The organ or tissue where a tumor began.

PRIMORDIAL. Referring to conditions that begin before birth or are characteristic of the embryo's earliest stages of development.

PRION. A protein that can fold in several different and distinctive ways, one of which can be transmitted to other proteins.

PROBAND. In genetics, a particular subject (person or animal) being reported on or studied. In most cases, the proband is the first affected member of a family with a genetic disorder who brings the condition to the attention of doctors and researchers.

PROBIOTIC. Micro-organisms believed to provide health benefits to humans.

PROCOLLAGEN. A collagen precursor formed by the twisting together of three pro-alpha1(II) chains.

PROGERIA. Genetic abnormality that presents initially as premature aging and failure to thrive in children.

PROGNATHISM. A protruding lower jaw.

PROGRAMMABLE NUCLEASES. DNA or RNA cutting enzymes from bacteria that can be programmed for

genome editing to cut at a specific location and stimulate changes in the sequence.

PROHORMONE. A precursor of a more active hormone. Thyroxine is the prohormone of triiodothyronine.

PROLACTIN. A hormone that helps the breast prepare for milk production during pregnancy.

PROLIFERATION. The growth or production of cells.

PROMOTER. The region of a gene that initiates transcription of the genetic information.

PRONUCLEAR TRANSFER. A mitochondrial replacement technique in which the mother's egg is first fertilized by the father's sperm; then the two pronuclei are inserted into a donor egg that has been fertilized and has had its own nucleus removed.

PRONUCLEUS. The nucleus of a sperm or egg cell during the process of fertilization.

PROPHYLACTIC. Referring to a medical or surgical intervention intended to prevent rather than treat disease.

PROPIONIC ACID. An organic compound that builds up in the body if the proper enzymes are not present.

PROPIONYL COA CARBOXYLASE. An enzyme that breaks down the amino acids isoleucine, valine, threonine, and methionine.

PROPORTIONATE DWARFISM. Dwarfism in which the person's body parts are all smaller or shorter than normal but remain in proportion to one another.

PROPTOSIS. Bulging of the eye outward from the orbit of the eye. It is also known as exophthalmos.

PROSTATECTOMY. The surgical removal of the prostate gland.

PROTEIN. Important building blocks of the body composed of amino acids, involved in the formation of body structures and controlling the basic functions of the human body.

PROTEIN TYROSINE PHOSPHATASE (PTP). A member of a protein family, including the PTEN protein, that modifies other proteins by removing a phosphate group.

PROTEINURIA. An abnormally high level of protein in the urine, defined as higher than 3.5 grams per day in adults or higher than 40 mg/m² per hour in children.

PROTEOLIPID PROTEIN GENE (PLP). A gene that makes a protein that is part of the myelin in the central nervous system. variants in this gene cause PMD.

PROTEOLYSIS. The breakdown of proteins into smaller units, usually polypeptides or amino acids.

PROTOCOL. A set of guidelines for medical tests or treatments.

PROTO-ONCOGENE. A gene involved in stimulating the normal growth and division of cells in a controlled manner.

PROTOPORPHYRIN. A precursor molecule to the porphyrin molecule.

PROTOSPACER. A regularly sized piece of phage DNA that has been excised and incorporated into the CRISPR array.

PROTOSPACER-ADJACENT MOTIFS (PAMS). Highly conserved short DNA sequences (2bp–5bp) that are necessary for the excision of adjacent protospacers.

PROTOZOA. One type of a class of single-celled organism.

PROXIMAL. Near the point of origin.

PROXIMAL 18Q. A deletion within the long arm of chromosome 18, near the centromere.

PROXIMAL MUSCLES. The muscles closest to the center of the body.

PSEUDOAUTOSOMAL DOMINANT INHERITANCE. The pattern of inheritance for a disorder caused by genes in the pseudoautosomal regions of the sex chromosomes. Individuals only require one mutated or nonworking copy of a gene to have signs and symptoms of the disorder. Affected individuals have a 50% chance to have an affected child with each pregnancy.

PSEUDOAUTOSOMAL REGION. Genes found on the sex chromosomes that contain the same genetic information whether they are on the X or Y chromosome.

PSEUDOCAMPTODACTYLY. A condition in which the fingers curve or bend when the hand is bent back at the wrist.

PSEUDOCYST. A fluid-filled space that may arise in the setting of pancreatitis.

PSEUDOSYNDACTYLY. A joining together of the fingers or toes from scarring that can occur with severe forms of epidermolysis bullosa.

PSORIASIS. A common, chronic, scaly skin disease.

PSYCHODYNAMIC THERAPIES. A form of psychological counseling that seeks to determine and resolve the internal conflicts that may be causing an individual to be suffering from symptoms of depression.

PSYCHOGENIC NON-EPILEPTIC SEIZURE (PNES). An event that resembles an epileptic seizure but lacks the electrical discharge associated with epilepsy. PNES is

associated with psychiatric disorders, most often conversion disorder, and is often triggered by a psychological trauma of some kind.

PSYCHOLOGIST. An individual who specializes in the science of the mind.

PSYCHOMOTOR. Movement produced by action of the mind or will.

PSYCHOSIS. A severe mental disorder characterized by loss of contact with reality, causing deterioration of normal social functioning.

PSYCHOTHERAPY. Psychological counseling that seeks to determine the underlying causes of a patient's depression. The form of this counseling may be cognitive/behavioral, interpersonal, or psychodynamic.

PSYCHOTIC DISORDER. A mental disorder characterized by delusions, hallucinations, or other symptoms of lack of contact with reality.

PTERYGIUM COLLI. Webbing or broadening of the neck, usually found at birth and usually on both sides of the neck.

PTOSIS. Drooping of the upper or lower eyelid.

PUBERTY. The stage of development when the gonads begin to function and secondary sexual characteristics begin to appear.

PULMONARY. Relating to the lungs; the pulmonary artery carries blood from the heart to the lungs.

PULMONARY ARTERY. An artery that carries blood from the heart to the lungs.

PULMONARY ATRESIA. A congenital malformation of the pulmonary valve in which the opening of the valve fails to develop. As a result, blood cannot flow out of the heart through the pulmonary artery to the lungs to be oxygenated.

PULMONARY EDEMA. A problem caused when fluid backs up into the veins of the lungs. Increased pressure in these veins forces fluid out of the vein and into the air spaces (alveoli). This interferes with the exchange of oxygen and carbon dioxide in the alveoli.

PULMONARY EMBOLISM. A blood clot in the lungs.

PULMONARY HYPERTENSION. A severe form of high blood pressure caused by diseased arteries in the lung.

PULMONARY HYPOPLASIA. Underdevelopment of the lungs.

PULMONARY STENOSIS. Narrowing of the pulmonary valve of the heart, between the right ventricle and the

pulmonary artery, limiting the amount of blood going to the lungs.

PULMONOLOGIST. A physician who specializes in lung diseases.

PULSENET. A network of laboratories across the United States, overseen by the Centers for Disease Control and Prevention (CDC) to identify bacteria responsible for foodborne outbreaks by using whole-genome sequencing.

PUNCTATED. Having a dotted pattern.

PUNNETT SQUARE. A grid used to determine the probability that the offspring of two parents with a single-gene trait being crossed will have a particular genotype. The square is named for Reginald Punnett, a British geneticist who first devised it in 1905.

PUPIL. The opening in the iris through which light enters the eye.

PURINES. A group of organic compounds that are important building blocks of RNA and DNA. Two of the four nucleobases found in DNA (adenine and guanine) are purines.

PURPURA FULMINANS. Dark, reddish-purple patches of dying tissue that result from clots in small blood vessels that would otherwise feed that tissue.

PUSTULE. A pus-filled lesion of the skin that resembles the "pimples" of adolescent acne.

PYELONEPHRITIS. Inflammation of the kidney commonly caused by bacterial infections.

PYGOPAGUS. Conjoined twins who are joined back-to-back with fused buttocks.

PYLORIC SPHINCTER. Circular smooth muscle found at the outlet of the stomach.

PYLORIC STENOSIS. Narrowing of the stomach due to thickening of the pyloric muscle at the end of the stomach.

PYOGENIC. Pus-forming.

PYREXIA. A medical term denoting fevers.

PYRIDOSTIGMINE BROMIDE (MESTINON). An anticholinesterase drug used in treating myasthenia gravis.

PYRUVATE CARBOXYLASE. The enzyme that is responsible for the first step in the conversion of pyruvate molecules into glucose molecules. Individuals with Type A PCD produce an highly inefficient form of pyruvate carboxylase. Individuals with Type B PCD either completely lack the ability to produce this enzyme,

or they cannot produce it in sufficient quantities to sustain life.

PYRUVATE DEHYDROGENASE COMPLEX. A series of enzymes and co-factors that allow pyruvate to be converted into a chemical that can enter the TCA cycle.

Q

QT INTERVAL. The section on an electrocardiogram between the start of the QRS complex and the end of the T wave, representing the firing or depolarization of the ventricles and the period of recovery prior to repolarization or recharging for the next contraction.

QUADRIPLÉGIA. Paralysis of all four limbs.

R

R117. A minor mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that can cause absence of vas deferens without causing cystic fibrosis.

RACHITIC. Pertaining to, or affected by, rickets. Examples of rachitic deformities include curved long bones with prominent ends, a prominent middle chest wall, or bony nodules at the inner ends of the ribs.

RACIAL DISPARITIES. Inequities and inconsistencies in the way people are treated based on the color of their skin, in terms of socioeconomic status, education, access to health care, housing, and other aspects of life.

RADIAL KERATOTOMY (RK). A surgical procedure involving the use of a diamond-tipped blade to make several spoke-like slits in the peripheral (non-viewing) portion of the cornea to improve the focus of the eye and correct myopia by flattening the cornea.

RADIATION THERAPY. Treatment using high-energy radiation from x-ray machines, cobalt, radium, or other sources.

RADICULOPATHY. A bulging of disc material often irritating nearby nerve structures resulting in pain and neurologic symptoms. A clinical situation in which the radicular nerves (nerve roots) are inflamed or compressed. This compression by the bulging disc is referred to as a radiculopathy. This problem tends to occur most commonly in the neck (cervical spine) and low back (lumbar spine).

RADIOGRAPHIC. Involving an x-ray.

RADIOLUCENT. Transparent to x-ray or radiation. The black area on x-ray film.

RADIUS. One of the two bones of the forearm, the one adjacent to the base of the thumb.

RANSON CRITERIA. A system of measurements, including age and blood testing, that can be used to predict the outcome of a person who has been hospitalized for an episode of pancreatitis.

RAYNAUD'S PHENOMENON/RAYNAUD'S DISEASE. A condition in which blood flow to tissues is reduced by a malfunction of the nerves that regulate the constriction of blood vessels. When attacks of Raynaud's occur in the absence of other medical conditions, it is called Raynaud's disease. When attacks occur as part of a disease, as in scleroderma, it is called Raynaud's phenomenon.

RB1. A cell-cycle control and tumor-suppressor gene; deletion or mutation of RB1 can lead to retinoblastoma.

RECEPTOR. A molecule in or on the surface of a cell that recognizes and binds with specific molecules, such as hormones, neurotransmitters, or drugs.

RECESSIVE. Refers to a genetic trait that is expressed only when present on both members of a pair of genes, one inherited from each parent.

RECESSIVE DISEASE. Condition caused by a pathogenic variant (mutation) in both copies of a particular gene. Two carriers of an autosomal recessive condition have a one-in-four (25%) chance of passing it on to their children.

RECESSIVE GENE. A type of gene that is not expressed as a trait unless inherited by both parents.

RECESSIVE TRAIT. An inherited trait or characteristic that is outwardly obvious only when two copies of the gene for that trait are present.

RECOMBINATION. The production of genetic combinations in offspring that are different from those of the parents. This process occurs during meiosis.

RECTAL SUCTION BIOPSY. The removal and examination of a sample of rectum tissue for diagnostic purposes.

RECTUM. The end portion of the intestine that leads to the anus.

RECURRENCE RISK. The possibility that the same event will occur again.

RECURRENT. Tending to repeat.

RED BLOOD CELL (RBC). Hemoglobin-containing blood cells that transport oxygen from the lungs to tissues. In the tissues, the red blood cells exchange their oxygen for carbon dioxide that is then brought back to the lungs.

RED NUCLEUS. A small structure present in the brain stem that is involved in the control of movement.

REFRACTION. The bending of light rays as they pass from one medium through another. Used to describe the action of the cornea and lens on light rays as they enter the eye. Also used to describe the determination and measurement of the eye's focusing system by an optometrist or ophthalmologist.

REFRACTIVE EYE SURGERY. A general term for surgical procedures that can improve or correct refractive errors by permanently changing the shape of the cornea.

REMISSION. The time during which symptoms of a disease or condition are reduced or not present.

RENAL. Pertaining to the kidneys.

RENAL AGENESIS. Absence or failure of one or both kidneys to develop normally.

RENAL ANGIOMYOLIPOMA. Benign (noncancerous) tumors in the kidney that are made up of vascular tissue (angio), smooth muscle (myo), and fat (lipoma).

RENAL CALCULUS (PLURAL, CALCULI). The medical term for a kidney stone. Kidney stones are formed from minerals dissolved in the urine.

RENAL CELL CARCINOMA. A cancerous tumor made from kidney cells.

RENAL COLIC. A spasmodic pain, moderate to severe in degree, located in the back, side, and/or groin area.

RENAL CYSTS. Fluid or air-filled spaces within the kidneys.

RENAL DYSPLASIA. A developmental anomaly of the kidney.

RENAL HYPOPLASIA. Abnormally small kidneys.

RENAL SYSTEM. The organs involved with the production and output of urine.

RENAL TUBULAR DISORDER. Various defects in the renal tubular transport processes and their regulation.

RENIN. An enzyme produced by the kidneys.

RENPENNING SYNDROME. X-linked intellectual disability with short stature and microcephaly not associated with the fragile X chromosome and occurring more

frequently in males, although some females may also be affected.

REPLICATION. The process by which a virus makes copies of itself.

REPOLARIZATION. Period when the heart cells are at rest, preparing for the next wave of electrical current (depolarization).

REPRODUCIBILITY. A major principle of the scientific method, used to confirm the validity of a new discovery by repeating the research that produced it.

REPRODUCTIVE ENDOCRINOLOGIST. A doctor (usually a gynecologist) with subspecialty training in hormonal functioning as it pertains to infertility.

RESECTION. The act of removing an organ or tissue surgically.

RESIDUAL RISK. The chance that an individual may still be a carrier for a certain condition even though the person screened negative.

RESPIRATORY. Having to do with breathing.

RETICULOCYTE. Immature red blood cells.

RETINA. The light-sensitive layer of tissue in the back of the eye that receives and transmits visual signals to the brain through the optic nerve.

RETINAL ACHROMIC PATCH. Defect in the coloration of the retina.

RETINAL DYSPLASIA. Improper development of the retina that can lead to detachment of the retina.

RETINAL DYSTROPHY. Degeneration of the retina, causing a decline in visual clarity.

RETINAL HAMARTOMAS. Benign (noncancerous) tumor found on the retina.

RETINAL LACUNAE. Small abnormal cavities or holes in the retina.

RETINAL PIGMENT EPITHELIUM (RPE). The pigmented cell layer that nourishes the retinal cells; located just outside the retina and attached to the choroid.

RETINITIS PIGMENTOSA. Progressive deterioration of the retina, often leading to vision loss and blindness.

RETINOBLASTOMA. A cancerous tumor of the eye.

RETINOID. A derivative of synthetic vitamin A.

RETINOPATHY. Any disorder of the retina.

RETT SYNDROME. An inherited progressive neurodevelopmental disorder that affects females, usually

beginning in infancy, and characterized by slow brain growth, cognitive and motor deterioration, and possibly ASD.

REVERSE TRANSCRIPTASE. An enzyme that makes DNA from an RNA template.

RH FACTOR. Rhesus factor, a protein on the surfaces of red blood cells of many people; if the fetus is Rh-positive but the mother is Rh-negative, the mother must be treated with immune globulin to prevent the production of antibodies that will cross the placenta and attack the fetal blood cells.

RHABDOMYOLYSIS. Breakdown or disintegration of muscle tissue.

RHABDOMYOSARCOMA. A malignant tumor of the skeletal muscle.

RHEUMATOID ARTHRITIS (RA). A chronic autoimmune disease marked by inflammation of the membranes surrounding joints.

RHEUMATOID FACTOR. Antibodies present in the majority of individuals with rheumatoid arthritis. A diagnostic marker for rheumatoid arthritis that is absent from ankylosing spondylitis and other seronegative spondyloarthropathies.

RHIZOMELIC. Term meaning “root limb,” which refers to the disproportionate shortening of the upper part of a limb compared to the lower part.

RHO/RAC GUANINE EXCHANGE FACTOR. Member of a class of proteins that appear to convey signals important in the structure and biochemical activity of cells.

RHOGAM. The trade name of a medication given by intramuscular injection to a pregnant woman to prevent Rh disease in the newborn. Its generic name is Rho (D) immune globulin.

RIBONUCLEIC ACID (RNA). The genetic material that is involved in creating proteins. During the creation of proteins, one of the strands of the double stranded DNA sequence is transcribed into single-stranded RNA, which is involved in creating proteins. In the RNA sequence, a base called uracil (U) replaces thymine (T) when it is found in the DNA sequence.

RIBOSOME. A complex molecule made of RNA and proteins that acts like a protein synthesis factory.

RICKETS. A childhood disease caused by vitamin D deficiency, resulting in soft and malformed bones.

RING. A structural chromosomal abnormality in which a portion of a chromosome breaks off and its

ends join to form a circle or ring. There may or may not be loss of genetic material in a ring chromosome.

RING CHROMOSOME. An abnormal chromosome in which the terminal ends of the short (p) and long (q) arms have been lost and the remaining p and q arms subsequently join to form a ring.

RING SIDEROBLAST. A sideroblast that contains five or more iron granules in its mitochondria, enough to form a ring surrounding a third or more of the cell nucleus. It is also called a ringed sideroblast.

ROBERTSONIAN TRANSLOCATION. A chromosomal abnormality in which the long (q) arms of two acrocentric chromosomes (chromosomes in which the p arm is much shorter than the q arm; in humans, these are chromosomes 13, 14, 15, 21, and 22, and the Y chromosome) fuse together. The anomaly is named for William R.B. Robertson (1881–1941), who first identified it in grasshoppers in 1916.

ROD. A photoreceptor that is highly sensitive to low levels of light and transmits images in shades of gray.

ROLLER-TUBE TECHNIQUE. A technique used in tissue culture in which test tubes containing tissue or cell samples are held in a wheel-shaped instrument at a 15° angle from the horizontal, and the wheel is rotated vertically every 2 minutes. George Gey developed this technique in 1933.

ROSENTHAL FIBERS. Abnormal and irregularly shaped structures that form in astrocytes.

RUSSELL SYNDROME. An alternative term for Russell-Silver syndrome. Many doctors use this term to mean a Russell-Silver syndrome affected individual who does not have body asymmetry.

S

SACROILIAC JOINT. The joint between the triangular bone below the spine (sacrum) and the hip bone (ilium).

SACROILIITIS. Inflammation of the sacroiliac joint.

SACRUM. Triangular bone at the base of the spinal column.

SADDLE NOSE. A sunken nasal bridge.

SANGER SEQUENCING. The earliest method for sequencing DNA, devised by Frederick Sanger in the United Kingdom in 1977 and used as the primary method of sequencing until 2002. It is still used to validate the results of so-called next-generation sequencing. The Sanger method involves first separating the two strands

of DNA and then adding chemically altered forms of the adenine, cytosine, guanine, and thymine bases. The altered bases stop the process of DNA replication as they are added to the strand of DNA, resulting in a series of short pieces of DNA. These short pieces are placed in order from shortest to longest in order to read the entire original sequence of DNA.

SARCOIDOSIS. A chronic disease characterized by nodules forming in the lymph nodes, lungs, bones, and skin.

SARCOMERES. The basic functional units of striated muscle tissue. Sarcomeres consist of fibrous proteins that slide past each other as the muscle contracts and relaxes.

SARCOPLASMIC RETICULUM. A system of tiny tubes located inside muscle cells that allow muscles to contract and relax by alternatively releasing and storing calcium.

SATELLITES. Small segments of genetic material at the tips of the short arms of chromosomes 13, 14, 15, 21, and 22.

SAVANTS. People with ASD who have unusual abilities in areas such as art, math, or music.

SCAPHOCEPHALY. An abnormally long and narrow skull.

SCAPULA. Shoulder blade.

SCAPULAR WINGING. The jutting-back of the shoulder blades that can be caused by muscle weakness.

SCHIZENCEPHALY. A rare disorder caused by abnormal slits within the brain.

SCHIZOPHRENIA. A psychotic disorder characterized by loss of contact with one's environment, deterioration of everyday functioning, and personality disintegration.

SCHWANNOMA. A tumor that grows from the cells that line the nerves of the body (Schwann cells).

SCINTIGRAPHY. Injection and detection of radioactive substances to create images of body parts.

SCLERA. The tough white membrane that forms the outer layer of the eyeball.

SCLERODERMA. A relatively rare autoimmune disease affecting blood vessels and connective tissue that makes skin appear thickened.

SCLEROSIS. Hardening.

SCOLIOMETER. A tool for measuring trunk asymmetry; it includes a bubble level and angle measure.

SCOLIOSIS. An abnormal, curvature of the spine. In this condition, the curvature is usually side to side.

SCRAPIE. A fatal disease of sheep and goats that is classified as a transmissible spongiform encephalopathy. Although scrapie is caused by a prion, it is not transmissible to humans.

SCREENING. Process through which carriers of a trait may be identified within a population.

SCROTUM. The sac of skin that holds the testicles.

SEASONAL AFFECTIVE DISORDER (SAD). A subset of depressive disorder in which the person experiences depressive symptoms in the winter (or summer) but feels consistent the rest of the year. SAD is also called the winter blues, summertime sadness, or seasonal depression.

SEBACEOUS. Related to the glands of the skin that produce an oily substance.

SEBASTIAN SYNDROME. A subgroup of the *MYH9*-related disorders characterized by the platelet disorder and inclusion bodies in the white blood cells.

SECOND-DEGREE RELATIVE. Two relatives (grandmother/father and grandchild or aunt/uncle and niece/nephew) who share 25% of their genes in common.

SECONDARY CRANIOSYNOSTOSIS. Abnormal closure of the cranial sutures caused by a failure of the brain to grow and expand.

SECONDARY FINDINGS. Incidental or unanticipated findings, often of a previously unsuspected disease risk, resulting from the use of WES or WGS.

SEDATIVE. Medication that has a soothing or tranquilizing effect.

SEIZURES. An abnormal electrical discharge from the brain that usually results in convulsion of the body.

SEMEN. A whitish, opaque fluid that is released at ejaculation and contains sperm.

SEMINAL FLUID. Semen without sperm.

SEMINAL VESICLES. The pouches above the prostate that store semen.

SENSITIVITY. The proportion of people with a disease who are correctly diagnosed (test positive based on diagnostic criteria). The higher the sensitivity of a test or diagnostic criteria, the lower the rate of "false negatives," people who have a disease but are not identified through the test.

SENSORINEURAL HEARING LOSS (SNHL). Hearing loss that occurs when parts of the inner ear, such as the cochlea and/or auditory nerve, do not work correctly. It is often defined as mild, moderate, severe, or profound,

depending upon how much sound can be heard by the affected individual.

SENSORY NEURONS. Class of neurons that specifically regulate and control external stimuli (e.g., sight, sound).

SEPSIS. An infection of the bloodstream.

SEPTAL. Relating to the septum, the thin muscle wall dividing the right and left sides of the heart. Holes in the septum are called septal defects.

SEPTAL DEFECT. A hole in the heart.

SEPTUM. In anatomy, a wall of tissue that divides a body cavity or structure into smaller sections. The intraventricular septum is the tissue that divides the two lower chambers of the heart.

SEPTUM PELLUCIDUM. A membrane between two of the normal cavities of the brain that prevents electrical signals from passing between different portions of the brain.

SEQUENCE. As a noun, it is the exact order of bases in a nucleic acid or of amino acids in a protein; as a verb it means to determine the sequence of chemical constituents in an amino acid or the bases in a strand of DNA.

SERIAL CASTING. A series of casts designed to gradually move a limb into a more functional position.

SEROLOGICAL. Pertaining to serology, the science of testing blood to detect the absence or presence of antibodies (an immune response) to a particular antigen (foreign substance).

SEROSITIS. Inflammation of a serosal membrane. Polyserositis refers to the inflammation of two or more serosal membranes.

SEROTONIN. A neurotransmitter that transmits signals between nerve cells; low levels are associated with depression and PTSD.

SEROTONIN DOPAMINE ANTAGONISTS (SDAS). The newer second-generation antipsychotic drugs, also called atypical antipsychotics, including clozapine (Clozaril), risperidone (Risperdal), and olanzapine (Zyprexa).

SEROTYPE. One form of a bacteria that has unique surface proteins. Each serotype causes a unique antibody response from a person's immune system.

SERUM. The liquid part of blood.

SERUM CK TEST. A blood test that determines the amount of the enzyme creatine kinase (CK) in the blood serum. An elevated level of CK in the blood indicates

that muscular degeneration has occurred and/or is occurring.

SERUM CREATININE. A chemical in the urine of kidney patients used to determine kidney disease and failure. Elevated levels of serum creatinine are an early marker for severe kidney disease or failure.

SEVERE COMBINED IMMUNODEFICIENCY (SCID). A group of rare, life-threatening diseases present at birth that cause a child to have little or no immune system. As a result, the child's body is unable to fight infections.

SEX CHROMOSOMES. The X and Y chromosomes that determine the sex of the individual.

SEX-LINKED. A gene located on, and thus a trait linked to, the X or Y chromosomes.

SHAGREEN PATCH. Area of tough and dimpled skin.

SHOCK. An inability to provide the body with the oxygen it requires, sometimes due to large amounts of bleeding or fluid loss.

SHORT RIB POLYDACTYLY SYNDROMES. A collection of genetic disorders characterized by abnormally short ribs and extra fingers or toes. Research is ongoing to determine if these disorders are the result of mutations in a common gene.

SHORT STATURE. Height of less than three standard deviations from the mean for age, race, and gender. Shorter than normal height, can include dwarfism.

SHORT TRUNK. An abnormally short torso or body.

SHUNT. A small tube placed in a ventricle of the brain to direct cerebrospinal fluid away from the blockage into another part of the body.

SIALIC ACID. N-acetylneuraminic acid, a sugar that is often at the end of an oligosaccharide on a glycoprotein.

SIALIDOSIS. An inherited disorder also known as neuraminidase deficiency.

SICKLE CELL. A red blood cell that has assumed an elongated shape due to the presence of hemoglobin S.

SICKLE-CELL DISEASE. A chronic, inherited blood disorder characterized by sickle-shaped red blood cells. It occurs primarily in people of African descent and produces symptoms including episodic pain in the joints, fever, leg ulcers, and jaundice.

SIDEROBLAST. An abnormal erythroblast that contains a cell nucleus with iron granules accumulated in mitochondria around the nucleus.

SIGMOIDOSCOPY. Examination of the rectum and lower colon with a flexible instrument passed through the

anus; also used to remove polyps and obtain biopsy samples.

SIGN. An indication of disease, injury, or other physical problem that can be observed by someone other than the person experiencing these conditions.

SILVER SYNDROME. An alternative term for Russell-Silver syndrome. Many doctors use this term to mean an individual with Russell-Silver syndrome who also has body asymmetry.

SINGLE-NUCLEOTIDE POLYMORPHISM (SNP). A DNA sequence variation in which a single nucleotide in the genome differs between two individuals of the same species or between two paired chromosomes. SNPs affect individuals' susceptibility to diseases.

SINGLE-PHOTON COMPUTED TOMOGRAPHY (SPECT). Nuclear imaging that uses gamma rays to produce 3D images of inside the body.

SIRENOMELIA. An extremely rare birth defect, also known as mermaid syndrome, in which affected infants are born with a single lower extremity or with two legs that are fused together.

SISTER-CHROMATID EXCHANGE (SCE). Exchange of DNA between sister chromatids during DNA replication; excessive SCE can cause the gaps, breaks, and structural rearrangements of chromosomes that are diagnostic of Bloom syndrome.

SITUS SOLITUS. Normal organ placement in the body with the heart, stomach, and spleen placed toward the left, and the liver and gallbladder on the right.

SJÖGREN'S SYNDROME. A chronic inflammatory disease often associated with rheumatoid arthritis.

SKELETAL DYSPLASIA. A group of syndromes consisting of abnormal prenatal bone development and growth.

SKELETAL MUSCLE. A muscle under voluntary control that attaches to bone and controls movement.

SKEWED INACTIVATION. Random inactivation of either the paternally or maternally derived X chromosome in the female; also called lyonization, and occurs early in embryonic development.

SKIN ERYTHEMA. Irregular red streaks of skin.

SKIN HEMATOMA. Blood from a broken blood vessel that has accumulated under the skin.

SLEEP APNEA. A potentially life-threatening condition in which the individual has episodes during sleep in which breathing temporarily stops.

SLEEP PARALYSIS. An abnormal episode of sleep in which the patient cannot move for a few minutes, usually occurring on falling asleep or waking up. Often found in patients with narcolepsy.

SLY DISEASE. Also called Sly syndrome, an autosomal recessive lysosomal storage disease caused by a mutation in a gene on chromosome 7. It is named for William Sly, the American biochemist who discovered it.

SMALL INTESTINE. The part of the digestive tract in between the stomach and the large intestine.

SMALL TESTES. Refers to the size of the male reproductive glands, located in the cavity of the scrotum.

SMOOTH MUSCLE CELLS (SMCS). The layered cells in the wall of the aorta and other arteries.

SNEDDON SYNDROME. Adenosine deaminase 2 deficiency that may be caused by mutations in the *CECRI* gene, with symptoms usually developing later than those of polyarteritis nodosa.

SOCIAL DETERMINANTS OF HEALTH. Conditions in the places where people live, learn, work, and play that affect a wide range of health and quality-of-life issue for individuals and groups.

SOMATIC. Relating to the nonreproductive parts of the body.

SOMATIC CELLS. All the cells of the body except for the egg and sperm cells.

SOMATIC MUTATION. Sporadic mutation; a gene mutation that is not inherited from a parent carrying the mutation but rather occurs in an egg or sperm cell or during fetal development.

SOMATOSTATIN. A body chemical, known as a cyclic peptide, involved in the release of human growth hormone from the pituitary gland.

SORE. An open wound or a bruise or lesion on the skin.

SPASMODIC TORTICOLLIS. A painful chronic neurological disorder in which involuntary contractions of the neck muscles cause the person's head to twist or turn from side to side or upward and downward. It is also called cervical dystonia.

SPASTIC PARAPLEGIA. Inability to walk, due to lack of proper neural control over the leg muscles.

SPASTIC QUADRIPARESIS. Muscle spasms involve both the legs and the arms.

SPASTICITY. Increased muscle tone or stiffness that leads to uncontrolled, awkward movements.

SPASTIN. A protein encoded by the *SPAST* gene that regulates the length of microtubules and dissolves microtubule structures that are no longer needed.

SPAWNING. The process of releasing both eggs and sperm into water by fish and other aquatic animals.

SPECIFICITY. The proportion of people without a disease who are correctly classified as healthy or not having the disease (test negative based on diagnostic criteria). The higher the specificity of a test or diagnostic criteria, the lower the number of “false positives,” people who don’t have a disease but who “test” positive.

SPEECH THERAPIST. Person who specializes in teaching simple exercises to improve speech.

SPHEROCYTE. A red blood cell that has an abnormal spherical shape rather than the normal shape of a concave disk.

SPHINGOMYELIN. A group of sphingolipids containing phosphorus.

SPHINGOMYELINASE. An enzyme needed to break down sphingomyelin into ceramide.

SPHYGMOMANOMETER. An inflatable cuff used to measure blood pressure.

SPINA BIFIDA. A birth defect in which there is incomplete closure of the spine and the meninges (membranes) over the spinal cord.

SPINA BIFIDA OCCULTA. The failure of vertebrae to close into the neural tube without nerves protruding. This is most often asymptomatic.

SPINDLE APPARATUS. A network of microtubules (also known as spindle fibers) that forms during cell division to pull chromosomes during metaphase to the poles of the cell. The microtubules are formed from a protein called tubulin.

SPINOCEREBELLAR ATAXIA, AUTOSOMAL RECESSIVE 14 (SCAR14). Spectrin-associated autosomal recessive cerebellar ataxia type 1 (SPARCA1).

SPITZ NEVUS. A benign reddish or reddish-brown skin lesion that is difficult to distinguish from melanoma and is usually removed for that reason. Spitz nevi are named for Sophie Spitz, an American pathologist who first described them in 1948.

SPLAY. Turned outward or spread apart.

SPLEEN. An organ located in the upper abdominal cavity that filters out old red blood cells and helps fight bacterial infections. It is responsible for breaking down spherocytes at a rapid rate.

SPLENECTOMY. Removal of the spleen.

SPLENIC FLEXURE. The area of the large intestine at which the transverse colon meets the descending colon.

SPLENOMEGALY. Abnormal enlargement of the spleen.

SPONDYLOARTHRITIS (SPONDYLITIS). Inflammatory disease of the joints of the spine.

SPONDYLOEPIPHYSEAL DYSPLASIA. Abnormality of the vertebra and epiphyseal centers that causes a short trunk.

SPONDYLOEPIPHYSEAL DYSPLASIA CONGENITA. A subtype of collagenopathy, types II and IX, with symptoms that are similar to but milder than those of hypochondrogenesis and achondrogenesis type II.

SPONDYLOSIS. Arthritis of the spine.

SPONTANEOUS. Occurring by chance.

SPOON HAND. A type of syndactyly in which the thumb is joined to the four fingers as well as the fingers being fused together. It is also known as “mitten hand.”

SPORADIC. Describes genetic diseases that develop in patients with no family history of the disease.

SPORADIC CANCER. A cancer that occurs at random in the population with no known cause.

SPORADIC INHERITANCE. A situation in which a gene mutates spontaneously, or for the first time, to cause the disorder in a person with no family history of the disorder.

SPORADIC RETINOBLASTOMA. A type of retinoblastoma where the cancer-causing gene variants happen in a retinal cell after birth and are not inherited.

SPUTUM. A mixture of saliva and mucus from the lungs.

STAGE. The extent of a tumor’s progress. Tests are done to determine whether a tumor is localized to an organ or whether it has spread to the lymph nodes and/or other organs. Treatment is determined by the stage of the cancer.

STAGING. A method of describing the degree and location of cancer.

STATIC ENCEPHALOPATHY. A disease of the brain that does not get better or worse.

STATUS EPILEPTICUS. A potentially life-threatening seizure that either lasts longer than five minutes or consists of two seizures within a five-minute period.

without the patient returning to normal consciousness between the seizures.

STELLATE. A star-like, lacy white pattern in the iris. Most often seen in light-eyed individuals.

STEM CELLS. Cells that can transform into any different type of cell and can make copies of themselves indefinitely.

STENOSIS. The constricting or narrowing of an opening or passageway.

STENT. A tubular device made of metal or plastic that is inserted into a body duct or tube to prevent collapse, blockage, or overgrowth.

STEREOTYPY. A repetitive movement, gesture, or utterance; examples include head banging, rocking, or repeatedly crossing and uncrossing the legs. Stereotypy is found in persons with intellectual disabilities and some forms of schizophrenia as well as autism spectrum disorders.

STERILITY. The inability of either a male or a female to produce offspring. Sterility may result from physical injury, disease, genetic disorders, or exposure to radiation.

STILLBIRTH. The birth of a baby who has died sometime during the pregnancy or delivery.

STOMACH. The organ that holds and begins digestion of food.

STRABISMUS. An improper muscle balance of the ocular muscles resulting in crossed or divergent eyes.

STRATUM CORNEUM. The outer portion of the epidermis made up primarily of dead, flattened cells filled with the protein keratin.

STRICTUREPLASTY. A surgical procedure in which a narrowed portion of the intestine is removed and the remaining section is reconnected to a healthy section of bowel.

STROKE. An obstruction (ischemic) or rupture (hemorrhagic) of a blood vessel in the brain, causing death of brain tissue and potentially affecting physical and mental functioning.

STROMA. Middle layer of the cornea, representing about 90% of the entire cornea.

STRUCTURAL VARIATIONS. Variations in the structure of an organism's chromosome that are larger than single-nucleotide polymorphisms but smaller than a chromosome abnormality. Structural variations can include deletions, duplications, and insertions as well as copy number variations. Many structural variations are linked to genetic diseases but many more are not.

SUBARACHNOID SPACE. The space between two membranes surrounding the brain, the arachnoid and pia mater.

SUBCORTICAL BAND HETEROTOPIA. A mild form of lissencephaly type 1 in which abnormal bands of gray and white matter are present beneath the cortex near the ventricles.

SUBCORTICAL INFARCTS. Obstruction of nerve centers below the cerebral cortex of the brain.

SUBPENDYMAL GIANT CELL ASTROCYTOMA. Benign (noncancerous) tumor of the brain comprised of star-shaped cells (astrocytes).

SUBPENDYMAL NODULE. Growth found underneath the lining of the ventricles in the brain.

SUBMETACENTRIC. A centromere located between the center and the top of the chromosome.

SUBSTANTIA NIGRA. One of the movement control centers of the brain.

SUBSTRATE. A compound on which an enzyme works in a biochemical reaction.

SUBTELOMERE. The section of a chromosome immediately next to the telomere at the end of the chromosome.

SUDDEN CARDIAC DEATH (SCD). A term used to describe an unexpected death due to cardiac causes that occurs within an hour of symptom onset in a person with known or unknown heart disease.

SUDDEN INFANT DEATH SYNDROME (SIDS). The unexpected, sudden death of a child under one year of age. Often called "crib death."

SUDDEN UNEXPLAINED DEATH IN EPILEPSY (SUDEP). A fatal complication of epilepsy that accounts for about 15% of deaths in epilepsy patients. It is thought to result from a combination of factors, including cardiac and respiratory as well as neurological factors.

SULFATE. A chemical compound containing sulfur and oxygen.

SURROGACY. The practice in which a woman, called a surrogate mother, carries a pregnancy to term for another person or persons who cannot have children, who will become the legal parent(s) of the child after birth. Surrogacy may or may not involve a legal contract.

SUTURE. A "seam" that joins two surfaces together.

SYMPHALANGISM. Fusion of phalanges at their ends.

SYMPTOM. An indication of disease, injury, or other physical problem reported by the person experiencing these conditions, not by an outside observer.

SYNCHRONOUS. Occurring simultaneously.

SYNCOPE. A brief loss of consciousness caused by insufficient blood flow to the brain.

SYNDACTYLY. A birth defect in which the fingers or toes are joined either by webs of soft tissue (simple syndactyly) or by fusion of the bones (complex syndactyly). Syndactyly may occur either as an isolated birth defect or as part of a genetic syndrome like CLSS.

SYNDROME. A group of signs and symptoms that collectively characterize a disease or disorder.

SYNDROMIC AUTISM. A term used to describe autism that exists in combination with other clinical features, including physical as well as developmental abnormalities.

SYNDROMIC HEARING LOSS. Hearing loss that occurs as part of an underlying genetic syndrome.

SYNKINESIA. Involuntary movement of a part of the body when another part of the body moves.

SYNOPHRYS. A feature in which the eyebrows join in the middle; also called blepharophimosis.

SYNOSTOSIS (PLURAL, SYNOSTOSES). The medical term for the fusion of two bones.

SYNOVITIS. Inflammation of the synovium, a membrane found inside joints.

SYRINGOMYELIA. Excess fluid in the spinal cord.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE). A chronic, inflammatory autoimmune disorder that is the most common type of lupus.

SYSTEMIC RACISM. Also known as institutional racism, this is racism written into the laws, regulations, and practices of institutions, organizations, and groups. Systemic racism results in discrimination in education, housing, employment, health care, the criminal justice system and other aspects of life.

SYSTEMIC SCLEROSIS. A rare disorder that causes thickening and scarring of multiple organ systems.

SYSTOLE. The rhythmic contraction of the heart, particularly of the ventricles, in which blood is pumped through the aorta and the pulmonary artery.

SYSTOLIC BLOOD PRESSURE. Blood pressure when the heart contracts (beats).

T

T CELLS. White blood cells that fight both virally and bacterially infected cells within the body.

TACHYCARDIA. An abnormally rapid heartbeat in an adult at rest (that is, not exercising), usually regarded as 100 beats per minute or faster.

TAFAZZIN GENE (TAZ). A human gene located on the X chromosome that encodes tafazzin, a protein expressed at high levels in cardiac and skeletal muscle. Mutations in this gene have been associated with a number of disorders, including 3-methylglutaconic aciduria type 2 and dilated cardiomyopathy.

TAI-CHI. A Chinese system of physical exercises that uses slow, smooth body movements to help with posture control and relaxation.

TALIPES EQUINOVARUS. A type of clubfoot characterized by a downward and inward pointing foot.

TARGETED CARRIER TESTING. Testing to see if a person is a carrier of only one or a few conditions that the person is at risk for based on personal or family history or ancestry.

TARGETED THERAPY. A type of drug or other substance that identifies and attacks specific types of cancer cells with less damage to normal cells. Most targeted therapy drugs are either monoclonal antibodies or small-molecule drugs.

TAU. A protein involved in maintaining the internal structure of nerve cells; tau is damaged in Alzheimer's disease and forms neurofibrillary tangles.

TAY-SACHS DISEASE. An inherited biochemical disease caused by lack of a specific enzyme in the body. In classical Tay-Sachs disease, previously normal children become blind and mentally handicapped, develop seizures, and decline rapidly. Death often occurs between the ages of three and five years. Tay-Sachs disease is more common among individuals of eastern European Jewish background, but it has been reported in other ethnic groups as well.

TCA CYCLE. Formerly known as the Krebs cycle, this is the process by which glucose and other chemicals are broken down into forms that are directly useable as energy in the cells.

TELANGIECTASIS. Very small arteriovenous malformations or connections between the arteries and veins. The result is red spots on the skin known colloquially as "spider veins."

TELANGIECTATIC ERYTHEMA. A localized collection of dilated blood capillaries near the surface of the skin; congenital telangiectatic erythema is another name for Bloom syndrome.

TELOGEN. The resting phase of the hair growth cycle.

TELOMERE. A region of repeated DNA sequences at each end of a chromosome that serves to stabilize the chromosome. Telomeres are progressively shortened each time the cell divides until cell division stops, usually around 50 divisions. HeLa cells are distinctive in that their telomeres are copied repeatedly during cell division, so that they are never shortened.

TEMPORAL LOBE. Region of the brain located at the bottom middle part of cortex, right behind the temples; it is responsible for processing auditory information.

TENDON. A strong connective tissue that connects muscle to bone.

TENDON REFLEX. Reflex contraction of the muscle that is observed by tapping on its tendon.

TENOTOMY. A surgical procedure that cuts the tendon of a contracted muscle to allow lengthening.

TERATOGEN. Any drug, chemical, maternal disease, or exposure that can cause physical or functional defects in an exposed embryo or fetus.

TERATOGENIC. Describes any agent that can cause birth defects or intellectual disability in a developing fetus. Common teratogens are medications or other chemicals, but they also include infections, radiation, maternal medical condition, and other agents.

TERATOZOOSPERMIA. A condition in which at least 85% of sperm are abnormal; caused by mutations in several different genes.

TERMINAL DELETION. The abnormal early termination of a chromosome caused by the deletion of one of its ends.

TESTES. The male reproductive organs that produce male reproductive cells (sperm) and male hormones.

TESTICLES. The testes and their enclosing structures.

TESTOSTERONE. Hormone produced in the testicles that is involved in male secondary sex characteristics.

TETRALOGY OF FALLOT. A congenital heart defect consisting of four (tetralogy) associated abnormalities: ventricular septal defect (VSD—hole in the wall separating the right and left ventricles); pulmonic stenosis (obstructed blood flow to the lungs); the aorta “overrides” the ventricular septal defect; and thickening (hypertrophy) of the right ventricle.

TETRAMER. Protein that consists of four amino acid chains.

TETRAPARESIS. Muscle weakness affecting all four limbs.

TETRAPHOCOMELIA. Absence of all, or a portion of, all four limbs. The hands or feet may be attached directly to the trunk.

TETRAPLEGIA. Paralysis of all four limbs. Also called quadriplegia.

TETRASOMY. Refers to the presence of four parts or copies of a chromosome or part of a chromosome.

THALAMUS. A pair of large egg-shaped structures near the brain stem that act as the main sensory relay station and help with control of movement.

THALIDOMIDE. A mild sedative that is teratogenic, causing limb, neurologic, and other birth defects in infants exposed during pregnancy. Women used thalidomide (early in pregnancy) in Europe and in other countries between 1957 and 1961. It is still available in many places, including the United States, for specific medical uses (leprosy, AIDS, cancer).

THERMOLABILE. Heat-sensitive. A thermolabile protein is a protein that easily loses its shape when heated even only slightly.

THIRD-PARTY INTERPRETATION (TPI) SERVICE. An online tool that analyzes the raw DNA data from a DTC genetic test and provides a genetic health risk report.

THIRD-PARTY REPRODUCTION. Any instance of human reproduction in which DNA or gestation is provided by a third-party donor other than the parent(s) who will rear the resulting child. It is also called donor-assisted reproduction.

THORACIC CAVITY. The chest.

THORACOPAGUS. Conjoined twins joined at the upper body who share a heart.

THORAX. Chest cavity.

THREE-PARENT BABY. A term used in the mass media to describe a baby produced from the genetic material of one man and two women through the use of mitochondrial replacement technologies and three-person in vitro fertilization (IVF). It is not a scientific term.

THROMBOCYTOPENIA. A persistent decrease in the number of blood platelets usually associated with hemorrhaging.

THROMBOEMBOLISM. A condition in which a blood vessel is blocked by a free-floating blood clot carried in the bloodstream.

THROMBOPHILIA. A disorder in which there is a greater tendency for thrombosis (clot in blood vessel).

THROMBOPHLEBITIS. Inflammation of veins due to blood clots.

THROUGHPUT. In general, the rate at which data can be processed, or the work that a computer can do in a specific period of time. High-throughput sequencing refers to any of a set of technologies that can produce large numbers of DNA sequences concurrently.

THYMUS GLAND. An endocrine gland located in the front of the neck that houses and transports T cells, which are part of the immune system and help to fight infection.

THYROID GLAND. A gland located in the front of the neck that is responsible for normal body growth and metabolism. The thyroid traps a nutrient called iodine and uses it to make thyroid hormones, which allow for the breakdown of nutrients needed for growth, development, and body maintenance.

THYROID-STIMULATING HORMONE (TSH). A hormone produced in the anterior lobe of the pituitary gland that stimulates the thyroid gland to produce thyroxine and triiodothyronine. It is also known as thyrotropin.

THYROTROPIN-RELEASING HORMONE (TRH). A hormone produced by the hypothalamus that stimulates the pituitary gland to release TSH.

THYROXINE (T4). The major form of thyroid hormone circulating in the blood. It is converted in the liver and the thyroid gland itself into triiodothyronine, the most active thyroid hormone.

TIBIALIS. Muscles of the calf.

TIC. Brief and intermittent involuntary movement or sound.

TISSUE. A group of cells that have a common function. The four types of tissue are: connective, epithelial (skin), muscle, and nervous tissue.

TITUBATION. Tremor of the head.

tone. A term used to describe the tension of muscles. Increased tone is increased tension in the muscles.

TONOMETER. A device used to measure fluid pressures in the eye.

TORSADE DE POINTES. A type of tachycardia of the ventricles characteristic of Jervell and Lange-Nielsen syndrome.

TORTICOLLIS. Twisting of the neck to one side that results in abnormal carriage of the head and is usually caused by muscle spasms. Also called wry neck.

TOXEMIA OF PREGNANCY. A condition characterized by high blood pressure and large amounts of protein in the urine. It is also called pre-eclampsia. If left untreated, it may result in the breakdown of red blood cells, liver and kidney dysfunction, and seizures.

TOXIC. Poisonous.

TRABECULAR MESHWORK. A sponge-like tissue that drains the aqueous humor from the eye.

TRACHEA. The long tube connecting from the larynx down into the lungs, responsible for passing air.

TRACHEO-ESOPHAGEAL FISTULA. Abnormal connection between the trachea and esophagus, frequently associated with the esophagus ending in a blind pouch.

TRACHEOSTOMY. An opening surgically created in the trachea (windpipe) through the neck to improve breathing.

TRACTION ALOPECIA. Hair loss caused by pressure or tension on the scalp related to certain types of hair styles or equipment worn on the head.

TRAIT. In genetics, a specific characteristic of an individual organism, such as height, weight, or blood type. Traits are determined both by genes and the interaction of the environment with genes.

TRANSABDOMINAL CVS. Chorionic villus sampling performed using a needle inserted through the abdomen.

TRANSCERVICAL CVS. Chorionic villus sampling performed using a catheter inserted through the vagina and cervix.

TRANSCRIPTION. The process by which DNA is changed into RNA.

TRANSCRIPTION FACTOR. A protein that binds to specific DNA sequences and controls the rate of transcription of genetic information from DNA to messenger RNA.

TRANSCRIPTIONAL REPRESSION. Methods that inhibit transcription such as protein binding to promoters to impede binding of RNA polymerase.

TRANSFER RNA (TRNA). A small RNA molecule that binds to a complementary mRNA sequence and then attaches the corresponding amino acid to the protein chain.

TRANSFERRIN. An iron-binding glycoprotein found in blood plasma that controls the level of iron in biological fluids. The serum transferrin level can be used to check for iron deficiency and hemochromatosis.

TRANSFUSION. The injection of a component of the blood from a healthy person into the circulation of a person who is lacking or deficient in that same component of the blood.

TRANSGENIC. Referring to an organism in which one or more sequences of DNA from another species have been introduced by artificial means. Animals are typically made transgenic by having a small segment of the other species' DNA injected into an egg or developing embryo.

TRANSIENT ISCHEMIC ATTACK (TIA). A neurologic dysfunction that comes and goes quickly and is similar to a stroke.

TRANSILLUMINATION. A diagnostic technique that involves shining a strong light through body tissues in order to detect defects. Transillumination of the iris may be used to diagnose congenital microcoria.

TRANSITION MUTATION. A point mutation where an (A) and (G) base are switched or a (C) and (T) base are switched.

TRANSLATION. The process of converting the sequence of messenger RNA into a series of amino acids in order to implement the genetic code of an organism.

TRANSLOCATION. The transfer of one part of a chromosome to another chromosome during cell division, which can create oncogenes, amplify oncogenes, or inactivate a tumor-suppressor gene.

TRANSPLANTATION. The implanting of an organ from either a deceased person (cadaver) or from a live donor to a person whose organ has failed.

TRANSPOSITION OF THE GREAT ARTERIES (TGA). A reversal of the two great arteries of the heart, causing oxygenated blood to be carried back to the lungs and deoxygenated blood to be transported throughout the body.

TRANSRECTAL ULTRASOUND. A procedure in which a probe is placed in the rectum. High-frequency sound waves that cannot be heard by humans are sent out from the probe and reflected by the prostate. These sound waves produce a pattern of echoes that are then used by the computer to create sonograms or pictures of areas inside the body.

TRANSVAGINAL ULTRASOUND. A way to view the ovaries by using sound waves. A probe is inserted into the vagina, and the ovaries can be seen. Color doppler

imaging measures the amount of blood flow, as tumors sometimes have high levels of blood flow.

TRANSVERSION. A genetic term referring to a specific substitution of one base pair for another. There are only four possible transversions: guanine for cytosine, cytosine for guanine, adenine for thymine, or thymine for adenine.

TRANSVERSION MUTATION. A point mutation where an (A or G) base is changed to a (T or C) or vice versa.

TRAUMA. Injury.

TREMOR. Involuntary rhythmic back-and-forth movements involving one or more parts of the body. Tremor is most commonly seen in the hands but can affect almost any part of the body.

TRICHOTILLOMANIA. A psychiatric disorder characterized by hair loss resulting from compulsive pulling or tugging on one's hair.

TRIGGER DRUGS. Specific drugs used for muscle relaxation and anesthesia that can trigger an episode of malignant hyperthermia in a susceptible person. The trigger drugs include halothane, enflurane, isoflurane, sevoflurane, desflurane, methoxyflurane, ether, and succinylcholine.

TRIGLYCERIDE. A type of lipid consisting of a molecule of glycerol and three fatty acid fragments.

TRIGONOCEPHALY. An abnormal development of the skull characterized by a triangle-shaped forehead.

TRIIODOTHYRONINE (T3). The most active and final form of thyroid hormone.

TRIMESTER. A three-month period. Human pregnancies are normally divided into three trimesters: first (conception to week 12), second (week 13 to week 24), and third (week 25 until delivery).

TRINUCLEOTIDE REPEAT EXPANSION. A sequence of three nucleotides that is repeated too many times in a gene sequence.

TRIOSE PHOSPHATE ISOMERASE. Abbreviated TPI, this is the enzyme responsible for the conversion of dihydroxyacetone phosphate (DHAP) into D-glyceraldehyde-3-phosphate (GAP). DHAP and GAP are the two major products of a step in the multi-step process that converts glucose into ATP to supply the body with the energy it needs to sustain itself. Only GAP can continue in this process, but DHAP is produced in much higher quantities. People with TPI deficiency cannot change DHAP into GAP as efficiently as unaffected people, resulting in insufficient amounts of ATP from glucose to maintain normal cell function.

TRIPHALANGEAL THUMB (TPT). A thumb that has three bones rather than two.

TRIPLOID. Three sets of chromosomes; in humans, this is 69 chromosomes.

TRISOMY. A type of aneuploidy in which there are three copies of a specific chromosome in cells instead of the normal two. Genetic disorders caused by trisomies include Down syndrome (trisomy 21) and Edwards syndrome (trisomy 18).

TRUNCUS ARTERIOSUS. A condition in which a structure present during fetal development fails to develop normally into two separate structures, the aorta and the pulmonary trunk. Thus there is only one arterial trunk structure leading from the heart instead of two. Often there is a ventricular septal defect (VSD) present.

TRYPSIN. A digestive enzyme found in pancreatic fluid that breaks down proteins. This enzyme is abnormal in hereditary pancreatitis.

TRYPTOPHAN. A crystalline amino acid widely distributed in proteins and essential to human life.

TUBEROUS SCLEROSIS. A genetic disorder of the skin and nervous system involving the formation of small tumors in various organs and sometimes causing ASD.

TUBULE. A small tube lined with glandular epithelium in the kidney.

TUMOR. An abnormal growth of cells. A tumor may be benign (noncancerous) or malignant (cancerous).

TUMOR-EDUCATED PLATELETS (TEPS). Platelets that have had their RNA profiles changed through association with cancerous tumors.

TUMOR NECROSIS FACTOR (TNF). A protein called a cytokine that mediates inflammation throughout the body and activates immune system cells; targeted by biologics for treating colitis.

TUMOR-SUPPRESSOR GENES. Genes that normally help prevent cancer from developing in a cell. Variants (mutations) in tumor suppressor genes make the cell more likely to become cancerous.

TURNER SYNDROME. A chromosomal disorder with a 45,X or 45,X0 karyotype that affects only females, in which one of the X chromosomes is either partially or completely missing. Most women with Turner syndrome are infertile because of a lack of ovarian function.

TYMPANOPLASTY. Any of several operations on the eardrum or small bones of the middle ear to restore or improve hearing in patients with conductive hearing loss.

TYPE 1 DIABETES MELLITUS (T1D). An autoimmune disorder that generally develops in childhood in which the immune system attacks and destroys insulin-producing beta cells; also called insulin-dependent diabetes mellitus (IDDM).

TYPE 2 DIABETES MELLITUS (T2D). A condition in which the body does not properly utilize glucose due to insulin resistance or decreased insulin production; also called non-insulin-dependent diabetes mellitus (NIDDM).

TYPE I INCONTINENTIA PIGMENTI. Sporadic IP. This disorder is caused by mutations in the gene at Xp11. These mutations are not inherited from the parents, they are de novo mutations. This type of IP probably represents a different disease than type II IP.

TYPE II INCONTINENTIA PIGMENTI. Familial, male-lethal type IP. This type of IP is the “classic” case of IP. It is caused by mutations in the NEMO gene located at Xq28. Inheritance is sex-linked recessive.

TYPE XI COLLAGEN. A type of collagen that produces an organic gel that helps cartilage to convert into bone and helps bone growth in the developing fetus.

TYROSINE (TYR). The amino-acid precursor of melanin.

U

UBIQUITIN-PROTEASOME SYSTEM. A multicomponent system that identifies and degrades unwanted proteins in the cytoplasm of all cells. It is involved in cell growth and differentiation, DNA replication and repair, apoptosis, and stress and immune responses.

ULCER. Inflammatory lesion of the mucous-like tissue in the stomach.

ULCERATIVE COLITIS (UC). A form of colitis characterized by ulcers in the colon that may bleed and produce pus.

ULNA. One of the two bones of the forearm, the one opposite the thumb.

ULTRASONOGRAPH. The image produced by the use of inaudible sound of high frequency called ultrasound to photograph a tissue, organ, or infant.

ULTRASOUND. An imaging technique that uses high-frequency sound waves to help display internal structures in the body.

UMBILICAL HERNIA. Protrusion of the bowels through the abdominal wall, underneath the navel.

UNDESCENDED TESTICLES. Testicles that failed to move from the abdomen to the scrotum during the development of the fetus.

UNILATERAL. Refers to one side of the body or only one organ in a pair.

UNIPARENTAL DISOMY (UPD). An unusual genetic status in an individual in which one parent is the source of both chromosomes of a pair.

UPSHOOT. Upward movement of the eye.

UREA. A nitrogen-containing compound that can be excreted through the kidney.

UREA CYCLE. A series of complex biochemical reactions that remove nitrogen from the blood so ammonia does not accumulate.

UREA CYCLE DISORDER. A disease caused by a lack of an enzyme that cleans the blood of ammonia.

UREMIC POISONING. Accumulation of waste products in the body.

URETERS. Tubes through which urine is transported from the kidneys to the bladder.

URETHRA. The tubular portion of the urinary tract connecting the bladder and external meatus through which urine passes. In males, seminal fluid and sperm also pass through the urethra.

URETHRAL ATRESIA. Abnormal closure of the tube that leads from the bladder to the outside of the body.

URETHRITIS. Inflammation of the urethra.

URINARY URGENCY. An exaggerated or increased sense of needing to urinate.

URTICARIA. Also known as hives. Usually associated with an allergic reaction.

USHER SYNDROME. The most common type of autosomal recessive syndromic hearing loss.

UTERUS. A muscular, hollow organ of the female reproductive tract. The uterus contains and nourishes the embryo and fetus from the time the fertilized egg is implanted until birth.

UVEA. The medical term for the pigmented middle layer of the three layers of tissue comprising the eye. The uvea includes the iris, the ciliary body, and the choroid. Melanomas that develop in these structures are called uveal melanomas.

UVEITIS. Inflammation of all or part of the uvea, which consists of the middle vascular portion of the eye, including the iris, ciliary body, and choroid.

V

VACCINE. An injection, usually derived from a microorganism, that can be injected into an individual to provoke an immune response and prevent future occurrence of an infection by that microorganism.

VACUOLATION. The formation of multiple vesicles, or vacuoles, within the cytosol of cells.

VACUOLE. A small cavity found within organic tissue.

VARIABLE EXPRESSION. Ability of the same gene to cause different symptoms in different people (with the same disorder).

VARIABLE NUMBER TANDEM REPEATS (VNTRS). Short repeated DNA sequences; VNTRs flanking the insulin gene may be involved in susceptibility to diabetes.

VARIABLE PENETRANCE. A term describing the way in which the same mutated gene can cause symptoms of different severity and type within the same family.

VARIANT. A change in the sequence of a genome.

VARICOCELE. Enlargement of the veins within the male scrotum. Sometimes described as resembling a bag of worms, varicoceles are a common cause of low sperm production and reduced sperm quality.

VASCULAR. Pertaining to blood vessels.

VASCULAR DEMENTIA (VAD). Dementias caused by damage to blood vessels in the brain.

VASCULAR MALFORMATION. Abnormality of the blood vessels that often appears as a red or pink patch on the surface of the skin.

VASCULAR SYSTEM. The network of blood vessels in the body.

VASCULITIS. Blood vessel inflammation.

VAS DEFERENS. The long, muscular tube that connects the epididymis to the urethra through which sperm are transported during ejaculation.

VASODILATOR. A drug that relaxes blood vessel walls.

VECTOR. A viral or non-viral vehicle that delivers the genetic material.

VEIN. A vessel that carries oxygen-poor blood from the tissues and extremities back toward the heart to be reoxygenated.

VELLUS HAIRS. The fine lighter-colored hairs that result from miniaturization.

VELO. Derived from the Latin word *velum*, meaning palate and back of the throat.

VENOUS. Term used to describe a vein or the entire system of veins.

VENOUS THROMBOEMBOLISM. A blood clot that breaks free of its location in a vein and moves elsewhere in the body.

VENOUS THROMBOSIS. A condition caused by the presence of a clot in a vein.

VENTILATOR. Mechanical breathing machine.

VENTRAL WALL DEFECT. An opening in the abdomen (ventral wall). Examples include omphalocele and gastroschisis.

VENTRICLES. In the brain, the fluid-filled spaces in the center of the brain that hold cerebral spinal fluid. Also, the two lower chambers of the heart. The right ventricle pumps blood to the lungs, and the left ventricle pumps oxygenated blood through the aorta into the general circulation.

VENTRICULAR SEPTAL DEFECT (VSD). An opening between the right and left ventricles of the heart.

VENTRICULOPERITONEAL SHUNT. A tube equipped with a low pressure valve, one end of which is inserted into the lateral ventricles, the other end of which is routed into the peritoneum, or abdominal cavity.

VERMIS. The central portion of the cerebellum, which divides the two hemispheres. It functions to monitor and control movement of the limbs, trunk, head, and eyes.

VERTEBRA. One of the 23 bones that compose the spine. "Vertebrae" is the plural form.

VERTEBRAL DIVISIONS. The human vertebral regions are divided into cervical, thoracic, lumbar, and sacral from the neck to the tailbone.

VERTEBRATE. Any animal with a segmented spinal column and a distinct head. Vertebrates include fishes, amphibians, reptiles, birds, and mammals.

VERTICAL GAZE PALSY. Uncontrolled up and down motions of the eye.

VERY LONG CHAIN FATTY ACIDS (VLCFA). A type of fat that is normally broken down by the peroxisomes into other fats that can be used by the body.

VESICLE. A membrane-bound structure within a cell in which enzymes and other materials are transported or stored.

VESTIBULAR SYSTEM. A complex organ located inside the inner ear that sends messages to the brain about

movement and body position. It allows people to maintain their balance when moving by sensing changes in their direction and speed.

VIRILIZATION. Masculinization; the development of male sexual characteristics in a female or increased male characteristics in a male caused by excess androgen production.

VISUAL ACUITY. The ability to distinguish details and shapes of objects.

VISUAL CORTEX. The area of the brain responsible for receiving visual stimuli from the eyes and integrating it to form a composite picture of an object.

VITAMIN DEFICIENCY. Abnormally low levels of a vitamin in the body.

VITAMIN K. A vital substance that is obtained by eating certain foods, such as leafy greens, but mainly through bacterial manufacture in the large intestine.

VITREOUS. Describes the jelly-like substance that fills the inner eyeball.

VOLTAGE-GATED CALCIUM CHANNEL. A type of voltage-gated (voltage-dependent) ion channel found in excitable cells (such as muscles, neurons) that are permeable to the calcium ion.

VOLUNTARY MUSCLE. A muscle under conscious control, such as arm and leg muscles.

VOLVULUS. A twisted loop of bowel causing an obstruction.

VON VOSS-CHERSTVOY SYNDROME. A very rare genetic disorder characterized by encephalocele, brain abnormalities, upper limb defects, and malformations of the urogenital tract.

VON WILLEBRAND FACTOR (VWF). A protein found in the blood that is involved in the process of blood clotting.

W

WAARDENBURG SYNDROME. The most common autosomal dominant form of syndromic hearing loss.

WALKER-WARBURG SYNDROME. A congenital form of muscular dystrophy that may be accompanied by encephalocele as well as muscular weakness and other abnormalities of the eyes and brain.

WARM-UP PHENOMENON. The progressive easing of the myotonic contraction of a muscle (in a patient with

myotonia congenita) with repeated voluntary contractions of the muscle.

WEYERS ACROFACIAL DYSOSTOSIS. The condition resulting from a mutation of the same gene that shows mutation in Ellis-van Creveld syndrome. As is usually the case when comparing expressions of the same gene mutation, the single-dose Weyers acrofacial dysostosis presents milder symptoms than the double-dose Ellis-van Creveld syndrome.

WHIPPLE PROCEDURE. Surgical removal of the pancreas and surrounding areas, including a portion of the small intestine, the duodenum.

WHITE BLOOD CELL (WBC). A cell in the blood that helps fight infections.

WHITE MATTER. The part of the brain that consists of fibers that establish long-distance connections between brain regions. It normally thickens as a child grows older, and the brain matures.

WHOLE-EXOME SEQUENCING (WES). Sequencing of the 1%–3% of the DNA in the genome that encodes for proteins; used to identify genetic disorders.

WHOLE-GENOME SEQUENCING (WGS). Sequencing of all the DNA in a genome. In people, WGS can be used to look for mutations that may cause a disease or disorder.

WILD TYPE (WT). The typical phenotype of a species as it exists in nature, without any genome editing.

WILSON DISEASE. A rare hereditary disease marked by high levels of copper deposits in the brain and liver.

WNT SIGNALING. A signal transduction pathway that functions to pass signals from the outside of the cell to the inside of the cell. Signals are transduced through the binding of proteins to receptors on the plasma membranes of cells. The receptor then transfers the signal to additional signaling proteins that function inside the cell. Wnt signaling pathways regulate cell shape and growth, cell polarity, and cell-cell communication, among other required cellular mechanisms.

WOLFFIAN DUCTS. Structures in the embryo that develop into epididymides, vasa deferentia, and seminal vesicles in males.

WOOD'S LIGHT. An ultraviolet light used in medical settings because of its ability to create fluorescence in the presence of substances such as porphyrins.

WORD SALAD. Speech that is so disorganized that it makes no linguistic or grammatical sense.

WORMIAN BONES. Extra pieces of bone that sometimes occur within one or more of the cranial sutures.

XYZ

X CHROMOSOME. One of the two sex chromosomes (the other is Y) containing genetic material that, among other things, determines a person's sex.

X-CHROMOSOME INACTIVATION. The molecular process that inactivates one of two X chromosomes in most cells present in female mammals. This inactivation prevents females from having twice as many X-chromosome gene products as males of that species.

XANTHOMA. Small, yellow fat deposits that appear in the skin.

XERODERMA PIGMENTOSUM (XP). A rare inherited skin disorder in which the skin cells lack an enzyme needed to repair damage to the cell's DNA caused by sunlight. People with XP are 1,000 times more likely to develop melanoma than people without the disorder.

XEROSTOMIA. The medical term for dry mouth. It is most often a side effect of medications but is also found in some genetic syndromes.

X-LINKED. A gene located on the X sex chromosome.

X-LINKED DISORDER. Any disorder caused by genes located on the X chromosome.

X-LINKED DOMINANT INHERITANCE. A gene or trait located on an X chromosome that is expressed in preference to the same gene on the other X chromosome; X-linked mutations are often lethal in males because males have only one X chromosome.

X-LINKED GENE. A gene carried on the X chromosome, one of the two sex chromosomes.

X-LINKED INTELLECTUAL DISABILITY. Subaverage general intellectual functioning that originates during the developmental period and is associated with impairment in adaptive behavior. Pertains to genes on the X chromosome.

X-LINKED MUTATION. An abnormal gene transmitted on the X chromosome.

X-LINKED OCULAR ALBINISM (XLOA). OA1; the most common type of ocular albinism, which primarily affects vision in males.

X-LINKED RECESSIVE INHERITANCE. The inheritance of a trait by the presence of a single gene on the X chromosome in a male, passed from a female who has the gene on one of her X chromosomes, who is referred to as an unaffected carrier.

XPR1A. The gene that encodes a receptor that is involved in exporting phosphate out of cells; mutations in this gene can cause PFBC.

X-RAY. An imaging test that uses beams of energy to create images of structures within the body.

Y CHROMOSOME. The sex chromosome (allosome) that is found together with an X chromosome in normal human males. Microdeletions in the Y chromosome can affect a man's fertility in adult life.

YOGA. An exercise that combines relaxation and breathing techniques to combat stress and help circulation

and movement of the joints; yoga has its origin in ancient Indian medicine.

ZOONOSIS (PLURAL, ZOONOSES). Any infectious disease of animals that can be transmitted to humans. A human disease that can be transmitted to animals is called a reverse zoonosis.

ZYGOTE. A fertilized egg cell that results from the union of two gametes, a female egg and a male sperm.

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